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Original scientific article

Pilot study on the welfare of laboratory rabbits after urethral stricture induction by electrocauterization and open urethrotomy

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Summary

The study assessed the welfare of rabbits after inducing urethral stricture. This is a pilot study to assess appropriate experimental model before further experiments on the treatment of urethral stricture with artificial tissue. A review of the literature revealed that electrocauterization, also known as electrocoagulation, is the most reliable method for inducing urethral stricture in rabbits. The results were compared to the simple urethral incision, otherwise known as open urethrotomy. Unfortunately, we experienced that electrocauterization is poorly tolerated by laboratory animals. Weight loss was the most important parameter, indicated the poor health of the rabbit after surgery. In addition, we monitored other parameters such as temperature, fur quality, urination, general behavior, urine and blood samples. No major difference was found between the groups in any other parameter except for weight change. 4 weeks after the operation, the weight of the rabbits in the electrocauterization group had decreased by 12% compared to their initial weight. Electrocauterization group animals started to recover at the 5th postoperative week and returned to normal weight by the end of the 12th week. It is proven that postoperative conditions of the laboratory rabbits, like stress, discomfort during urination, pain or postoperative ileus could cause their weight loss. Open urethrotomy was tolerated better, the weight of rabbits in this group did not change notably, but urethral stricture did not develop either. In summary, we can conclude that electrocauterization is a reliable method of inducing urethral stricture, but in order to improve animal welfare, more intense analgesics and anti-inflammatory drugs should be administered. We suggest using an additional pain scale to monitor the welfare of rabbits, and continuing further experiments no earlier than 6-8 weeks after the initial urethral stricture induction, when the rabbits have recovered from the surgical intervention.

Introduction

Urethral strictures remain a serious challenge in modern urology (King and Rouke 2019). Traditional treatments such as urethral dilatation, primary anastomosis, substitution urethroplasties often fall short of achieving long-term success (Güller 2021), with outcomes that may not always meet the desired expectations (Lumen 2009). Bioengineering holds promise for discovering new treatment methods, with artificial biological tissues offering a potential breakthrough in restoring damaged urethras (Chapple 2020).

Currently, a lot of laboratory research is underway to create the right biologically relevant tissue that can be used in clinical practice. However, these studies require testing in animals before experiments can progress to trials in humans. To solve the issues of formation and treatment of urethral strictures, first, a stricture of the urethra is induced in animals, and then methods of treating are studied (Horiguchi et al. 2021).

An appropriate animal model of urethral stricture is needed for further in-depth investigation of the mechanisms of stricture formation and treatment. Rabbit and dog models of urethral stricture have recently been produced by open surgery, electroresection, electrocoagulation (Meria et. al. 1999), laser ablation (Hu et al. 2014) and pharmaceutical agent induction methods (Hua et al. 2018). Animal models created by open surgery have desirable reproducibility because of precise control of the procedure, but open surgery may result in severe wounds and has a higher incidence of urethral fistula formation (Yao et al. 2022).

Most of the studies on the development of urethral stricture patterns are limited to the final results, indicating whether the urethral stricture was formed successfully, what was its length and depth, how many animals survived (Xue et al. 2016). Unfortunately, there is lack of data on how the animals felt during the experiment and the challenges that researchers faced. These features are very important, especially considering that the animals with urethral strictures will have to participate in further studies when the strictures are treated with artificial tissues. Pain, stress, and fatigue are common to many animals, including rabbits. Controlling pain and stress improves animal well-being and postoperative outcomes (Wenger 2012). In rabbits, pain recognition can be particularly challenging because, as with many other prey species, these animals are predisposed to mask any sign of pain (Benato et al. 2019).

There is evidence that pain causes a decrease in activity and nutrition in rabbits (DiVincenti et al. 2016). Since rabbits' metabolism is geared to a constant supply of nutrients from the digestive tract, a decreased or absent food intake and the subsequent mobilization of fat reserves can lead to ketoacidosis and hepatic lipidosis (Varga 2013). Weight loss is known to contribute to complications such as increased susceptibility to infections, delayed wound healing, and in severe cases, mortality (DiVincenti et al. 2016).

It is important to pay attention to the behavioral changes of rabbits postoperatively (Gargiulo et al. 2025). One of the main behavioral features presenting when rabbits respond to pain is freezing and distress by remaining motionless, especially in the presence of an observer (Johnston 2005).

The purpose of our pilot study was to evaluate the welfare of rabbits after the induction of urethral stricture, with the intention of preparing the animals for further experiments. Rabbits must be in good health before they can participate in further studies on the treatment of urethral strictures. This was the initial phase of a larger project, aiming to compare different urethral stricture treatment methods.

Materials and Methods

Four New Zealand white rabbits (*Oryctolagus cuniculus*) (Animalab, Hungary Kft.) were selected in this pilot study. The average age of rabbits was 12 months, the average weight was 4465 g.

They were randomly divided into two study groups, each consisting of 2 animals. Group A was assigned for a simple open urethrotomy, group B was assigned for open electrocauterization of the urethral endothelium to induce stricture formation.

During surgery, rabbits were anesthetized by intramuscular injection of ketamine hydrochloride (35 mg/kg, bioketane, vetoquinol) and xylazine (5 mg/kg, Xylamedo, Bimeda). Intraoperative monitoring of animal pulse and oxygenation was caried out. (Figure 1A) The operative field in the perineal area was sterilized with Povidone-iodine solution. A single intramuscular injection of the antibiotic Enrofloxacin 2.5 mg/kg (Bayer B.V.) was performed to prevent infections, and the non-steroidal analgesic Carprofen 4.0 mg/kg (Rycarfa, KRKA) was administered intramuscularly to relieve postoperative pain.

In both groups, a ventral incision of the middle part of the penile urethra was performed under general anesthesia (Figure 1B). In group A, the urethral lumen was opened for a length of 2 cm. A 10 Ch Nelaton type catheter was inserted. The wound was closed with two layers of Vicryl rapid 4-0 sutures, suturing subcutaneous tissue and skin, but leaving the edges of the urethral endothelium free of sutures. As a result, the urethral defect was left not repaired, and a stricture is expected to form. The catheter was sutured to the foreskin with two 3-0 PDS sutures to remain in place for 5 days (Figure 1D).

In rabbits of group B the same ventral incision of the middle part urethra was made. After opening the lumen, the endothelium of the urethra was superficially electrocauterized using bipolar electrocautery, avoiding perforation and damage to the surrounding tissues. (Figure 1C) The wound was closed in the same manner as in group A, leaving a 10 Ch Nelaton catheter indwelling.

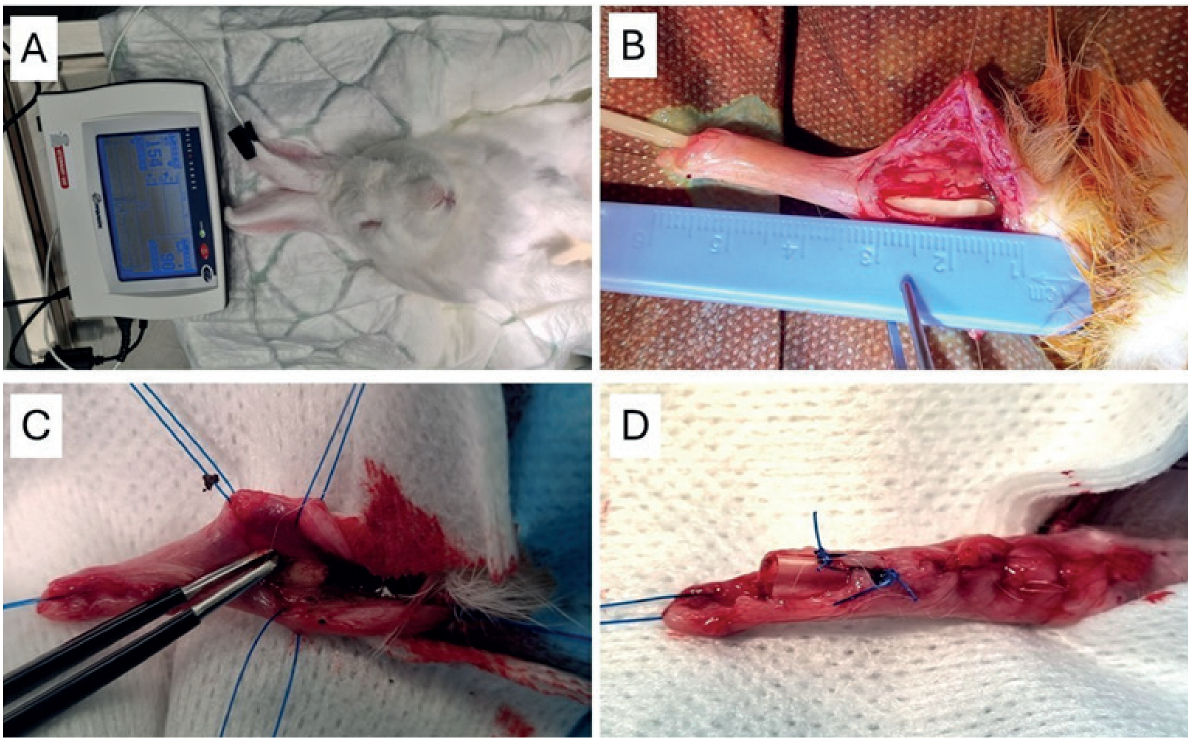

Figure 1. Surgical methodology. 1A Monitoring of anesthetized rabbit. 1B Urethral ventral incision 2cm in length. 1C Bipolar urethral cauterization induces fibrosis in urethral wall. 1D Final postoperative view with the catheter indwelling sutured to the foreskin.

The rabbits were housed individually in a temperature-controlled cage (TechnoPlast) with a humidity of 50-55 % for a 12-hour light-dark cycle and had free access to chow (Maintenance Diet for Rabbits, Altromin) and tap water. During the first week after surgery, the rabbits' wounds were cared daily and, later, weekly.

Urethral catheters were secured to the foreskin and shortened to the level of the foreskin to minimize the likelihood of dislodgement. Nevertheless, most catheters were lost or actively removed by the rabbits within the first two postoperative days. Even though rabbits have lost catheters they did not experience urinary retentions. There was mild hematuria seen during first 3 days postoperatively.

The rabbits were cared for by a qualified veterinarian. To standardize the follow-up procedure, we used the scale of physical and behavioral symptoms. The scale consisted of these parameters: wound condition, behavioral manner, fur quality, urination quality, nutrition quantity. Each parameter was evaluated in scale 0-1-2, meaning: 0 – poor, 1 – average, 2 – good. Total sum of parameters showed general level of rabbits' welfare during postoperative follow-up period.

The rabbits were weighed once per week; the urethral wound was disinfected and evaluated periodically. The body temperature was measured once per week at the inner surface of the ear using an appropriate non-contact infrared thermometer.

After 4 and 12 weeks, urethrograms were performed under general anesthesia. It was performed in the same manner as initial surgery by intramuscular administration of Ketamine hydrochloride (35 mg/kg) and Xylazine (5 mg/kg). The rabbit was placed on its back, the perineal area was disinfected with Octisept (octenidine dihydrochloride/phenoxyethanol, Schülke & Mayr GmbH) spray. The penis was stretched in the caudal direction, the 8fr catheter inserted into the urethra aproximatelly 2cm, positioned at the site of the urethroplasty and fixed with a Vicril 2/0 thread. Urografin® (76%, Sodium Amidotrizoate / Amidotrizoate Meglumine, Bayer B.V.) solution was diluted with sterile saline to 38% and injected through the catheter. Radiographs were captured by the digital Madical ECONET mex+100 X-ray equipment, 50kV, 2.0sec/mAs, 100mA mode.

12 weeks after urethral stricture induction the rabbits were sacrificed and the urethra was dissected. The rabbit penis was cut at the root part and fixed in 10% formalin solution. The formalin-fixed samples were embedded in paraffin, sectioned every 5 mm and stained with hematoxylin and eosin. Samples were analyzed under a bright-field microscope using a Leica M205C stereomicroscope at 0.78 times magnification and an Olympus AX70 microscope with 2x and 10x magnification objectives. All histological specimens were blinded and evaluated by the same pathologist.

Statistical analysis

Due to the small sample size, appropriate statistical analysis was not performed. Analysis of the study results was limited to descriptive statistics, reporting absolute data values and medians. A larger cohort would have increased statistical power and perhaps provided more reliable comparisons between groups. However, even with the limited sample size, the apparent differences between groups strongly support our main conclusion, therefore it was decided not to increase the sample size until the study protocol could be improved.

Results

The average surgery time was 23.75 minutes. The duration of surgery was longer in electrocauterization (B) group (25.00 minutes) compared to simple incision (A) group (22.50 minutes). All 4 rabbits survived the surgery fluently and no intraoperative complications occurred. The rabbits were observed for 6 hours after surgery until they fully woke up from anesthesia. The rabbits were active and showed no signs of illness. Based on previous experimental studies and a review of the literature, no additional analgesia or antibiotics were administered. Apart from the nutritional problems of group B animals described in the weight change and welfare paragraphs, all animals survived to the last stage of the experiment. Minimal blood was found on the bedding on the first postoperative day, which was considered normal postoperative course. Although the urethral catheter was planned to be kept for 5 days, the rabbits removed the catheters from the urethra already on the first postoperative day.

Urethrograms

Urethrograms were performed after 4 and 12 weeks of follow-up. Under general anesthesia, Urographin 38% solution was instilled into the urethra, clearly revealing its lumen architecture. Urethrograms did not show any extravasation or urethral fistulas in the animals of both groups. The iodine-based contrast solution easily passed the site of previous surgery and filled the bladder. It did not reveal any side effects or reactions from the rabbit.

In both animals of A group, no signs of urethral stricture were detected either at 4-week urethrogram or at 12-week urethrogram. (Figure 2, A. and B.) Otherwise, in both animals of B group the urethral stricture was clearly detected at 4-week as well as at 12-week urethrograms (Figure 2, C. and D.) Urethral stricture retained the same size when comparing urethrograms at 4 and 12 weeks.

Urethrograms

Final histological examination revealed a difference between the two methods of stricture induction. Although urethral incision appears to be a serious injury and severe strictures would be expected in humans, complete recovery was confirmed in rabbits. The urethra had a normal lumen and was lined by normal transitional urothelium. Mild infiltration with polymorphonuclear leucocytes was observed in the urethral wall. The pathologist did not observe any evidence of fibrosis or stricture. (Figure 3.1 and Figure 3.2)

Clearly different findings were obtained in samples from electrocauterization (B) group animals. In this group, serious damage to the urethra was detected, and a proper stricture was formed after 12 weeks. The histological findings replicated the results we had observed during the urethrograms. The surgical site was fibrotic, the lumen of the urethra was narrow, covered with squamosal epithelium, which indicates poor wound healing. Inflammatory infiltration of the urethral wall was observed, with abundant neutrophils and fibroblasts present within the tissue. Inflammatory elements were also found in the urethral lumen. (Figure 3.3 and Figure 3.4)

Histological findings showed notable difference between two surgical methods – simple incision versus incision and electrocauterization of the urethral wall. The second method showed severe lesion to the urethra, generating stable urethral stricture after 3 months.

Welfare

The experiment aimed to evaluate the welfare of rabbits during follow-up period. We used the standardized scale of welfare symptoms, that was described in methodology. The measurements of temperature, weight, blood tests, and urine samples supported our data.

One rabbit of incision (A) group had mild postoperative hematuria, and a swollen wound 1 week after surgery. These changes disappeared naturally within the second postoperative week. One rabbit in electrocauterization (B) group had nutrition difficulties for 3 days postoperatively and needed supportive nutrition with syringe. Finaly in 4th day the rabbit started eating and drinking normally. The wound of mentioned group B rabbit was suspicious on 12th week postoperative, and it was confirmed as prompt stricture after final autopsy.

Temperatures of group A rabbits were markedly higher comparing to the B group rabbits. Otherwise the temperatures of all rabbits was constantly stable through all experiment time and did not change indicating any inflammation or other reactions (Figure 4).

Weight change is one of the most typical indicators of animal welfare. When experiencing stress, pain or illness, animals change their eating habits and lose weight (Benato et al. 2019). This was also seen in the rabbits in this experiment. Rabbits with more extensive urethral lesions lose a greater percentage of weight compared to their associates. A reduction in body weight was observed over the first 4 weeks, followed by a gradual recovery. This was most relevant for the electrocauterization (B) group animals (Figure 5).

Clinical signs like fur change, habits change, urination manner, wound or hematuria signs did not express any considerable difference between A and B group animals.

Blood and urine tests were performed at 2, 4 and 12 weeks of follow-up. Slight decreases in some blood parameters were observed in electrocauterization (B) group animals at the 12th week of the experiment. Red blood cell count (RBC), hemoglobin (HGB) and hematocrit (HCT) levels were reduced in group B rabbits. In urine sample - leukocyturia varied and did not differ between A and B groups (Figure 6).

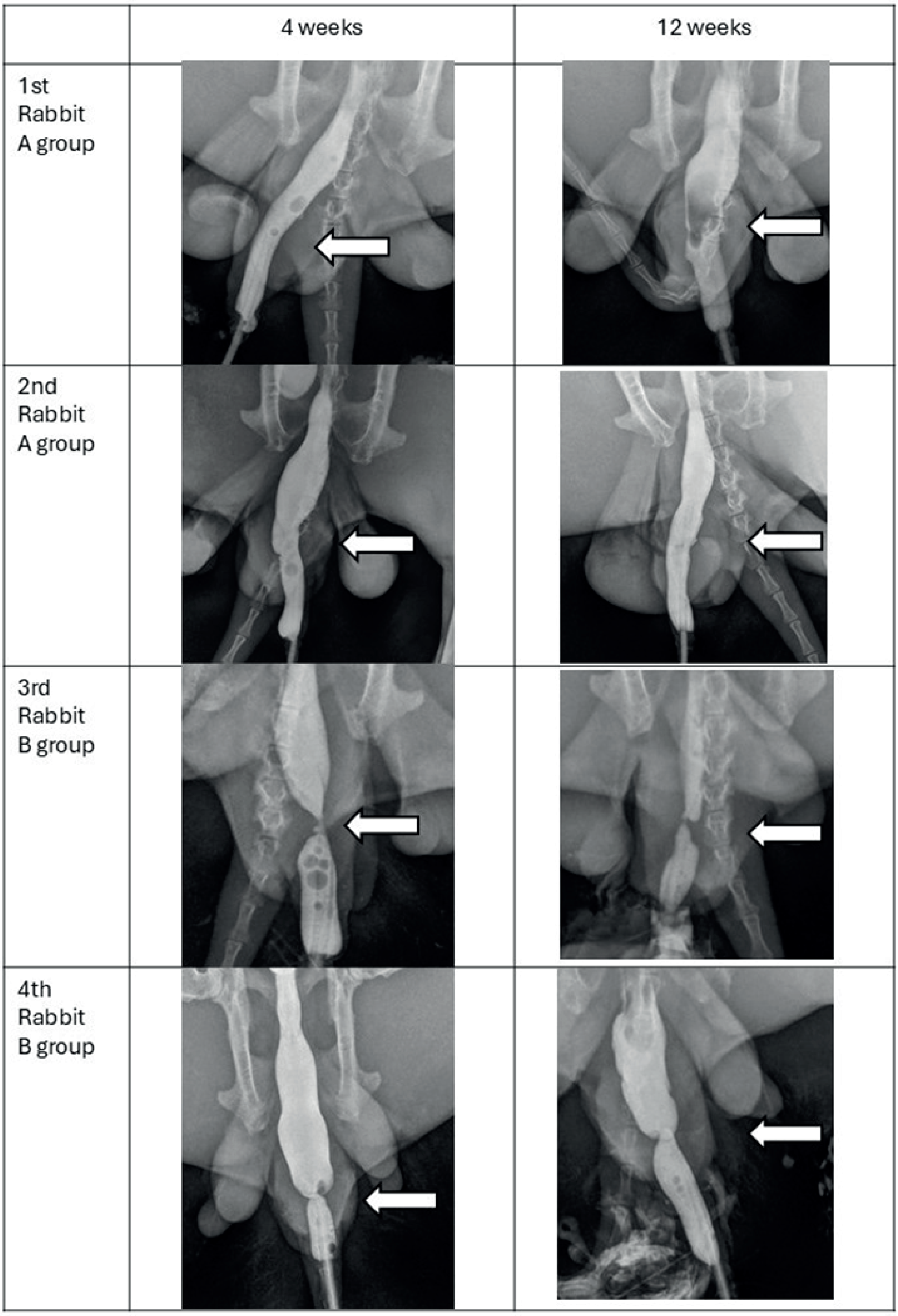

Figure 2. Urethrograms, performed on all 4 rabbits, 4 and 12 weeks after surgery, with Urographin 38% solution instilled. Arrows indicate the surgical site.

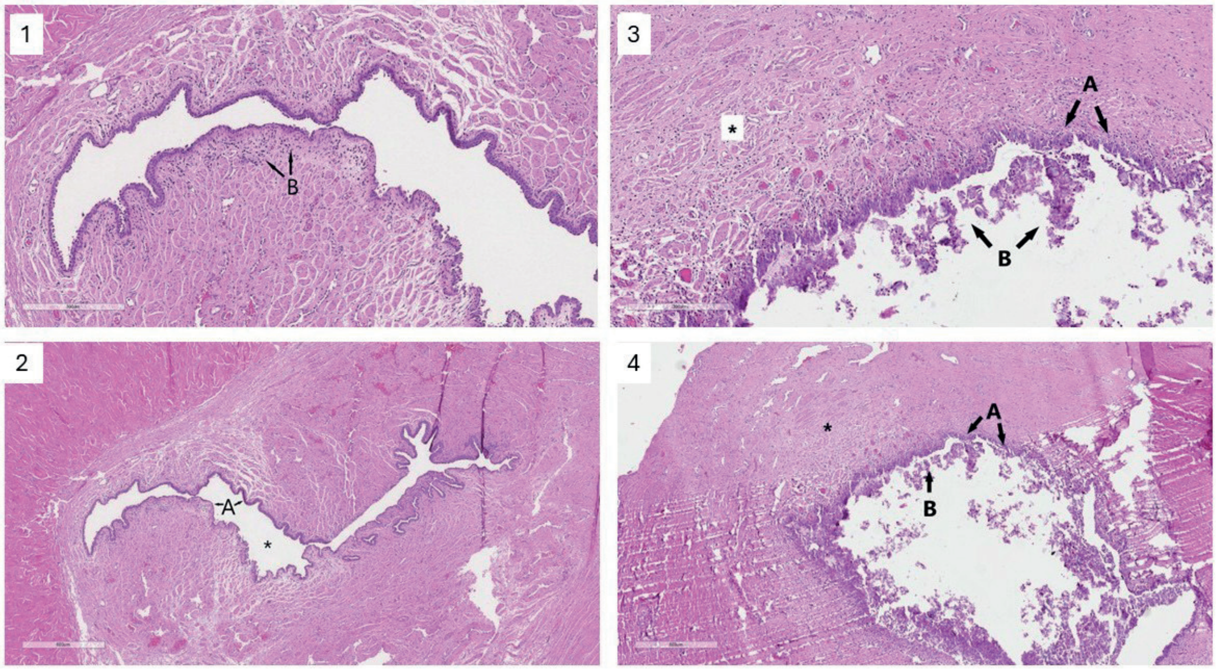

Figure 3. Histology. 3.1 – Rabbit 1, group A. Minimal neutrophil infiltration in the subepithelial stroma (B) (10x). 3.2 – Rabbit 1, group A. Urethra covered by normal urothelium (A), normal lumen (asterisk) (4x). 3.3 – Rabbit 4, group B – urethra covered by partially damaged urothelium (A), extensive inflammatory infiltration in the lumen (B) and perifocal fibrosis in the urethral wall (asterisk) (10x). 3.4 – Rabbit 4, group B. Image of the specimen at 4x magnification.

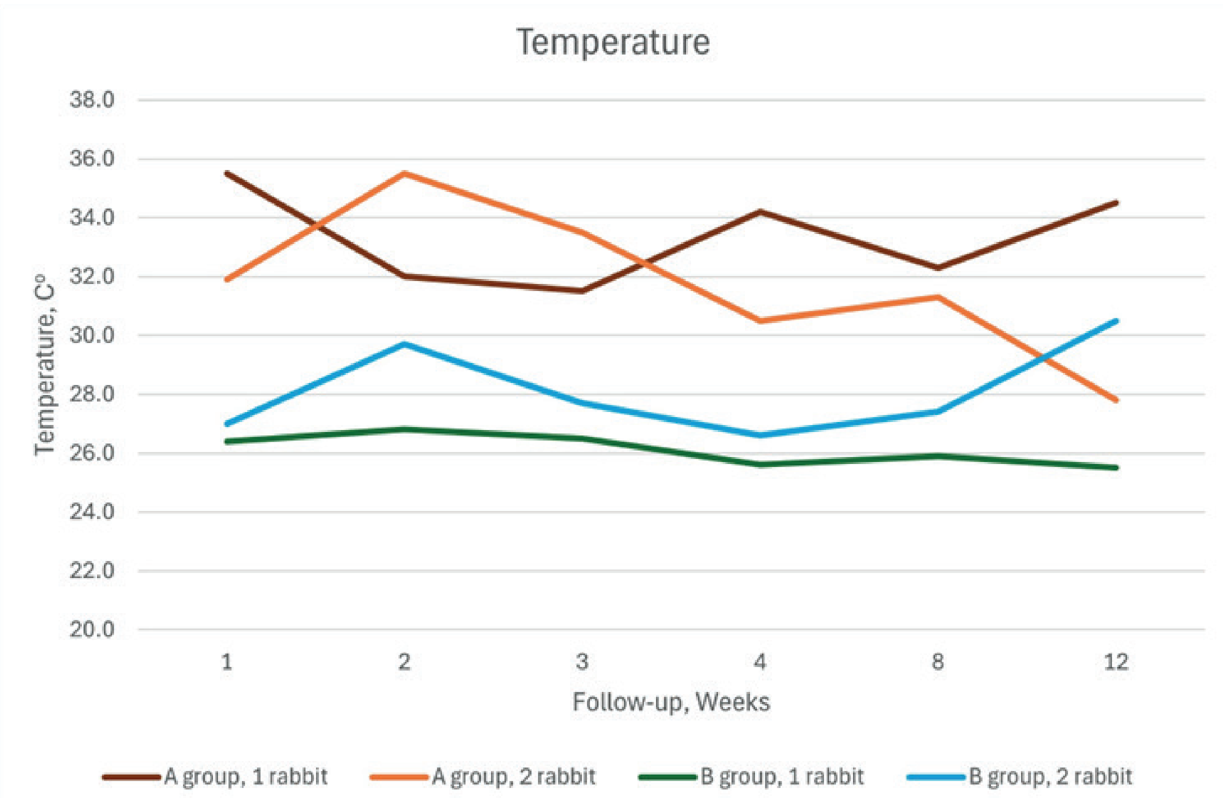

Figure 4. Temperature, Co, measured once per week at the inner surface of the ear using an appropriate non-contact infrared thermometer.

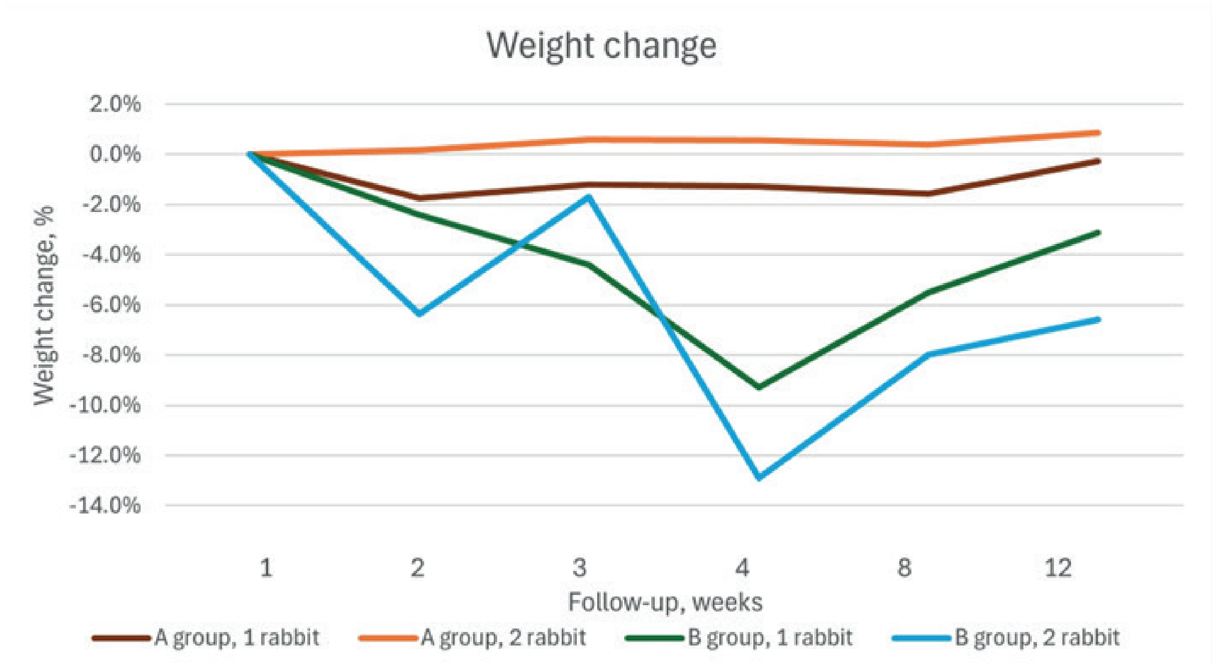

Figure 5. Rabbit weight change. Percentage change in weight of rabbits measured weekly compared to weight on the day of surgery.

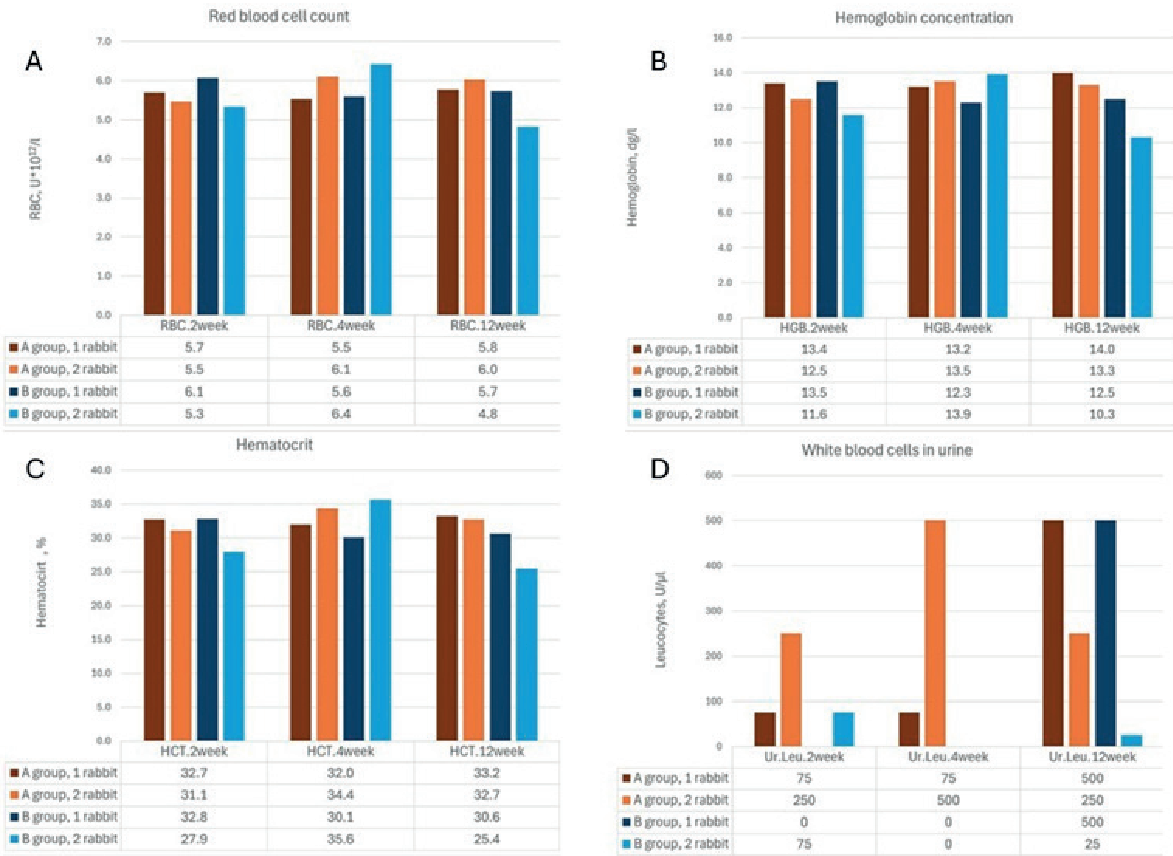

Figure 6. Laboratory analyses of rabbit blood and urine. A. Red blood cell count, U*10^{12}/µl. B. Hemoglobin concentration, dg/l. C. Hematocrit, %. D. Urine white blood cells, U/ µl.

Discussion

The aim of the study was to identify a suitable method for inducing urethral strictures for future artificial tissue research, with careful consideration of laboratory animal welfare. Electrocauterization models tended to develop stable urethral strictures in previous studies, but the long-term results needed to be proven (Meria et al. 1999). Effective animal models for the creation of urethral stricture are needed to allow urethral reconstruction studies, but appropriate methods are still under investigation (Faydaci et al. 2012).

This study confirmed that electrocauterization reliably induced urethral stricture in the electrocauterization (B) group, as evidenced by urethrograms at both 4 and 12 weeks. By 4 weeks, the stricture was fully formed and remained stable through week 12. Histological examination supported these findings, revealing fibrosis of the urethral wall, lumen narrowing, and epithelial damage, indicating the formation of a true long-term stricture. In contrast, no stricture was observed in the incision (A) group at either time point. Our study, which observed the rabbits for a longer duration compared to others, demonstrated that electrocauterization in the B group is a reliable method for inducing urethral stricture. The desired stable outcome was achieved by 4 weeks and additional time was not necessary for the development of a tight, firm stricture.

Based on previous studies (Nikolavsky et al. 2016), we aimed to catheterize the bladder of rabbits postoperatively to prevent urinary retention or fistula formation. Although 10 Ch Nelaton catheters were attached with sutures to the foreskin and shortened to the tip of the penis, the rabbits removed them as soon as they recovered from anesthesia on the first postoperative day. It is noteworthy that despite this, there was no urinary retention or other early postoperative complications. Some studies suggest that it is not worth leaving a catheter in the urethra after surgery (Micol et al. 2012). As we observed, the catheter did not improve the postoperative condition, so we believe that a catheter is not necessary after open urethrotomy in rabbits.

The welfare of rabbits after the induction of urethral stricture is of great importance. This is important not only for the sake of good laboratory practice (Directive 2010/63/EU; Srinivasan et al. 2021), but also because these rabbits will be involved in subsequent experiments related to the treatment of the induced stricture.

Body weight can be monitored as a percentage change from values recorded immediately before stricture induction and measuring it periodically after the operation. According to the data of our study, despite the strictures formed in the rabbits of electrocauterization group, serious complications were avoided - all the rabbits survived, without fistulas, abscesses or urinary retentions, the rabbits urinated until the end of the experiment.

However, rabbits in the electrocauterization (B) group consumed less food and lost more body weight during the first postoperative weeks compared with the incision (A) group. Reduced food and water consumption, along with the consequent body weight loss, are also common indicators of pain in laboratory rabbits (Goldschlager et al. 2013; Weaver et al. 2010). Assessment and quantification of pain in this species can be challenging in a clinical environment, because rabbits tend to hide clinical signs of pain (Benato et al. 2019). Pain assessment scales, including composite scales such as the Glasgow Composite Measure Pain Scale and its short form (CMPS-SF), the French Association for Animal Anesthesia and Analgesia pain scoring system, and the 4A-Vet, are usually recommended for use (Mathews et al. 2014). Unfortunately, not all of those are valid to assess rabbit pain. Recently, the Rabbit Grimace Scale (RbtGS) has been validated as an effective method to assess acute pain in laboratory rabbits (Haddad et al. 2022). It is based on five action units, making it more accurate and less time-consuming than assessing several behavioral indicators (Pinho et al. 2023).

Rabbit body temperature was monitored repeatedly throughout the experiment. Notably, the electrocauterization (B) group exhibited lower body temperatures compared to the incision (A) group. Despite fluctuations in body temperature, no notable changes were observed in relation to the animals' overall well-being or body weight. Additionally, blood tests revealed no substantial changes, with hemoglobin levels and red blood cell count remaining within the normal range for both groups.

Although multiple parameters were monitored to assess rabbit well-being — such as behavior, fur quality, urination, nutrition, drinking habits, and wound healing—no meaningful differences were observed between the groups. The most reliable indicator of well-being was body weight. In the electrocauterization (B) group, body weight decreased by 9-12% during the first 4 postoperative weeks, while the incision (A) group showed stable or increased weight. Notably, after 4 weeks, electrocauterization (B) group rabbits began to regain weight, and by 12 weeks, their body weight nearly returned to baseline levels. This suggests that the factors contributing to weight loss in the electrocauterization (B) group diminished over time.

These findings highlight the importance of using more effective and consistent parameters for monitoring rabbit health in future studies. We recommend the implementation of rabbit pain scales and emphasize the importance of monitoring body weight, temperature, and blood parameters. Given that rabbits often mask signs of illness, the prophylactic administration of analgesics should be considered to ensure proper pain management.

A limitation of this study is the relatively small sample size. The study was conceived as a pilot project, and the number of animals was deliberately kept low in accordance with the 3R principle, to minimize animal suffering and potential complications such as renal failure or death. While a larger sample would increase statistical power and allow more robust comparisons, the clear and reproducible results between the two groups suggest that the main conclusion remains valid. Future research with larger groups is required to confirm these findings.

Conclusions

Based on the results of this pilot study, electrocauterization appeared to be a reliable method for inducing urethral stricture in rabbits, although it did worsen their general well-being. On the other hand, urethral stricture itself can affect the well-being of rabbits, regardless of the method by which it was induced. Electrocauterization established a stable and firm urethral stricture within 4 weeks after surgery, providing a robust model for future studies of regenerative therapy. In contrast, the incision method did not result in the formation of a stricture, highlighting the effectiveness of electrocauterization in reliably inducing this condition.

Body weight was identified as the primary parameter for assessing the rabbits' well-being, while other measures such as temperature, hemoglobin, and red blood cell count varied but did not comprehensively reflect overall health.

For future studies in regenerative medicine aimed at treating urethral stricture, it is essential to improve the well-being of the rabbits, to minimize pain and discomfort during the experimental intervention as per welfare guidelines for laboratory animals. We recommend closely monitoring body weight, ensuring proper nutrition, administering appropriate analgesia during the early postoperative period, and initiating further regenerative treatments 6-8 weeks after stricture induction. By that time, a stable stricture will have formed and the rabbits will have recovered from the surgical intervention, which will allow for the effective application of tissue engineering therapy later.

Ethical approval

All experimental procedures were approved by the State Food and Veterinary Service of Lithuania, No. G2-158. The study was conducted following the guidelines outlined in the EU Directive 2010/63/EU.

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Conflict of interest statement

The authors declare no conflict of interest.

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