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RESEARCH ARTICLE

Lengthening Bowel Endoscopically: Hydrogel-Enabled Endoscopic Spring-Mediated Distraction Enterogenesis

Rafael Gonzalez[1] | Narelli de Paiva Narciso[2] | Pamela Emengo[3] | Gillian Fell[3] | Helene Nepomuceno[3] | Carly Celebrezze[3] | Renato S. Navarro[2,4] | Neil J. Baugh[2] | Jayniana Williams[2] | Anne-Laure Thomas[3] | Sarah C. Heilshorn[2] | James C. Y. Dunn[3,5]

[1]Division of Pediatric Gastroenterology, Department of Pediatrics, Stanford University School of Medicine, Stanford, California, USA | [2]Department of Materials Science and Engineering, Stanford University, Stanford, California, USA | [3]Division of Pediatric Surgery, Department of Surgery, Stanford University School of Medicine, Stanford, California, USA | [4]Department of Materials Science and Engineering, University of Florida, Gainesville, Florida, USA | [5]Department of Bioengineering, Stanford University, Stanford, California, USA

Correspondence: James C. Y. Dunn (jdunn2@stanford.edu)

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ABSTRACT

We evaluated the feasibility to lengthen small bowel endoscopically utilizing a spring device constrained by an engineered, slow biodegrading, hyaluronan and elastin-like protein (HELP) hydrogel as a potential treatment for short bowel syndrome. While we previously demonstrated that the HELP hydrogel could provide device confinement and enable non-invasive device removal, here we demonstrate that the HELP hydrogel can also be designed to be catheter-injectable while still being stiff enough to achieve device confinement. Six pigs underwent endoscopic spring-mediated distraction enterogenesis (ESMDE), the lengthening of existing intestine using axial mechanical force. A compressed spring that was encapsulated in gelatin was placed into pig jejunum via enterotomy. The spring was confined on each end by endoscopic catheter-injection of HELP gel into the intestinal submucosa to cause transient luminal narrowing. The gelatin capsule rapidly biodegrades to deploy the spring, while the HELP gel slowly biodegrades to transiently constrain the device, applying tension to the bowel segment. On postoperative day 7, of the six pigs that underwent ESMDE, four had successful bowel lengthening, up to 172% of the initial length. None of the animals experienced any complications such as obstruction or perforation, and there were no mortalities. In this proof-of-concept study, we demonstrate that a hydrogel can be designed with the appropriate catheter-injection properties, stiffness, and biodegradation rate to achieve hydrogel-enabled, endoscopic spring-mediated distraction enterogenesis, making it a possible future treatment for short bowel syndrome.

1 | Introduction

Short bowel syndrome (SBS) is a life-threatening disease defined by reduced length of functional bowel [1, 2]. Causes include acquired or congenital loss of bowel and result in nutrient malabsorption, excessive fluid loss, electrolyte abnormalities, and poor growth [3].

SBS is fatal without treatment, which is largely supportive and includes long-term parenteral nutrition, treatments to increase absorptive capacity of the bowel by slowing transit, and invasive surgical lengthening [4]. Unfortunately, long-term parenteral nutrition (PN) is associated with central line infections, sepsis, and liver disease [2]. Thus, several surgical techniques aiming to lengthen the bowel and improve nutrient absorption have

Rafael Gonzalez and Narelli de Paiva Narciso contributed equally to this work.

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been developed, including longitudinal intestinal lengthening and tailoring (LILT), serial transverse enteroplasty (STEP), and spiral intestinal lengthening and tailoring (SILT) [5]. Among previous studies with these techniques, the reported intestinal elongation typically ranged from 50% to 100% with respect to targeted area, with the STEP technique leading to an average of 42%–43% of patients weaned off PN within 2 years after surgery with lengthening of 6% to 67% [5]. However, isolated mortality rates are not readily reported, since mortality in SBS is typically multifactorial and literature is scarce [5]. Current surgical techniques have high rates of complications, including tissue death, bowel obstructions, liver failure, sepsis, and even death [1, 6, 7], with some studies suggesting a 26% mortality rate for the LILT technique [8].

Here, aiming to decrease surgical complications and risks, we report a proof-of-concept of an innovative potential SBS endoscopic treatment: hydrogel-enabled, endoscopic spring-mediated distraction enterogenesis (ESMDE). Distraction enterogenesis is the use of axial mechanical force to lengthen the existing intestine [7, 9]. Previously, we successfully lengthened bowels using plicating sutures to surgically confine a spring device [2, 7, 9–24]. With the use of internal plications, we reached an average of 72% increase in length in the targeted, spring-containing bowel region [20]. While we reached positive results, these surgical methods require invasive surgeries to both place and remove the spring devices [13, 16, 18, 19, 23–25]. To devise a less invasive surgical procedure, we previously reported the use of engineered hydrogels that were directly syringe-injected into the submucosa to transiently anchor the spring at each end, leading to an average of 32% to 88% lengthening of the target site, depending on the hydrogel formulation [24]. These results demonstrated a proof-of-concept that the spring could be naturally evacuated as the hydrogel underwent biodegradation, but an invasive surgery to place the device was still required.

Here, we further develop this biomaterials-enabled strategy into a clinically translatable procedure by demonstrating a less invasive, endoscopic delivery for device placement. A compressed spring encapsulated in gelatin is placed into the jejunum of a piglet. The spring is transiently anchored on each end with endoscopic, submucosal catheter injections of a bioengineered hydrogel, termed HELP gel, composed of hyaluronic acid (HA), a biopolymer present in the native intestinal extracellular matrix (ECM) [26–28], and elastin-like protein (ELP), a recombinant protein that mimics elastin, which is endogenous to the bowel ECM (Figure 1A–C) [26, 29, 30]. These biopolymers are functionalized with benzaldehyde (BZA) and hydrazine (HYD) motifs respectively (Figure 1B), yielding HA-BZA and ELP-HYD, such that when mixed together they spontaneously form dynamic covalent chemistry (DCC) crosslinks, forming the hydrogel network (Figure 1C) [29–31]. After implantation, the gelatin capsule rapidly dissolves and the spring deploys to exert force against the HELP gel injections on each end, resulting in bowel lengthening. We provide a theoretical analysis of the required gel stiffness to secure the spring once the capsule dissolves.

To achieve endoscopic device placement in a potential clinical setting, the hydrogel must be extrudable through a long, thin catheter, which provides significant resistance compared to a syringe needle [30, 32, 33]. To meet this design criteria, the HELP gel is crosslinked through reversible, dynamic-covalent bonds that provide mechanical robustness while still enabling extrusion [29, 30, 34]. HELP is also highly mechanically tunable through molecular parameters, allowing for catheter-injectability [30]. Our previous study in which dynamic covalent chemistry (DCC) gels were directly syringe-injected into the submucosa to transiently secure the spring demonstrated that the inclusion of ELP in the gel system delays degradation in vivo [24]. At the study endpoint, DCC formulations containing ELP presented about four times more residual hydrogel than formulations composed of HA alone. Further, we showed that formulations with ELP led to longer lengthening of the target site, with an average of 88% lengthening for ELP-containing formulations versus 32% for HA-only formulations, likely due to the increase in the duration of spring confinement [24].

The recombinant ELP sequence also contains an extended RGD peptide derived from the matrix protein fibronectin, Figure 1A, a cell-adhesion cue that is commonly found in intestinal stem cell crypts [26, 35, 36]. In other work, the HELP system has been shown to provide a suitable environment for in vitro intestinal organoid culture, promoting cell proliferation and differentiation into mature intestinal cell subtypes [26, 35]. We hypothesized that this biomimicry of the intestinal ECM would allow for good biocompatibility of the material in vivo. Both the HA and ELP can be degraded by endogenous enzymes, notably hyaluronidase and elastase, respectively. HA has a comparatively short in vivo half-life relative to elastin [37, 38]. Thus, gel formulations that include ELP will degrade more slowly, enabling the spring to start slipping [24], being naturally evacuated, and eliminating the need for surgery to remove the device. This suture-free procedure enables less invasive, endoscopic placement of the spring device, serving as a potential future treatment for SBS.

2 | Methods

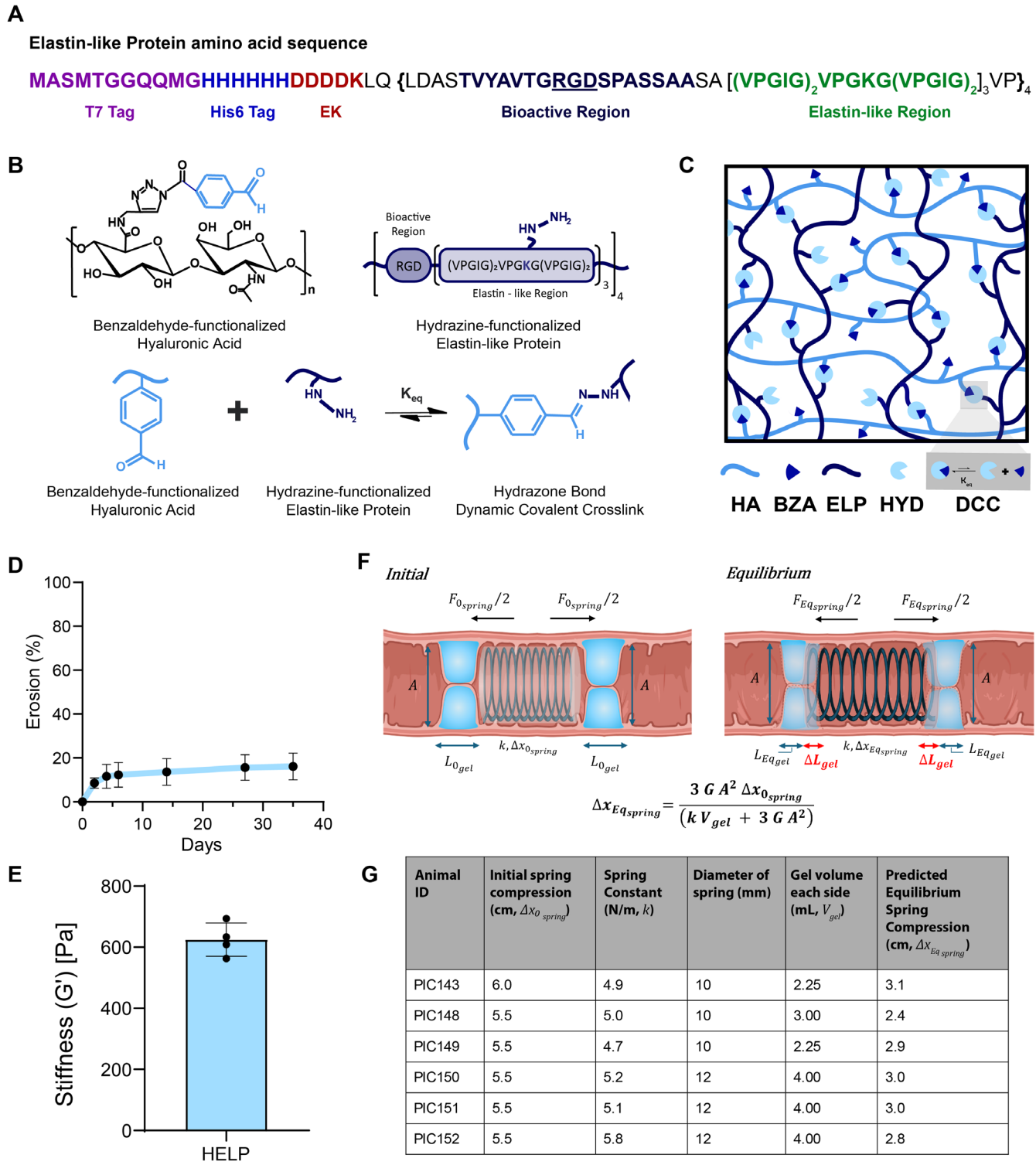
2.1 | Biopolymer Synthesis

The hydrogel components, chemically modified elastin-like protein (ELP) and hyaluronic acid (HA), were synthesized as previously described (Figure 1) [26, 30, 34, 39–44]. Briefly, the recombinant ELP was expressed in *Escherichia coli*, yielding a 37.7 kDa protein [40, 44]. After purification, ELP was functionalized with hydrazine (HYD) motifs through click chemistry on the lysine residues [29], yielding ELP-HYD. HA (LifeCore, HA60K-5, Table S1, Supporting Information) was functionalized with benzaldehyde (BZA) motifs through a two-step synthesis, yielding HA-BZA [29]. Proton nuclear magnetic resonance (H^1 NMR) characterization of HA-BZA quantified the degree of functionalization at 12% BZA. All biopolymers were sterile filtered, lyophilized, and stored at −80°C [45].

2.2 | Hydrogel Formation

HA-BZA and ELP-HYD were dissolved at 2 wt% in sterile phosphate-buffered saline (PBS) overnight at 4°C [30]. For all injections, equal volumes, 500 μL, of 2 wt% HA-BZA and 2 wt% ELP-HYD were loaded in individual 1-mL syringes and

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Animal ID	Initial spring compression (cm, $\Delta x_{0\ spring}$)	Spring Constant (N/m, k)	Diameter of spring (mm)	Gel volume each side (mL, V_{gel})	Predicted Equilibrium Spring Compression (cm, $\Delta x_{Eq\ spring}$)
PIC143	6.0	4.9	10	2.25	3.1
PIC148	5.5	5.0	10	3.00	2.4
PIC149	5.5	4.7	10	2.25	2.9
PIC150	5.5	5.2	12	4.00	3.0
PIC151	5.5	5.1	12	4.00	3.0
PIC152	5.5	5.8	12	4.00	2.8

FIGURE 1 | Chemical structure and mechanical analysis of HELP gel. (A) Primary amino acid sequence of the engineered elastin-like protein (ELP). In addition to a fibronectin-derived bioactive region and an elastin-like region, the protein includes T7 and histidine (His6) tags for easy identification and an enterokinase cleave site (EK) for optional tag removal. (B) Chemical structure of benzaldehyde-functionalized hyaluronic acid (HA-BZA) and schematic representation of hydrazine-functionalized elastin-like protein (ELP-HYD) (top). Mixing of HA-BZA with ELP-HYD spontaneously forms hydrazone bonds, a type of dynamic covalent crosslink (DCC) (bottom). (C) Schematic of hydrogel polymer network formed upon mixing, termed HELP gel. (D) In vitro erosion of HELP gel in an excess of saline. (E) Shear storage modulus, G', commonly referred to as "stiffness" of the HELP hydrogel. (F) Schematic of initial spring placement and spring at equilibrium state after in vivo deployment and derived equation to predict spring compression by HELP gel after deployment. (G) Predictions of equilibrium spring compression after deployment for each spring used in the six pigs.

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connected through a luer fitting, allowing easy mixing of the solutions on ice [30]. Once mixed, the biopolymers spontaneously crosslink, forming hydrazone bonds through reaction between BZA-HYD motifs. Oscillatory rheology quantified gel stiffness (shear modulus, G').

2.3 | Injection Force Measurements

Injection force was measured through a load cell (FUTEK 50 lb load cell, LLB250) coupled to a controlled flow rate syringe pump (KDS Legato 100). A 1-mL syringe with an endoscopic injection therapy needle catheter (Boston Scientific, 25 G × 240 cm) was loaded with HELP gel mixed with 0.5 μL blue food dye for visualization. After gel equilibration at room temperature for 15–30 min, the maximum force required to eject the gel at 2 mL per minute was recorded ($n = 3$).

2.4 | Erosion Studies

HELP gels (30 μL, 1 wt% HA, 1 wt% ELP, $n = 8$) were cast in microtubes and covered with 300 μL PBS at 37°C. Supernatant was collected and replenished on days 2, 4, 6,14, 27, 35 to assess HELP gel erosion in the absence of enzymes, cells, or mechanical movements from the bowel. HA concentration was quantified with a colorimetric uronic acid assay [46, 47].

2.5 | Spring Design and Preparation

A shape setting heat treatment using a nitinol filament wrapped around a coiled mold was used to form the springs, as previously described [18, 22, 48]. Uncompressed spring lengths were measured, and an Instron device (Illinois Tool Works Inc., Glenview, Ill) was used to continuously extend each spring while measuring the force [18, 49]. This was used to calculate the spring constant (k) in accordance with Hooke's law, $F = -kx$, where k = spring constant (N/m), F = force (N), and x = displacement (m) [18]. Springs were compressed and placed into hard gelatin capsules (Torpac Inc., Fairfield, NJ) [18]. All capsules were coated with three layers of cellulose acetate phthalate in acetone to prevent premature spring deployment in vivo [18]. Utilizing the rod of a cotton swab, a hole was made through the gelatin capsule to allow insufflation and water to flow through the capsule during endoscopic placement [18]. Capsules were sterilized under UV light for 24 h preoperatively [48].

2.6 | Procedure

Stanford University's Institutional Care and Use Committee reviewed and approved all animal procedures (Protocol # 32278). Six juvenile, miniature Yucatan piglets underwent endoscopic spring-mediated distraction enterogenesis (ESMDE). The springs measured either 10-mm or 12-mm in diameter, depending on animal bowel size, and the spring constant was 4.7–5.8 N/m. All springs had the same expanded, uncompressed length of 7.5 cm. The initial compressed length of the spring encapsulated in fast-dissolving gelatin ranged from 5.5 to 6 cm. Each pig underwent laparotomy, and a segment of jejunum was isolated. An enterotomy was performed, and a sterile Olympus GIF-Q180 gastroscope was introduced into the jejunum. Utilizing a Boston Scientific 25 G × 240 cm injection therapy needle catheter, a small bolus of normal saline dyed blue was injected into the mucosa of the bowel. This effectively created a pocket of fluid beneath the mucosa that served as a larger target to inject the HELP hydrogel, which was also dyed blue for better visualization. HELP hydrogel was injected in between the submucosal and muscularis layers by way of the saline pocket at two sites that would serve as the distal anchoring points for the spring. The compressed spring encased in a dissolvable gelatin capsule was inserted into the jejunum and advanced until it abutted the HELP gel injections. Additional saline and HELP gel were then injected at two sites just proximal to the spring, resulting in complete confinement of the spring. Gel injection volume was distributed evenly among four total injection sites. The volume of injected gel was selected to achieve a predicted length of the deployed spring of ~3 cm in order to exert sufficient tension to achieve intestinal lengthening.

2.7 | Bowel Measurements

As a control, 2.5 cm of untreated jejunum were measured and identified with marking sutures at each end in each animal, serving as our untreated control (Ctrl). The initial length of the compressed spring within the jejunum was measured with two marking sutures on each end [18]. Pigs were given a liquid diet and observed until euthanized at post-procedure day 7, when the laparotomy was repeated. At the endpoint, the distance between the marking sutures was measured to assess the final length of the jejunum after spring treatment. The length of spring that "slipped" past the distal HELP injections as the device began the process of natural evacuation was also measured.

2.8 | Tissue Processing, Histology, and Immunostaining

After excision, three different regions were evaluated for histology: the lengthened jejunum (spring-containing target region), HELP-injected jejunum (the areas adjacent to the spring that received the gel), and control jejunum (untreated tissue from the same animal). The samples were fixed in 10% buffered formalin and paraffin-embedded. Embedded tissue was sectioned and stained with hematoxylin and eosin (H&E) [18]. Once processed, crypt depth, mucosal thickness, muscularis thickness, lamina propria diameter, and bowel outer diameter of the specimens were analyzed in the three corresponding regions.

2.9 | Statistics

Data are reported as mean and standard deviations. Data analyses, which included paired Student's t-test and two-way analysis of variance (ANOVA), were performed using GraphPad Prism 10 software (GraphPad Software, San Diego, CA). Paired Student's t-test compared the average length of tissue gained between the jejunal segments that underwent ESMDE. Two-way

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ANOVA compared crypt depth, mucosa thickness, muscularis thickness, diameter of lamina propria, and bowel outer diameter among lengthened jejunum, jejunum containing HELP gel, and control jejunum.

3 | Results

3.1 | Mathematical Analysis of Hydrogel Stiffness for Spring Confinement

We developed a simplified theoretical model to predict whether gel stiffness would be sufficient for proper spring confinement (Figure S1, Supporting Information). Each spring device is designed to exert a specific force when deployed in the intestine based on the initial spring compression and the spring constant. The gel injected into the submucosa must be sufficiently stiff to resist the force applied by the spring after deployment. To simplify our model, we assume: (1) the cross-section of the bowel is constant and equal to the spring cross-section during deployment, (2) the HELP gel has constant volume (i.e., gel incompressibility) [50, 51] and constant stiffness. Initially, a gelatin capsule compresses the spring during surgical placement, with an initial spring compression $\Delta x_{0_{spring}}$ (Figure 1E, left) [52].

Once the gelatin capsule dissolves, the spring exerts a force against the HELP gel located at both ends. In response, the stiff HELP gel will become deformed as the spring lengthens, and the forces reach an equilibrium, confining the spring in place. The amount of HELP gel deformation (which is determined by the HELP gel stiffness) dictates the spring length after deployment (Figure 1E, right). This equilibrium spring length must be less than the fully relaxed spring length, so that the spring exerts tension on the bowel and promote distraction enterogenesis. Our model predicts the spring compression (i.e., change in spring length relative to its relaxed length) once the spring is deployed and confined by the gel, which we define as $\Delta x_{Eq_{\text{Spring}}}$.

$$\Delta x_{0_{\text{spring}}} = x_{\text{relaxed}} - x_{\text{gelatin compressed}} : F_{0_{\text{spring}}} = k\ \Delta x_{0_{\text{spring}}} \tag{1}$$

$$\Delta x_{Eq_{\text{Spring}}} = x_{\text{relaxed}} - x_{\text{confined by gel}} : F_{Eq_{\text{spring}}} = k\ \Delta x_{Eq_{\text{spring}}} \tag{2}$$

Such that k is the spring constant, x_{relaxed} is the length of the uncompressed spring, $x_{\text{gelatin compressed}}$ is the length of the spring when it is compressed inside the gelatin capsule, and $x_{\text{confined by gel}}$ is the length of the spring after the gelatin capsule dissolves [25]. Once the gelatin dissolves, the spring will push against the hydrogel and reach an equilibrium by compressing the HELP gel on either side an amount of ΔL_{gel}, such that:

$$x_{\text{confined by gel}} = x_{\text{gelatin compressed}} + 2\Delta L_{\text{gel}}$$

Replacing this in our equation (2):

$$\Delta x_{Eq_{\text{Spring}}} = \Delta x_{0_{\text{spring}}} - 2\Delta L_{\text{gel}} \tag{3}$$

$$\Delta L_{\text{gel}} = \frac{\Delta x_{0_{\text{spring}}} - \Delta x_{Eq_{\text{Spring}}}}{2} \tag{4}$$

At equilibrium, the stress applied by the spring is the same as the stress on the hydrogel (σ_{Eq}), which is defined as the force applied on the gel ($F_{Eq_{\text{spring}}}/2$) on each side over the bowel's cross-section (A). The stress within the gel is given by the Young's modulus (E) times the strain (ϵ, deformation) of the gel.

$$\sigma_{Eq} = \frac{F_{Eq_{\text{spring}}}/2}{A} = \frac{F_{Eq_{\text{spring}}}}{2A} \tag{5}$$

$$\sigma_{Eq} = E\epsilon \tag{6}$$

Due to the presumed incompressibility of the hydrogel, the Poisson ratio, $\nu = 0.5$ [50], and the Young's modulus, E, is related to the shear modulus, G [53], as follows:

$$E = 2G(1+\nu) = 3G \tag{7}$$

The hydrogel strain, or deformation, is the variation of gel length (ΔL_{gel}) over the original length of the hydrogel $\left(L_{0_{\text{gel}}}\right)$.

$$\epsilon = \frac{\Delta L_{\text{gel}}}{L_{0_{\text{gel}}}} \tag{8}$$

Assuming a constant gel volume at each injection site (V_{gel}) and that the gel occludes the entirety of the bowel lumen so that the injected gel forms a cylindrical volume, the volume of gel would be as follows:

$$V_{\text{gel}} = L_{0_{\text{gel}}} A : L_{0_{\text{gel}}} = V_{\text{gel}}/A \tag{9}$$

Combining equations (4), (6) through (9), we can correlate the strain and the stress applied on the hydrogel directly to spring parameters:

$$\epsilon = \frac{\Delta L_{\text{gel}}}{L_{0_{\text{gel}}}} = \frac{\left(\Delta x_{0_{\text{spring}}} - \Delta x_{Eq_{\text{Spring}}}\right)A}{2\,V_{\text{gel}}}$$

$$\sigma_{Eq} = E\epsilon = \frac{3GA\left(\Delta x_{0_{\text{spring}}} - \Delta x_{Eq_{\text{Spring}}}\right)}{2\,V_{\text{gel}}} \tag{10}$$

As we are assuming that the stress applied on the hydrogel is solely coming from the pressure applied by the spring, we must equate equations (5) and (10):

$$\sigma_{Eq} = E\epsilon = \frac{3GA\left(\Delta x_{0_{\text{spring}}} - \Delta x_{Eq_{\text{Spring}}}\right)}{2\,V_{\text{gel}}} = \frac{F_{Eq_{\text{spring}}}}{2A} = \frac{k\Delta x_{Eq_{\text{Spring}}}}{2A}$$

$$3GA^2\left(\Delta x_{0_{\text{spring}}} - \Delta x_{Eq_{\text{Spring}}}\right) = k\Delta x_{Eq_{\text{Spring}}} V_{\text{gel}}$$

$$G = \frac{k\Delta x_{Eq_{\text{Spring}}} V_{\text{gel}}}{3A^2\left(\Delta x_{0_{\text{spring}}} - \Delta x_{Eq_{\text{Spring}}}\right)} \tag{11}$$

Constants in our model include the bowel diameter (same as the implanted spring), bowel cross-sectional area (A), and hydrogel stiffness (G). With this relationship, we can estimate the minimum stiffness necessary to achieve a spring compression at equilibrium of at least ~30% (e.g., $\Delta x_{Eq_{\text{Spring}}} \cong 2.0$ cm). Assuming

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we inject $V_{gel} = 3$ mL on either side to confine a 10-mm diameter ($A = 7.85 \times 10^{-5}$ m^2), spring with $k = 5.8$ N/m, that was originally compressed $\Delta x_{0_{spring}} = 6$ cm, we would need a hydrogel with $G \geq 470$ Pa.

3.2 | Materials Selection and Mechanical Characterization

Our previous work demonstrates that we can control the injectability and stiffness of the HELP gel system by tuning the molecular weight (MW) and degree of functionalization (DoF) of the HA component [22]. Specifically, we have shown that by selecting HA with intermediate molecular weights (MW ≤ 60 kDa) and with DoF close to the stoichiometric ratio of the crosslinking hydrazone bonds (1:1 BZA:HYD), we can achieve catheter-injectable, stiff hydrogels [30]. Higher HA molecular weights within the HELP system have been shown to double the required injection force, hindering injectability and limiting clinical translation [30].

Using this previous knowledge of the HELP system, we selected a formulation with 60-kDa HA (Table S1) and 12% BZA functionalization, which we expected to have a plateau shear storage modulus, G', of ~800 Pa, surpassing our needed threshold, and an injection force, F, of ~10 N, considered easily hand injectable [30]. In vitro studies showed about 75%–80% of submerged HELP gels were still present on day 35 after exposure to excess saline, demonstrating slow erosion over time (Figure 1D). Within one week, 85%–90% of the HELP gel was remaining. While we expect the overall biodegradation rate of the HELP gel to be faster in the enzymatically and mechanically active bowel environment in vivo, these results supported the use of HELP gels to transiently constrain the spring for at least 7 days, a time frame that we have previously shown is sufficient for distraction enterogenesis [10–12, 14, 18].

Upon mechanical characterization, the storage modulus (stiffness, G') was assessed to be G'~630 Pa, fulfilling the estimated requirement (Figure 1E). To theoretically validate this stiffness would be enough to secure the compressed spring in each animal of our trial, we predicted our spring compression at equilibrium using the theoretical framework presented above (Figure 1F):

$$\Delta x_{Eq_{Spring}} = \frac{3GA^2 \Delta x_{0_{spring}}}{\left(kV_{gel} + 3GA^2\right)} \quad (12)$$

The estimates for each spring used in our animal trial can be found in Figure 1G. The diameter of each spring was selected by the surgeon to match the intestinal inner diameter, while the spring constant was experimentally determined by directly measuring the applied force upon continuous extension using an Instron device [49]. Per Hooke's Law, the spring constant (k) is the slope of the force versus displacement graph [49]. Gel volumes were selected so that the deployed spring would remain compressed with a length of ~3 cm (predicted range of 2.4–3.1 cm), thereby applying tension to the bowel for distraction enterogenesis.

3.3 | Selected HELP Gel Formulation Is Easily Catheter-Injectable

A force of about 8.1 N was needed to inject the HELP gel through the selected catheter (Figure 2A). This HELP gel injection force is much lower than the maximum threshold of 38 N for hand injectability [33, 54]. This ease of injectability through a catheter supports the clinical translatability of this surgical approach to place the spring device using a long, thin catheter (Figure 2B,C).

3.4 | Hydrogel-Enabled ESMDE Is Able to Successfully Lengthen the Bowel

The HELP gels were endoscopically injected into the intestinal submucosa to transiently immobilize the gelatin-compressed spring (Figure 2B,D). There were no complications resulting from these experiments. The pigs tolerated a liquid diet during the 7-day post-procedure observation period. Signs or symptoms of obstruction or perforation were not observed in any of the animals. They stooled normally, and all pigs had minimal weight loss between 0% and −1% of weight difference compared to their pre-procedure weight.

Marking sutures were used to identify the initial (Figure 3A) and final (Figure 3B) intestinal segment lengths, both on the spring-containing segments and on an untreated bowel segment to serve as our control. The untreated control segments did not present any statistically significant lengthening. The length of tissue gained in all six pigs after ESMDE ranged between 0.0 and 1.8 cm. (Figure 3C). This represented a statistically significant increase in the average final length of the bowel segment following ESMDE treatment (Figure 3C,D, $p < 0.05$). The percent of length of the lengthened segment relative to the initial segment length ranged between 100% and 172% (Figure 3D).

Four of six pigs had significant lengthening of bowel within the treated region, with final lengths of 150%–172% compared to pre-spring deployment length (Figure 3D). Interestingly, out of these four, more lengthening was observed in the two animals that received the larger-diameter 12-mm spring. Although this was not statistically significant given the small sample size in this proof-of-concept study (Figure 3E), it suggests spring diameter might be an important variable to consider in future studies. The experiment that resulted in the most tissue-length gained (1.8 cm) and the greatest percent change in intestinal segment length (172%) utilized 8 mL of total injected HELP gel and a 12-mm diameter spring.

Consistent with our previous findings [24], in all pigs, we observed that the spring device had slipped past the distal HELP gel injections at sacrifice (Figure 3B,F), suggesting that the process of natural evacuation had begun. In the animals that received a 10-mm diameter spring, the device slipped between 1.0 and 3.0 cm, and in the 12-mm spring, the spring slipped between 3.25 and 3.5 cm past the distal HELP injection site (Figure 3F,G).

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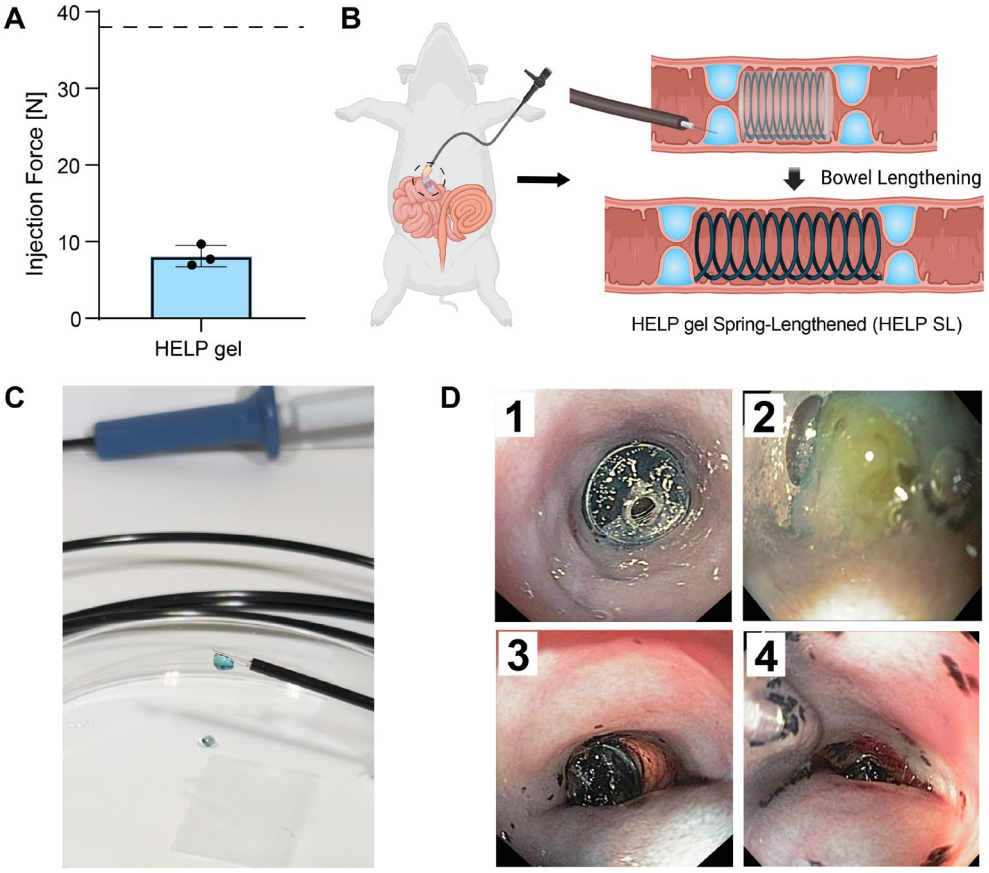


FIGURE 2 | Hydrogel-enabled endoscopic spring-mediated distraction enterogenesis. (A) Injection force required to extrude the HELP gel from a 1-mL syringe through a catheter (25-G, 240-cm) compared to reported maximal hand-injection force (dashed line). (B) Schematic of endoscopic anchoring of intestinal lengthening device through submucosal HELP injections. (C) HELP gel can be injected through a 25-G, 240-cm catheter by hand. (D) Endoscopic view of spring placement, (1) spring placed, (2) creating saline pocket for gel anchoring, (3) first of two HELP injections obstructing the lumen, (4) final HELP injections to secure the spring.

3.5 | Histological Changes in Lengthened Tissue Are Consistent With Previous Studies

At the end of the treatment time, the tissue was explanted for histological analysis. We compared tissue morphology among an untreated control segment that had not been treated ("control"), the spring-lengthened jejunum ("spring"), and the jejunum that contained the HELP gel injection ("HELP") (Figure 4A–C). Measurements are the averages for each of the six animals. The lamina propria diameter of the control segment (20.3 mm) was statistically larger than that of the spring-treated segment (11.7 mm) and the HELP-injected segment (11.2 mm) (Figure 4D, $p < 0.05$). There was no statistical difference in lamina propria diameter between the spring-treated and HELP-injected segments. For the outer bowel diameter, there were statistically significant differences among all three groups, with the largest outer diameter present in the HELP-injected segment (14.6 mm), followed by the spring-treated segment (12.7 mm), then the control untreated segment (10.9 mm) (Figure 4E, $p < 0.05$).

We next evaluated higher magnification images of the explanted tissue for quantitative analysis (Figure 5A–C). The muscularis propria was thickest in the untreated control segment (468 μm), then the spring-treated segment (446 μm), followed by the HELP-injected segment (393 μm), although these differences were not statistically significant (Figure 5D). In contrast, statistically significant differences in crypt depth and mucosal thickness were observed among all three groups. The spring-treated segments had the deepest crypts (102 μm), followed by the HELP-injected segments (84.8 μm), and finally the untreated control segments (73.2 μm) (Figure 5E, $p < 0.05$). The mucosa was thickest in the HELP-injected segments (869 μm), followed by the spring-treated segments (799 μm), and then the untreated control segments (594 μm) (Figure 5F, $p < 0.05$). These histological observations were consistent with previous studies demonstrating changes in tissue structure during intestinal lengthening [2, 55–58].

4 | Discussion

The current proof-of-concept work shows that our engineered hydrogel can be designed to be catheter-injectable to enable endoscopic device placement while still being sufficiently stiff to achieve spring-mediated tension that results in intestinal lengthening. This study significantly improves the potential clinical translatability of gel-enabled ESMDE by demonstrating an endoscopic procedure that has the potential to be an effective method to lengthen bowel. No symptoms of distress nor any signs of obstruction or perforation were observed. Pigs tolerated a liquid diet and lost minimal weight in the 7-day

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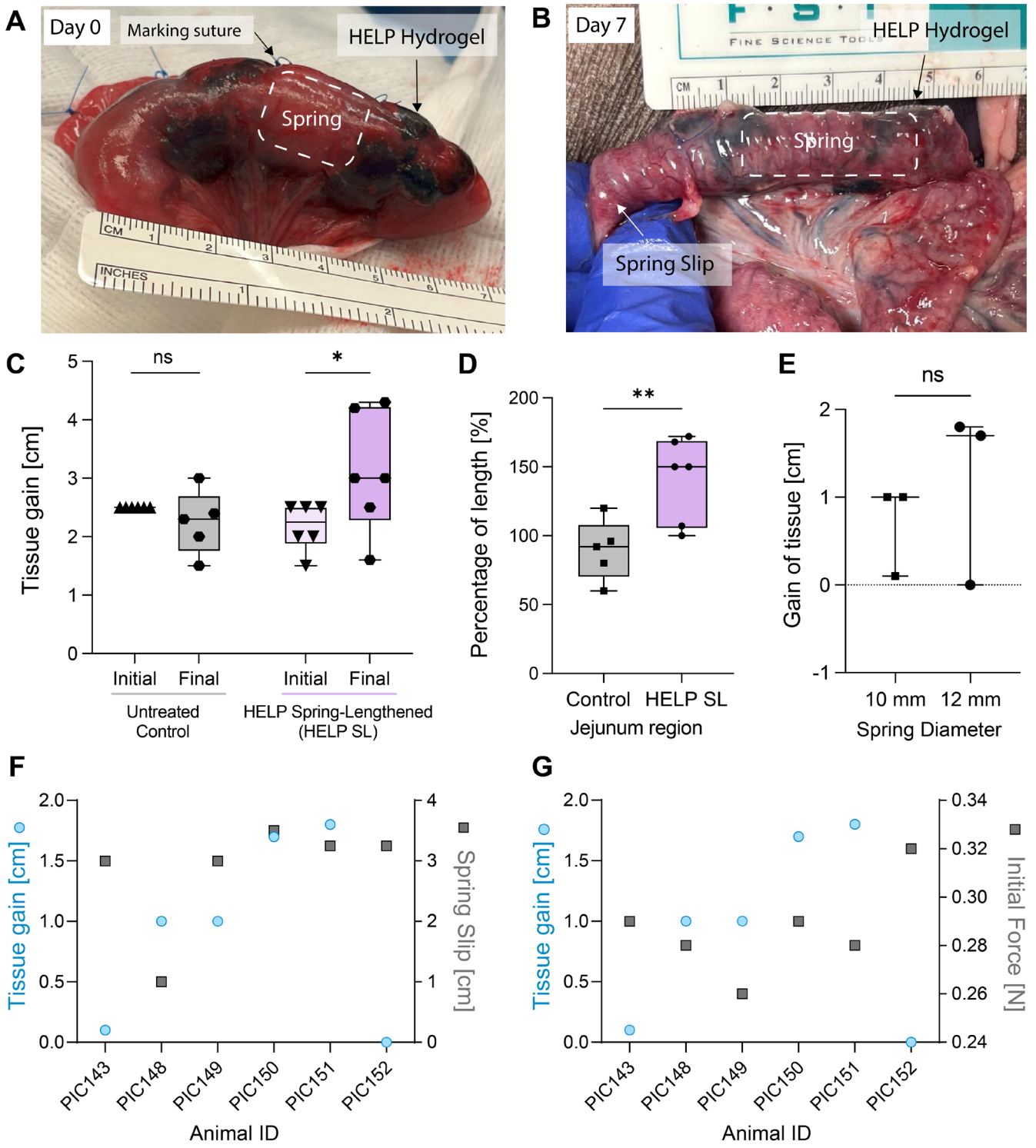


FIGURE 3 | Analysis of intestinal lengthening. (A) Photo on day of surgery showing anchored, gelatin-compressed spring with HELP gel injections (dyed blue) at both ends of the spring and marking sutures for identifying ends of the bowel segment. (B) Deployed spring inside lengthened bowel at day 7; hydrogel injections remained in place, and spring slipped distally through the gel to begin evacuation, indicated as spring slip. (C) Comparison of initial and final lengths of untreated bowel control (Control) marked with sutures and of HELP gel anchoring spring-containing (spring-lengthened) segments (HELP SL). Paired Student's *t*-tests, $*p < 0.05$ for each group. (D) Initial and final segment length as a percentage of initial length for all animals both Control and HELP SL. (E) Gain of tissue per spring diameter applied to each animal, no statistical significance was observed between the groups (ns). (D, E) Unpaired Student's *t*-tests, $***p < 0.001$. (F, G) Parameters for each animal in the study (PIC143, PIC148, PIC149, PIC150, PIC151, PIC152) that underwent ESMDE in the HELP SL region. Left *y*-axis, in blue, represents the final gain in tissue length (cm) by spring treatment. (F) Spring distal slip past the HELP gel injection at euthanasia (Day 7). (G) Right *y*-axis, in gray, initial spring force in newtons (N) by the gelatin-encapsulated compressed spring at the time of surgical implantation.

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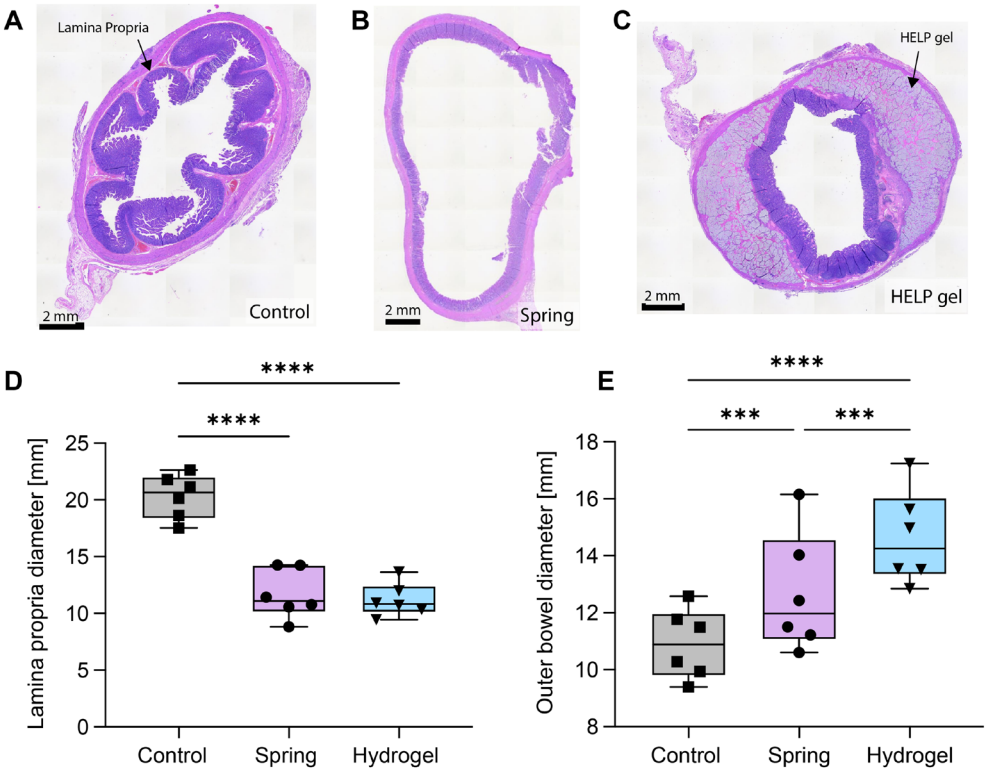


FIGURE 4 | Analysis of explanted bowel cross-sections. (A–C) Representative histology of cross-sections of the bowel: (A) control untreated bowel, (B) spring-lengthened bowel, (C) bowel at HELP injection site. (D) Diameter of lamina propria per location. (E) Outer diameter of bowel per location. Two-way ANOVA, ***$p < 0.001$, ****$p < 0.0001$.

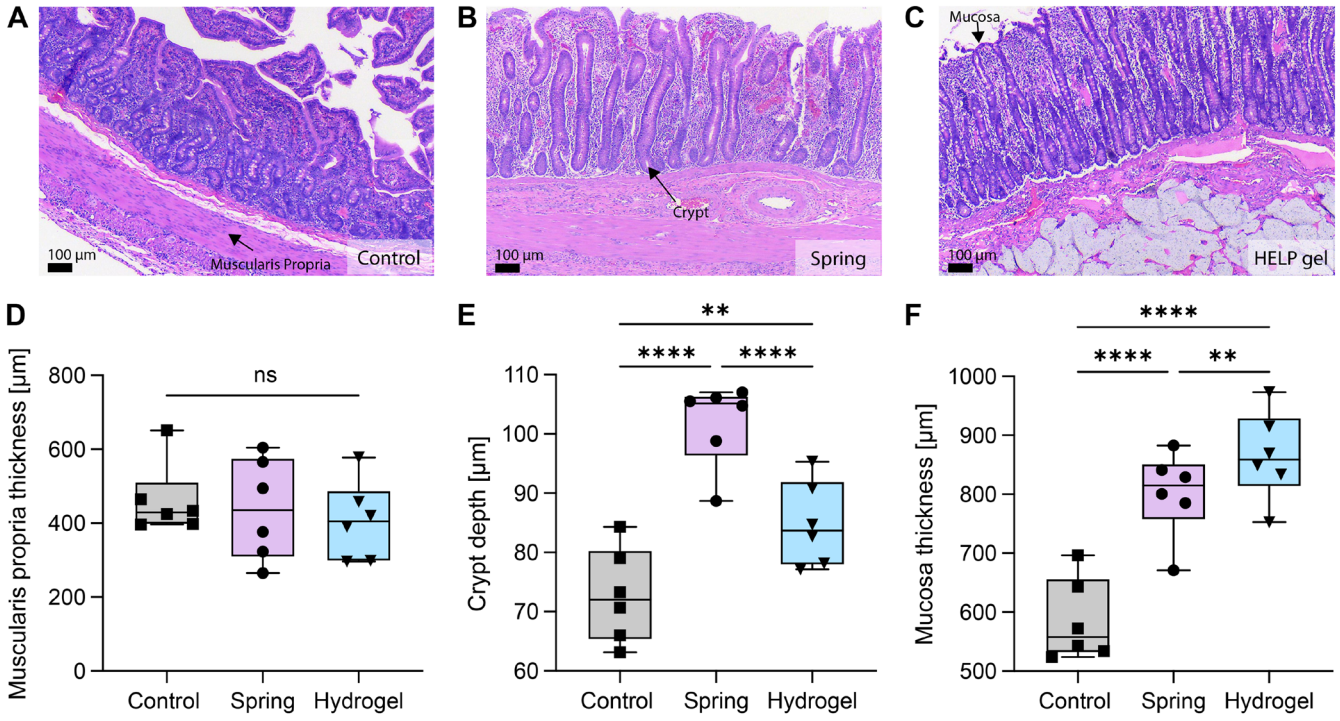


FIGURE 5 | Histological analysis of lengthened bowel. (A–C) Representative histology of cross-sections of the bowel: (A) control untreated bowel, (B) spring-lengthened bowel, (C) bowel at HELP injection site. (D–F) Quantified comparison of (D) muscularis propria thickness, (E) crypt depth, and (F) mucosa thickness, in the control, spring-lengthened, and gel-injected tissue. Two-way ANOVA, **$p < 0.01$, ****$p < 0.0001$, ns, not significant.

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observation period. Our untreated control segments did not present any lengthening, in fact some of them had a reduced length, which has been previously observed and is attributed to surgical manipulation and post-operative adhesions [59, 60]. Further, we did not evaluate the lengthening potential of an unanchored spring (i.e., a spring with no hydrogel injections nor sutures at either end), as prior work has shown that unanchored springs fail to stay in place and do not lead to lengthening [25].

The gel-injected, spring-treated intestinal segments achieved statistically significant lengthening compared to pre-treatment lengths, despite a small sample size ($n = 6$). Particularly, four out of the six animals had an increase of the targeted regions from 50% to 72% which is consistent with currently clinically applied techniques, such as STEP and LILT [5, 8]. Further, while our targeted region in this study was limited to the length of the relaxed spring ($x_{relaxed}$), we have previously demonstrated that multiple springs can be applied in sequence within the same bowel, leading to a larger targeted region and achieving larger absolute lengthening [61]. It is important to highlight that any lengthening of bowel is meaningful, because for every 1% increase in intestinal length, the chance of weaning patients off parenteral nutrition increases by 3% [62].

Bowel adaptation was also appreciated after HELP gel injection and bowel lengthening. The lamina propria diameter was larger in the untreated control segments compared to the spring-lengthened and HELP-injected segments. This is because the bowel lumen becomes narrower with the injection of HELP gel, and the mucosal folds become eradicated by the spring treatment. As expected, the outer bowel diameter increased upon HELP injection due to the gel volume increasing the intestinal caliber, dilating the bowel. Bowel diameter was also increased in the spring-lengthened segment because of the outward circumferential forces exerted by the spring on the intestine under continuous peristalsis [59]. Crypt depth increased most in spring-lengthened segments. As intestinal crypts are sites of epithelial cell proliferation [63], this is likely due to cell proliferation after the applied stimulating force, as seen in multiple studies across labs that study distraction enterogenesis [13, 63, 64]. We also observed deepening of the crypts in segments injected with HELP gel, which was also likely due to cell proliferation in response to axial and radial forces, as the mucosa was stretched by the gel volume. Similarly, mucosal thickening in the HELP-injected and spring-lengthened segments was likely a response to stimulating mechanical forces, which cause the stem cells to rapidly divide. As in our previous studies of spring-mediated distraction enterogenesis, we did not observe any statistically significant differences in muscularis thickness among all groups [20]. Literature suggests these morphological changes induced by this rapid cellular division upon stretching of the bowel happen due to mechanotransduction, triggering pathways such as the Wnt/β-catenin and Hedgehog signaling mechanisms, leading to the upregulation of several genes involved in cell proliferation and tissue regeneration [58, 64]. While these changes in architecture are significant, we have shown in prior work that spring-lengthened bowel regains its architecture and maintains its function after lengthening [59]. Our positive results support future studies with longer time points to evaluate if bowel segments treated by HELP gel-enabled ESMDE undergo similar functional remodeling. In future work, ESMDE with Using chamber testing can assess for the function of HELP-injected bowel [55, 65].

We observed spring displacement ("slipping") past the distal HELP gel injection point in all animals, which suggests that the spring can be naturally stooled as the HELP gel biodegrades in response to endogenous enzymes. Bowel peristalsis also plays a role in the movement of the springs through the bowel. Early spring slipping is what likely resulted in no bowel lengthening in two of the pigs. In one of these animals, we hypothesize the lack of lengthening was due to the high force of the applied spring (0.32 N), which was the highest spring force for all of our procedures (Figure 3G). This initial high force could have shortened the total time during which the spring was able to be confined by the HELP gel. Four of the six pigs (all with lower applied forces, ≤0.29 N) underwent successful, significant bowel lengthening. This suggests that the HELP gel stiffness and biodegradation rate were appropriate to transiently confine lower force springs for sufficiently long times to enable distraction enterogenesis before the onset of natural evacuation. Previous studies using sutures to immobilize the spring have shown that 1 to 3 weeks is sufficient to achieve significant bowel lengthening [13, 20]. Therefore, the onset of evacuation identified around 7 days suggests that our HELP hydrogel properties are on the edge of the potential optimal time range. Thus, in future studies, it will be important to evaluate different HELP gel formulations [30, 31] and characterize their biodegradation rate in vivo and stiffness over time to ensure that springs are confined for a sufficiently long period of time for distraction enterogenesis prior to spring evacuation. Confining the spring for a longer amount of time may be beneficial for improving lengthening results.

There were some limitations to this project. First, there were instances when the HELP gel was not injected into the bowel wall and spilled into the lumen. While this did not result in any harm to the animals since the gel is biocompatible, it led to a loss in injected volume. Second, this is a highly technically challenging procedure as the wall of porcine jejunum is thin, requiring precise placement of the needle catheter into the correct bowel layer for successful injection. We note that juvenile porcine bowel is thinner compared to that of a child, so deposition into the correct space within the pediatric bowel wall should be easier [66]. In our study, we performed these experiments through an open laparotomy and could visualize when our catheter pierced through the bowel wall, which was not uncommon. Again, no pigs showed any signs or symptoms of perforation. In the future, a Roux-en-Y ostomy pig model will be useful in proof-of-concept studies of gel-enabled ESMDE through an ostomy. While an ostomy model will have more limited surgical visualization, we believe this approach can be successful with additional practice and improved technique.

Further, we found it was key to first inject saline into the correct space within the bowel to create a region between the submucosal and muscularis layers that was more easily injectable with HELP gel. We hypothesize that the lower viscosity of the saline makes it easier to inject at continuous, fast flow rates, creating a pocket of space into which the gel could be delivered. In contrast, the HELP gel often required an initial high amount

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of hand force to initiate flow, making continuous, smooth delivery challenging. As different formulations of the HELP gel are known to have different viscosities and require different amounts of injection force to initiate flow [30], further optimization to select a HELP gel formulation that is more fluid upon injection will enable easier endoscopic translation. Taken together, our data provide critical proof-of-concept that injectable gels can be used to temporarily anchor spring devices without sutures for successful ESMDE.

5 | Conclusion

ESMDE has the potential to be a safe, effective method to lengthen bowel, making it a possible treatment for short bowel syndrome. The use of an engineered, biodegradable gel that is catheter-injectable and then self-heals to achieve a stiffness suitable for temporary device constraint improves the potential clinical translatability by allowing for less invasive surgical procedures.

Additionally, these positive results suggest it would be beneficial to understand how hydrogel-enabled intestinal lengthening scales with relaxed spring length. We have previously developed a computational tool that allows one to test different spring, patient, and bowel parameters to estimate tissue response in a suture-based anchoring system [7]. In future studies, this computational model could be adapted to model the hydrogel-enabled anchoring of the spring, considering the mechanical properties and degradation profile of the hydrogel, improving its translation potential. Overall, this proof-of-concept requires further research to determine long-term effects of spring lengthening, particularly in the areas of gel injection.

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Disclosure

The authors disclose the patent application publication (18/653,524) entitled "*Hydrogel Injection for Intestinal Anchoring*."

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are openly available in Stanford Digital Repository—Research Data at https://doi.org/10.25740/kw814qq1998.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Molecular weight of unmodified biopolymers used in the hydrogel system. **Figure S1:** Derivation of mathematical model to predict spring compression by HELP gel after deployment.

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