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Original article

Impact of Ureteral Muscle Layer Damage on Ureteral Healing after Endoureterotomy: Experimental Animal Study

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Abstract

Background: Endoureterotomy is a procedure that depends on healing by secondary intention. Healing of the ureteral muscle layer can provoke re-stricture after endoureterotomy. The aim of this comparative study was to assess the impact of ureteral muscle layer damage on ureteral healing after four endourological techniques. ***Methods:*** A total of 96 female pigs underwent initial endoscopic, nephrosonographic, and contrast fluoroscopic assessment of the urinary tract. After baseline studies, a ureteral stricture was created. Three weeks later, the ureteral stricture was diagnosed and treated. Animals were randomly assigned to four groups (Group-I, Balloon dilatation endoureterotomy; Group-II, Cold endoureterotomy with scissors; Group-III, Monopolar hot electrocautery; Group-IV, Holmium laser retrograde endoureterotomy) in which a double-pigtail ureteral stent was placed for 3 weeks. Follow-up evaluations were performed at 3–6 weeks. The final follow-up was completed at 5 months and included the aforementioned diagnostic methods and pathological study. ***Results:*** In terms of therapeutic success, complete resolution was observed in 83% of cases. No evidence of vesicoureteral reflux nor urinary tract anomalies were observed. None of the endoureteromy procedures showed statistically significant differences in ureteral muscle layer remodeling. However, less ureteral muscle layer damage was significantly associated with higher success rates in ureteral treatment and healing. The presence of a positive uroculture was associated with more extensive ureteral muscle layer damage. ***Conclusions:*** The results of this comparative study in a porcine model indicated that ureteral muscle layer damage after endoureterotomy did not differ significantly between the different analyzed endourological techniques. The extent of ureteral muscle layer damage is a predictive factor of successful ureteral healing after endoureterotomy.

Keywords: ***endoureterotomy, ureter, muscle layer, ureteral healing***

Introduction

A ureteral stricture (US) is a decrease in ureteral caliber, the origin of which may be congenital or acquired, malignant or benign and even intrinsic or extrinsic. Its etiopathogenesis is related to the crossing or impaction of ureteral stones, after endourology procedures, radiotherapy and different surgeries like gynecological, urological, vascular, or digestive [1]. Most (70%) ureteral strictures are iatrogenic and benign [1,2].

The gold standard treatment is ureteral reconstructive surgery, but the development of minimally invasive endourological techniques has enabled treatment of ureteral strictures with less morbidity, fewer analgesic requirements, and a shorter surgical time and length of hospital stay [3]. However, appropriate selection of patients is essential for success in these endourological techniques [4]. Currently, the different techniques mentioned in the scientific literature are as follows: Balloon dilatation endoureterotomy, Acucise® balloon endoureterotomy, cold endoureterotomy, monopolar hot electrocautery and Ho:YAG laser [3,4].

Endourological techniques are based on healing by secondary intention, which requires the formation of granulation tissue. This is an elaborate process that depends on cell proliferation and regeneration. In contrast, healing by primary intention occurs when the edges of the incision are directly apposed [5]. Ureteral healing by secondary intention has been poorly investigated, and ureteral muscle layer healing differs from that of primary tissue, with heterogeneous results in the scientific literature [6-9].

It has been theorized that endourological techniques that have a thermal effect without endoscopic visualization show worse results with regard to endourological techniques without a thermal effect and with endoscopic visualization [1]. Due to endoscopic visualization, it is more likely to be a controlled and targeted endoureterotomy.

We hypothesize that if there is appropriate remodeling of the ureteral muscle layer, it will be less likely to develop a ureteral re-stricture after ureteral stricture treatment. The hypothesis of this study is based on the involvement of muscle layer damage on ureteral healing by secondary intention and its impact on success after endoureterotomy. Considering that greater muscle damage causes worse healing and thus a greater risk of re-stricture and failure of endourological techniques. The aim of this experimental comparative study was to assess the impact of ureteral muscle layer damage on ureteral healing after different endourological techniques, and to identify the endourological technique that causes the least ureteral muscle layer damage.

Materials and Methods

Ninety-six healthy female pigs weighing 35–40 Kg were used in this study. The experimental protocol was under a project license (NO.: IEND207) and was approved by the Minimally Invasive Surgery Center´s Ethical Committee for Animal Research. This Committee also certified that the research study was carried out following the guidelines for animals used for scientific purposes (Directive 2010/63/EU-European Commission).

All animals underwent a three-phase study:

Phase I: Ureteral stricture animal model.

Blood and urine samples were collected to assess blood and biochemical parameters and confirm urine sterility. Next, nephrosonography was performed to assess the degree of upper collecting system dilatation, according to the SFU guidelines (Society for Fetal Urology) [10]. Simulated voiding cystourethrography (SVCUG) was performed to evaluate VUR (vesicoureteral reflux) at baseline, and at 3 and 6 weeks, and a final follow-up at 20 weeks. To perform SVCUG, a Foley catheter was inserted into the urinary bladder and filled. To simulate micturition, the bladder was manually compressed until the pressure reached 50 cm H2O for 60 sec [11]. Serum urea, creatinine levels, urinalysis and urine culture were evaluated during all study phases.

Intravenous urography (IVP), retrograde ureteropyelography (RUPG) and ureteroscopy were performed in the right ureter to assess morphological and functional parameters. The left kidney and ureter were used as controls.

After baseline studies, the proximal ureter was identified and ligated with a short-term biodegradable ligature in the same surgical procedure and via a laparoscopic approach. Ligation was performed by manual laparoscopic knotting and to avoid a complete obstruction, the ureter was intubated with 5 Fr ureteral catheter. Finally, resulting in the unilateral ureteral stricture model [11].

Phase II. Ureteral stricture treatment.

Three weeks later, which is time enough to develop a stricture according to previous experimental studies [11-13], the ureteral stricture was diagnosed [14]. The ureteral stricture creation model is used and validated, and the experimental model of ureteral stenosis is based [11,12,14-16]. The experimental stenosis model is based on ureter ligation, giving rise to ischemic stenosis that produces fibrosis in the ureter, which is the basis of ureteral stenosis. The upper urinary tract was reevaluated (nephrosonography, urea and creatinine serum levels, IVP, RUPG, urinalysis and urine culture). Once the imaging studies described above had confirmed the existence of obstructive uropathy, animals underwent simple randomization and were divided into four homogeneous groups, depending on the endourology treatment performed. The ureteral incision was anteromedial to avoid blood vessels, at seven o'clock in right ureter.

- Group-I, Balloon dilatation endoureterotomy.
- Group-II, Cold endoureterotomy with scissors.
- Group-III, Monopolar hot electrocautery. BipoTrode® (R. Wolf®, Germany).
- Group-IV, Holmium laser retrograde endoureterotomy (1.2 J/pulse-10 Hz).

Full-thickness incision of the stricture segment was confirmed by extravasation of contrast medium and visualization of periureteral fat. A 7Fr polymeric ureteral double pigtail stent was placed in all groups for a 3-week period (Universa® Soft, 22 cm, Cook® Medical).

After 3 weeks, the ureteral stent was cystoscopically retrieved and reassessment was performed with excretory urography, ultrasound and retrograde ureteropyelography. According to the animal model scientific literature, three weeks is time enough to adequate healing and decrease ureteral oedema13,16,17. Urine culture by cystocentesis was taken the day before of the ureteral stent. All study animals were administered an antibiotic treatment on the day before and 2 days after each study phase (Enrofloxacin, IM). To assess success, nephrosonography and RUPG are used to assess the absence of dilatation according to the SFU grade and the absence of ureteral stricture in the RUPG, where visualization of ureteral patency is possible.

Phase III: End-study evaluation and post-mortem studies.

The final follow-up was performed at 5 months by means of ultrasonography, urinalysis, cystoscopy, ureteroscopy, and contrast fluoroscopy. Once the follow-up imaging studies were complete, necropsies were carried out in all cases, harvesting the kidneys, ureters and bladder en bloc. Slices were obtained from the healed ureteral segments and stained with Hematoxylin Eosin, PAS and Masson's trichrome stains. The histopathological evaluations were performed by the same pathologist blinded to the animal group. A healing score was developed that included fibrosis in the muscular layer and muscle layer integrity [12]. To this end, each parameter was graded independently with a 0 to 3 semi quantitative scale, where 0=no pathological changes and 3=highest pathological alteration in the ureteral architecture [16,17]. (**Figures 1,2**).

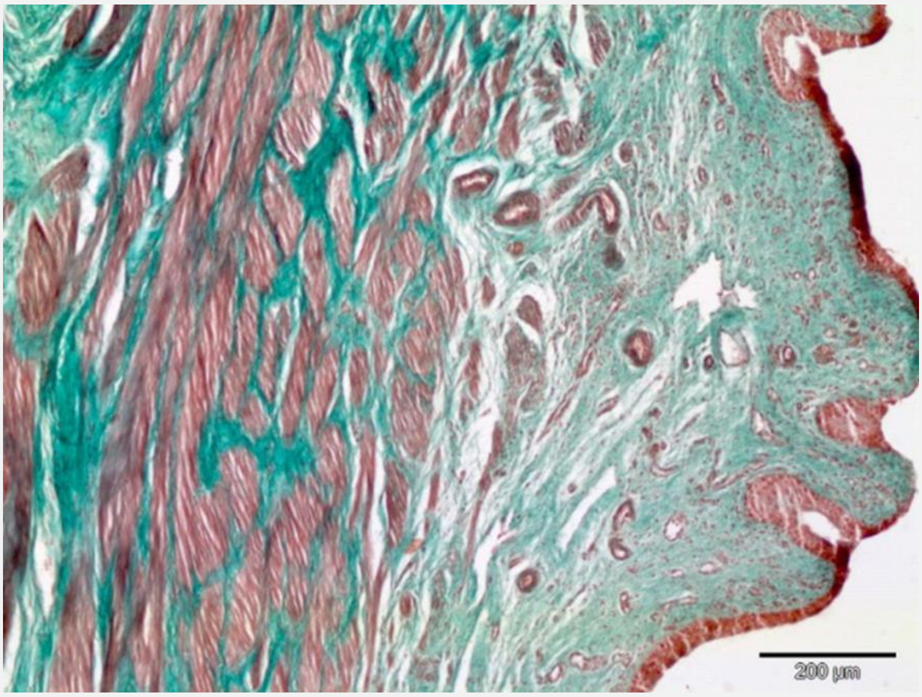

Figure 1: Masson trichrome tinction. Ureteral muscle layer without pathological alteration.

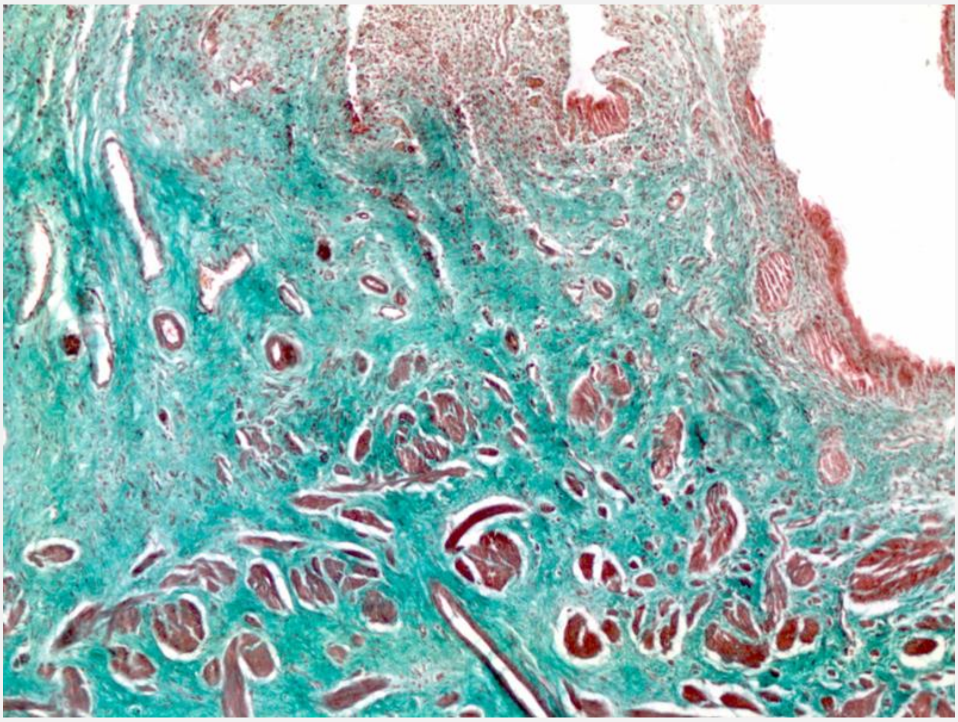

Figure 2: Masson trichrome tinction. Ureteral muscle layer with high pathological.

Global success was strictly defined as the following: relief of signs, and ultrasound and fluoroscopic resolution of US and obstructive uropathy at the end of the study.

Statistical analysis

To determine the sample size, a hypothesis contrast was implemented (the means were compared); taking the previous success rate into consideration in experimental studies according to similar investigations [12,13]. As the results show, the sample size required per group is 24 and the total sample size required is 96. The statistical significance level, α, is typically 5% (0.05) and statical power of 95%. The histological data of ureteral muscle layer damage was formulated as mean ± standard deviation (SD). The histological scores underwent statistical analysis with ANOVA and "t Student" analysis. In the case of significant differences between means, "a posteriori" Bonferroni test or regression analysis was conducted. Differences were considered significant at $p<0.05$.

Results

Phase I

None of the study animals showed ureteral abnormalities or VUR. Serum urea and creatinine values were within the normal range for porcine animals. In this phase, all of urine cultures were negative.

Phase II

Three weeks after creating the ureteral stricture model, all study animals showed single, proximal, and short (9.44 ±3.54 mm) ureteral strictures, without other ureteral abnormalities that would exclude them from this study. After three weeks and simultaneously with the cystoscopic ureteral stent retrieval, 76 of 96 (79.2%) animals had negative urine cultures and 20 (20.8%) had positive urine cultures.

Phase III

After performing the endourological techniques, the overall success rate was 83%, with a failure rate of 17%. The histological analysis revealed muscular healing defined by muscular fibrosis and muscular integrity. The histological analysis found no significant differences between endourological techniques, although cold endoureterotomy involved less damage to the ureteral muscle layer (**Table 1**).

Table 1: Ureteral muscle layer damage (fibrosis+integrity of ureteral muscle layer). ANOVA Analysis.

N	Endourological techniques	Mean (-/+SD) (0-3)	P
24	Group I	1.62±0.91	0.861
24	Group II	1.41±0.97	
24	Group III	1.47±0.96	
24	Group IV	1.58±0.88	

In the current study, less damage in the ureteral muscle layer was significantly associated (p<0.05) with success of the endourological techniques and ureteral healing (**Table 2**).

Table 2: Ureteral muscle layer damage in relation to overall success rate. "t" Student test.

	Success	Failure	P
Ureteral muscle layer damage (0-3)	1.36±0.87	2.31±0.75	0.001

Regression analysis confirmed this conclusion(p<0.05) (**Table 3**).

Table 3: Ureteral healing as independent success factor. Regression analysis.

Likelihood Ratio test			
Effect	**Chi-Square**	**df**	**P**
Endourological techniques	4.556	3	0.207
Urine culture	0.225	1	0.635
Muscular healing	21.669	6	0.001

Ureteral muscle layer damage was significantly influenced by the presence of bacteriuria (p<0.05), with more extensive ureteral muscle layer damage associated with positive urine cultures (Table 4), but regression analysis did not confirm this association. In contrast, bacteriuria had no significant effect (p<0.26) on the overall success rate in ureteral stricture.

Table 4: Ureteral muscle layer damage in relation to urine culture. "t" Student test.

	Positive urine culture	Negative urine culture	P
Ureteral muscle layer damage (0-3)	1.90±0.91	1.42±0.90	0.041

Discussion

The success rates of endourological techniques range from 55 to 85% in benign ureteral strictures in routine clinical practice [1,18,19], and from 80 to 100% in experimental studies [13,20]. In this study, the success rate was 83% due to appropriate choices based on stricture characteristics. Appropriate stricture selection is fundamental to the success of endoureterotomy since healing occurs by secondary intention, which requires a good vascular supply to ensure adequate ureteral wall healing.

Features favoring successful outcome in endourological techniques are benign, non-ischemic strictures, short length <2 cm, renal function >20%, short duration, and stricture location at the distal and proximal ends of the ureter [2,4], as such strictures show less ureteral fibrosis and a better vascular supply, encouraging healing by secondary intention [5]. These features were present in our experimental model, as practical clinical selection is very important to ensure adequate vascular supply in the ureteral muscle layer and proper optimization. Midureteral strictures have a success rate of around 20% in comparison to 80% in proximal strictures [21].

Likewise, success rates are lower in ischemic strictures such as after radiotherapy [1]. Stricture length is also important, with ureteral strictures >2 cm having a lower success rate (50%) than shorter ureteral strictures (<2 cm) (80%) [22]. Some authors have reported that stricture length is the most important success factor after endoureterotomy [21]. In contrast, in experimental studies, the selection of strictures is based on less fibrosis and a better vascular supply, increasing the success rate to 100% [11,13,20].

Endourological techniques rely on healing by secondary intention, which needs tissue formation to fill the edges of the incision, so the quality of vascular supply and tissue is essential for success [5]. Furthermore, ureteral healing differs from other tissues because it has deficient vascular supply and direct and continuous contact with urine [23]. Animal models and porcine species have been used in different studies to assess ureteral healing in recent years. Porcine species are particularly useful as they have anatomical, histological and physiological similarities with humans [6,9].

Ureteral healing after intubated uretorotomy was described by Davis et al using a canine model and ureteral healing after 6 weeks of ureteral stenting [24]. Subsequent studies verified ureteral muscle layer regeneration in canine models [8,25]. However, Schmeller et al found no evidence of ureteral muscle layer regeneration in humans [26]. Moreover, other studies described ureteral muscle layer healing as progressive tissue contraction that covers and replaces the muscular defect with fibrous tissue [8,25]. The essential difference between the porcine and canine models is the lack of ureteral regeneration in the porcine model.

Subsequent studies by Bégin et al and Andreoni et al observed ureteral healing in the porcine model, and found myofibroblasts in the ureteral defect, more fibrous tissue in the ureteral muscle layer and worse healing without regeneration [9,27]. Consistent with Andreoni et al, our study shows that more extensive ureteral muscle layer damage and histological changes can lead to worse healing [9].

Healed ureteral muscle differs from the original tissue by exhibiting disorganized muscular fibers and collagen deposits between muscular fibers. Greater histological changes in the ureteral muscle layer after endoureterotomy were associated with a lower success rate. Therefore, ureteral muscle layer damage is an independent factor affecting success and healing by secondary intention.

There is no scientific literature to compare ureteral muscle layer damage after endourological techniques and their impact in ureteral healing. In the current experimental study, at 5 months follow-up, ureteral muscle layer damage did not show histological differences and success rate between different endourological techniques. Therefore, ureteral muscle layer damage is similar and there is no scientific evidence of the greatest endourological technique. However, ureteral muscle layer healing has an impact on success rate after endoureterotomy, as the propulsion of urinary bolus can be impaired by aperistaltic ureteral segment. Although after these endourological procedures the damage produced in the ureteral muscle layer causes the loss of peristalsis in a 1.5-2cm ureteral segment, it is usually without clinical impact. Consequently, endourological techniques has the most successful outcomes in short ureteral strictures (<2cm) [1,2,12,18,21,22].

Currently, Holmium laser endoureterotomy is one of the most useful and common endourological technique in clinical practice [1,2,4]. However, the results of this experimental study found, ureteral muscle layer healing did not show histological differences in our comparative study between endourological techniques. These results do not go against the routinary use of holmium laser, as a comparative study in humans was not conducted.

Healing by secondary intention can be affected by urinary tract infection or bacterial colonization [26,27]. The rate of bacteriuria in patients with JJ stent ranges between 10-50% and increases the longer the duration of catheterization [28]. These findings were validated in our study, which showed greater ureteral muscle damage in animals that presented positive urine culture. The presence of infection impairs healing in any tissue. There are no studies indicating that bacteriuria affects ureteral healing in the scientific literature, although a higher rate of ureteral re-strictures in the presence of bacteriuria has been described [9,18,20]. At the ureteral level, there is no clear indication for the antibiotics to be used after endoureterotomy and there is a lack of scientific evidence about the influence of bacteriuria on ureteral healing. On the other hand, at the urethral level, there are studies that show more urethral strictures and fistulas in the presence of bacteriuria or urinary tract infection, and thus antibiotic treatment is recommended after urethroplasty and hypospadias repair [28-30]. Based on the findings of our study, the presence of a positive urine culture implies increased damage to the ureteral muscle layer. Although, a positive urine culture influences the ureteral muscle layer healing, it is no have impact on success rate of endoureterotomy. Being that their influence is no sufficiently strong to change the end outcomes.

Among the limitations in our study is the use of an animal model that is not entirely the same as the human model. Using an animal model precludes identifying different levels of pain or other signs. Regarding the availability of diagnostic techniques, the lack of an isotopic renogram meant we could not assess renal function.

Conclusions

Ureteral muscle layer damage after endoureterotomy does not differ between the analyzed endourological techniques 5 months after surgery. Ureteral muscle layer damage is a predictor of success after endoureterotomy. Our study found that bacteriuria has a significant impact on ureteral muscle layer healing.

Ethics approval and consent to participate

The experimental protocol was approved by the Minimally Invasive Surgery Center´s Ethical Committee for Animal Research. This Committee also certified that the research study was carried out following the guidelines for animals used for scientific purposes (Directive 2010/63/EU-European Commission).

List of abbreviations

US: Ureteral stricture
SFU: Society for Fetal Urology
SVCUG: Simulated voiding cystourethrography
VUR: Vesicoureteral reflux
IVP: Intravenous urography
RUPG: retrograde ureteropyelography
SD: Standard deviation

Data Availability

“Not applicable”.

Conflicts of Interest

“The authors declare that there is no conflict of interest regarding the publication of this paper.”

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None.

Authors' contributions

Study concept and design: VMG and FS.
Data acquisition: FS and FMSM.
Data analysis: VMG and FS.
Drafting of manuscript: VMG, FS; TFA and FMSM.
Critical revision of the manuscript: VMG, FS; TFA and FMSM.

All authors read and approved the final manuscript.

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Supplementary Materials

Not applicable.

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