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Automated Uretero-Intestinal Anastomosis with Absorbable Staples

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ABSTRACT

Bladder cancer is the 5th most common cancer in the United States. When cancer cells invade the bladder muscle, surgical removal of the bladder, called radical cystectomy, is the desired treatment. A neobladder is formed out of a portion of intestine, and the ureters are currently attached via absorbable sutures. We have designed rigid absorbable staples comprised of 85:15 poly(lactide-co-glycolide) (PLGA) and a surgical anastomosis stapler to fire two concentric rings of six staples each. Degradation testing shows that the staples will retain strength for at least 20 days, long enough to promote healing of the tissue. Functional testing shows that the average grip strength of a single staple is 5.34 ± 1.5 N and 11.58 ± 2.28 N for a single suture stitch. Future testing will analyze the anastomosis strength of 12 staples fired using the circular stapler.

INTRODUCTION

According to the National Cancer Institute, bladder cancer is the 5th most common cancer in the United States. In 2012, there will be over 73,000 new cases reported in the United States and 15,000 people will die from bladder cancer[1]. When the tumors invade the bladder muscle, the desired treatment is radical cystectomy, surgical removal of the entire bladder[2]. Following removal of the bladder, a surgeon will commonly construct a new, internal neobladder using a portion of the intestine. The ureters are currently attached to the neobladder with absorbable sutures. This attachment must be watertight so urine does not leak into the abdominal cavity.

Absorbable sutures are currently used to attach the ureters to the bladder, typically using 7-9 stitches around the circumference of the anastomosis. This procedure is time consuming and has variable results, depending on the skill level of the surgeon.

For this reason, we have developed an automated method to attach the ureters to the neobladder using an anastomosis stapler that delivers absorbable staples in two concentric rings around the circumference of the anastomosis. There are other anastomosis staplers on the market,

but they are too large and fire titanium staples, which are not compatible with the urinary tract as they may lead to the formation of kidney stones. We have also designed absorbable staples made from poly(lactide-co-glycolide) (PLGA). This material hydrolyzes to lactic acid, which is produced naturally by the body, and glycolic acid, which is easily cleared from the body. PLGA has also been used for many medical applications including sutures and other currently available absorbable staples such as Insorb and Polysorb staples[3,4]. Furthermore, PLGA is generally accepted by the FDA for use in medical devices.

In summary, this stapler will reduce procedure time and ensure more consistent results between surgeons. Increased consistency and reduced procedure time will translate into fewer complications for patients, shorter hospitalization times, and minimized need for subsequent interventions.

Materials and Methods

Staples

Staples were fabricated from 85:15 PLGA from Purac Biomaterials (Netherlands). This ratio of polymers should have a half-life of nearly two months[5]. This indicates that the staples will maintain their strength long enough for the anastomosis to heal. There are two key features of the staple design, shown in figure 1A and 1B. First, there are two barbs on each leg that are designed to hold the tissue together. Having multiple barbs allows the staples to hold the tissue even if there is variability in tissue thickness. Secondly, the staples are designed to pierce the tissue, minimizing the need for external devices to puncture the ureter and neobladder tissue. The staples are 5.5 mm wide, 10.8 mm long, and 1 mm thick. These dimensions will allow for two concentric rings with six staples in each ring to secure the anastomosis of a 7-10 mm diameter ureter. Furthermore, the length of the staple will allow them to pierce through both the neobladder and ureter tissue, as illustrated in the anastomosis schematic in figure 1C.

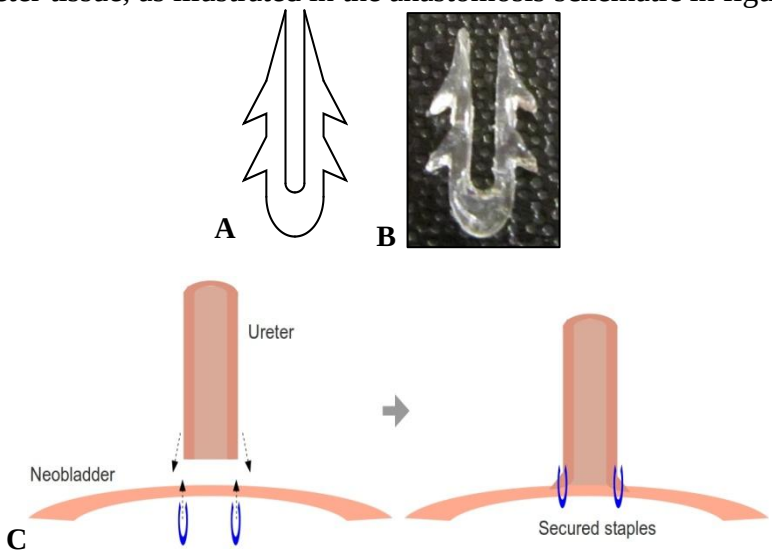

Figure 1. Staples for uretero-intestinal anastomosis. (A) Line drawing. (B) Actual staples. (C) Schematic of anastomosis illustrating that staples will be introduced from inside the neobladder and will pierce through both the neobladder and ureter tissue.

To fabricate the staples, an aluminum mold with a 45 mm x 16 mm x 1 mm well was fabricated with a CNC mill. Using a standard hot plate, 0.9 g of PLGA (density = 1.24 g/cm^3) was heated in the mold for thirty minutes at 182°C. An aluminum plate was then placed on top of the mold, and the material was then compressed using a cool steel block, resulting in a 1 mm thick plate of PLGA. 2-dimensional drawings for the staples were made using Corel Draw X3 and cut from a PLGA plate with an Epilog Mini CO_2 40 Watt laser cutter. The laser cutter was operated in vector mode with settings optimized to cut through PLGA plates (1200 dpi, 60% speed, 100% power, 5000 Hz, double laser pass). Due to the width of the laser cut, actual dimensions after laser cutting were slightly smaller than the original image; in most cases the difference was less than 0.05 mm, although sharp points such as barbs lost as much as 0.4 mm.

Stapler

A stapler prototype was designed using SolidWorks computer aided design software. The SolidWorks drawings were 3-dimensionally printed from acrylonitrile butadiene styrene (ABS) using fusion deposition modeling (FDM) at the Wisconsin Institutes for Discovery in Madison, Wisconsin. The circular stapler, shown in figure 2, fires two concentric rings of staples into the ureter and neobladder tissue, connecting them. The stapler consists of a firing mechanism, a disposable staple cartridge, an anvil, and a ring clamp (figure 2, supplementary table 1). The firing mechanism deploys the staples, and can be used multiple times with appropriate sterilization procedures. The staple cartridge consists of the sheath and the staple base; it is disposable and contains enough staples for one ureter. After stapling one ureter, a new cartridge can be screwed onto the firing mechanism. The anvil and ring clamp secure the ureter tissue, as shown in figure 2C, and ensure correct placement of the ureter and staples during the stapling process. The anvil is also hollow to allow the surgeon to place a stent through the ureter after stapling.

Functional Testing

This test compared the grip strength of a single staple to a single suture in *ex vivo* bovine intestinal tissue. An Ethicon size 4-0 Vicryl suture (product number J773D) was formed into a loop by tying the ends together. The suture loop was placed between the legs of the staple and the staple was manually inserted into a piece of bovine small intestine (donated by Black Earth Meats, Black Earth, WI) until all of the barbs were in the tissue. The hook of an OHAUS spring gauge (Model 8014-N) was connected to the suture loop. The spring gauge was then pulled vertically while the intestine was held to the table, and the maximum force during staple removal was recorded. For comparison, sutures were also tested by threading the suture once through the intestine, tying a loop at the ends, attaching the spring gauge to the loop, and pulling the spring gauge vertically while holding down the intestine. For statistical data, five staples and five sutures were tested.

Degradation Testing

The mechanical strength of the PLGA was tested to ensure that the staples would retain sufficient strength during the initial period of degradation. Dimensions for the tensile bar test specimens were determined using ASTM D638-10 Standard Test Method for Tensile Properties

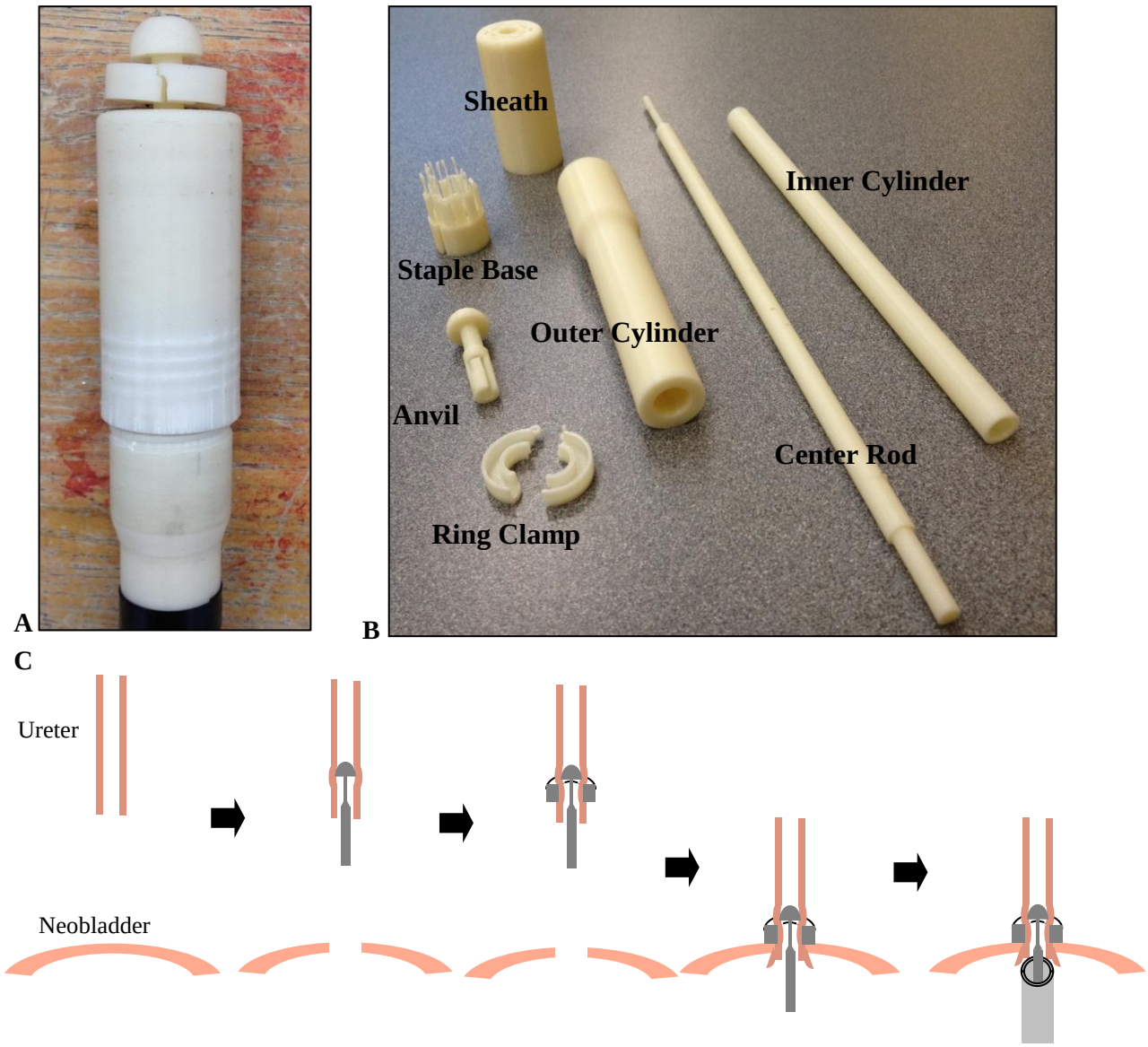

Figure 2. Circular stapler for uretero-intestinal anastomosis and individual components. (A) Assembled stapler prototype. (B) Individual components fabricated out of ABS (handle not shown). (C) Schematic diagram illustrating the process of securing the ureter with the anvil and ring clamp followed by attachment to the rest of the stapler.

of Plastics for a Type I material. The dimensions given in the standard were scaled to fit the molded PLGA sheet and 1 mm thickness of the staples. The test specimens were then cut from a PLGA plate with an Epilog Mini CO_2 40 Watt laser cutter using the previously optimized settings. It should be noted that a different method was used to make the PLGA plates used in these tests instead of the method described previously. These PLGA plates were made by compression molding using a different aluminum mold having the same dimensions as described previously; however, this compression molding technique produced more undesirable bubbles in the PLGA plates than the hot plate method. Ethicon size 4-0 Vicryl sutures (product number J773D) were used as a comparison to the PLGA test specimens since these are the sutures commonly used for uretero-intestinal anastomosis.

Since the staples will contact urine, which has a pH ranging from 4.5-8.0[6], degradation testing was performed at the two extreme pHs of 4.5 and 8.0 to quantify the material strength of the staples after degradation at these pHs. 200 mL of 0.1 M phosphate buffered saline (PBS) was set to the desired pH of 8.0 using NaOH. 0.1 M acetate buffer was made by mixing 1.75 g of sodium acetate (13.6 g/L), 0.433 mL of 16.5 M acetic acid, and about 200 mL of water. It was set to the desired pH of 4.5 using HCl. Three PLGA specimens and three sutures were tested per degradation time point at each pH. At least five test specimens would be ideal; material limitations prevented this. Specimens were left in 3 mL of the respective pH solution for 0, 10, or 19 days in a six-well plate in an incubator at 37 °C. Solutions were changed every five days.

Once the respective degradation time had passed, a tensile test was conducted on the specimens using an Instron 5566 Universal Testing Machine. The sutures were cut to a length of 50 mm before beginning the tensile test. A crosshead velocity of 5 mm/min was used per the ASTM standard and the specimens were tested to failure.

Results

Functional testing of staple and suture strength show the average grip force of a staple is 5.34 ± 1.51 N (mean ± SD, n=5), shown in figure 3. This is about half of the average suture removal force of 11.58 ± 2.28 N (mean ± SD, n=5). A two-tailed Student's t-test was performed on the data and a p value of 0.002 was obtained, indicating a significant difference between the force required to remove the staples and the sutures.

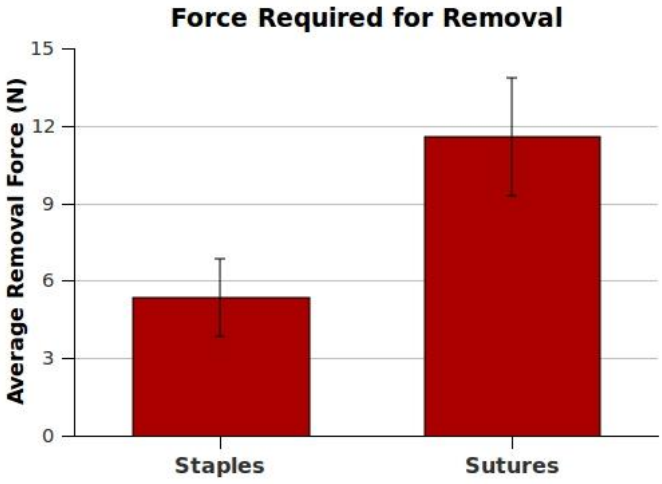

Figure 3. Functional testing of PLGA staples and Vicryl sutures. Average removal force in Newtons. Error bars show standard deviation, n=5.

Figure 4 shows the tensile testing data in graphical format for all PLGA and Vicryl sutures. Tables S2 and S3 summarize the ultimate strength, yield strength, yield strain, and modulus for each degradation time point for sutures and PLGA test specimens. The different pH conditions for both the PLGA and sutures do not significantly impact the mechanical strength when comparing within respective days. This is encouraging because it indicates that the staples should be able to withstand the wide range of pHs of the urine. As figure 4 shows, the ultimate strength of the PLGA specimens is between 33 and 38 MPa for days 0 and 10, but there is a drop in ultimate strength at day 19 where the ultimate strength was 23.8 ± 7.0 MPa for pH 4.5 and

25.7 ± 5.7 MPa for pH 8.0. For the sutures, the ultimate strength decreased from 843.0 ± 79.4 MPa at day 0 to 820.4 ± 31.8 MPa for pH 4.5 and 702.3 ± 42.4 MPa for pH 8.0 at day 19. The PLGA degrades slightly more quickly than the sutures, as the ultimate strength of the PLGA decreased by about 25% by day 19 and the ultimate strength of the sutures decreased by about 16% by day 19. This indicates that the staples and sutures have begun to degrade by day 19, although additional testing over a longer time period is required to find when the burst effect occurs and strength dramatically decreases. The sutures had a much higher ultimate strength than the PLGA specimens over the testing duration. This is to be expected because of manufacturing differences. However, since the PLGA staples have a larger cross-sectional area than the Vicryl sutures, the load-bearing capacity is comparable between the two. PLGA still maintains a significant amount of strength at day 19. This indicates that the staples should maintain enough mechanical strength to secure the ureter to the neobladder at least through day 19, at which point significant tissue healing has already occurred.

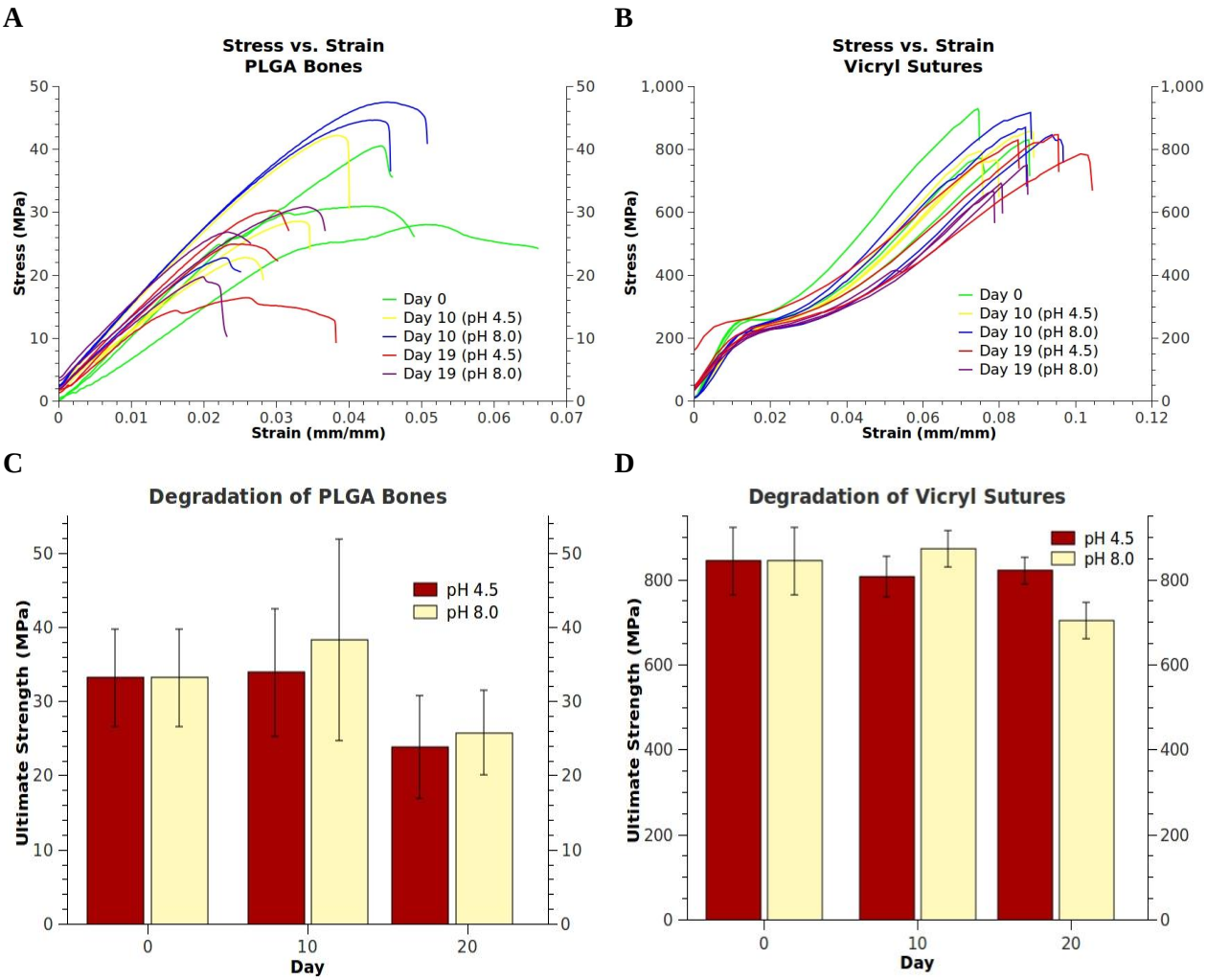

Figure 4. Degradation testing of PLGA bones and Vicryl sutures. (A) Stress vs. strain for all PLGA test specimens. (B) Stress vs. strain for all Vicryl sutures. (C) Ultimate strength of PLGA test specimens and (D) Vicryl sutures during the degradation testing period. Error bars show standard deviation, n=3.

Discussion

For patients with bladder cancer, a radical cystectomy is often required in which the surgeon will remove the patient's bladder, construct a neobladder from intestinal tissue, and then suture the ureters to the neobladder. The stapler and absorbable staples we designed will make the uretero-intestinal anastomosis procedure quicker and more consistent between surgeons. The absorbable staples will minimize subsequent interventions and prevent complications associated with the use of metallic staples in the urinary tract.

It has been shown that the staple material should have sufficient strength to hold the anastomosis. Testing performed on the grip strength of a single staple shows that the grip strength is about half that of a single suture. The staple barbs were effective in gripping the tissue, even though they did not grip as effectively as a suture stitch, but the strength of twelve staples in two concentric circles should create a water-tight anastomosis. It was also shown that the staple alone is sharp enough to pierce through a bovine small intestine alone, and should, therefore, be able to pierce through the ureter and neobladder tissue.

A working metal prototype of the stapler will be developed in the future. The prototype from this study will first be scaled down to better accommodate the dimensions of the ureter and neobladder. This was not possible in this study due to FDM tolerance constraints; however, a metal prototype with the exact dimensions and features of the design will be fabricated. Furthermore, an anvil, ring clamp, and stapler cartridges of various sizes will be developed to accommodate patients with ureters of various sizes. Once this is done, the staples and stapler can be integrated, and *in vitro* functional testing of the whole stapler can be performed. It will be important to test the strength of the anastomosis by analyzing burst strength and to prove that the stapler creates a water-tight seal between the ureters and neobladder. Eventually, the stapler can be tested *in vivo* in an animal model to further demonstrate the functionality of the device. Finally, we would like to perform a force analysis for stapler use to determine the force required by the surgeon to deploy the stapler and ensure it will be comfortable to use.

Conclusion

An ABS prototype of an uretero-intestinal anastomosis circular stapler was developed as were PLGA staples to be used with the stapler. Future work will involve fabricating a metal prototype with slightly smaller dimensions than those of the prototype described here. This will allow the stapler to be integrated with the staples so that *in vitro* functional testing of the whole stapler can be performed. When a final design is validated, the dimensions can be scaled down or up for use in other anastomosis surgeries. In general, this stapler with absorbable staples has the potential to make anastomosis surgeries quicker, more consistent, and minimize the need for subsequent interventions.

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Author Disclosure Statement

No competing financial interests exist.

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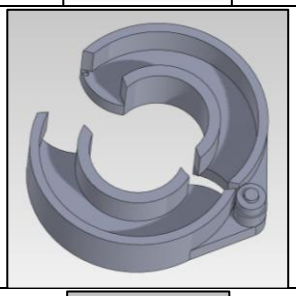
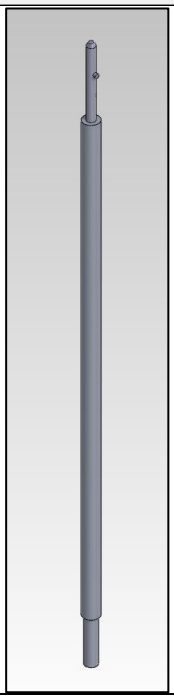
Supplementary Data

Table S1

Part	Purpose	Picture
Anvil	The anvil enters the ureter then attaches to the stapler. This piece secures the ureter tissue prior to stapling. This piece is hollow to allow for a stent to pass through.	
Ring Clamp	The ring clamp secures the ureter to the anvil and supports the neobladder tissue during stapling.	
Center Bar	The center bar provides a stationary base to which the anvil can attach.	

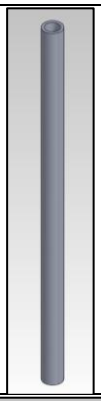
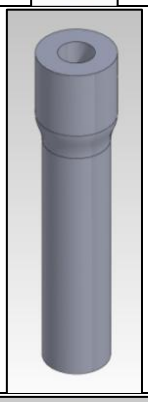
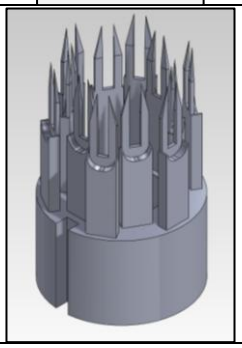
Interior Cylinder	The interior cylinder translates the force generated by compressing the stapler handle to the stapler base.	
Outer Cylinder	The outer cylinder contains the threads that allow the sheath to attach to the stapler firing mechanism.	
Sheath	The sheath houses the staples and maintains their sterility prior to surgery.	
Staple Base	The staple base comes pre-loaded with twelve staples. This piece contains twelve pairs of needles to help puncture the tissue and guide the staples during stapling.	

Table S2

Degradation of PLGA Specimens (n = 3)				
Average (standard deviation)				
Day		**0**	**10**	**19**
Ultimate Strength (MPa)	pH 4.5	33.1 (6.5)	33.9 (8.6)	23.8 (7.0)
	pH 8.0		38.2 (13.5)	25.7 (5.7)
Yield Strength (MPa)	pH 4.5	25.0 (1.0)	27.7 (4.6)	20.7 (6.1))
	pH 8.0		30.0 (8.7)	22.3 (2.9)
Yield Strain	pH 4.5	0.027 (0.006)	0.027 (0.005)	1.018 (0.004)
	pH 8.0		0.024 (0.005)	0.019 (0.002)
Elastic Modulus (GPa)	pH 4.5	1.04 (0.19)	1.03 (0.21)	1.07 (0.07)
	pH 8.0		1.17 (0.09)	0.97 (0.11)

Table S3

Degradation of Vicryl Sutures (n = 3)				
Average (standard deviation)				
Day		**0**	**10**	**19**
Ultimate Strength (MPa)	pH 4.5	843.0 (79.4)	805.5 (47.5)	820.4 (31.8)
	pH 8.0		872.4 (42.4)	702.3 (42.4)
Yield Strength (MPa)	pH 4.5	803.3 (45.1)	753.3 (32.1)	760.0 (65.6)
	pH 8.0		750 (26.5)	680.0 (20.0)
Yield Strain	pH 4.5	0.074 (0.009)	0.072 (0.005)	0.084 (0.006)
	pH 8.0		0.074 (0.010)	0.081 (0.005)
Elastic Modulus (GPa)	pH 4.5	12.90 (1.45)	12.60 (0.78)	9.85 (0.48)
	pH 8.0		12.50 (0.69)	10.84 (0.09)