

## SHORT COMMUNICATION

# A canine model of reversible urethral sphincter insufficiency

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## Abstract

This study developed an animal model with internal and external urethral sphincter insufficiency by bypassing the sphincter without major damage so that the animal under study can return to normal life after the study. There is a need for a reliable, applicable, and reproducible animal model for studying urinary incontinence disease due to incorrect sphincter function. Seven adult male dogs were used for this study. The urethral sphincter was bypassed by inserting a catheter between the bladder neck and the distal sphincter. The animals' physical condition was closely monitored for 9 weeks, and standard urodynamic and radiologic studies were performed before and 1–2 months after surgery. The animals were killed at 9 weeks after surgery for pathological assessment. Catheter placement caused complete incontinence in the animal, with urodynamic assessments indicating that the animal was unable to control urination and radiological assessments indicating an empty bladder with a residual volume of  $50 \pm 10$  cc. Tissue analysis did not show significant histological damage and inflammation. The study shows that by bypassing the urethral sphincter, which is a reliable and reproducible method, an animal model of urinary incontinence can be developed, which can be used in various studies such as assessing the adequacy of artificial sphincter function. The animals under study did not have any permanent defect, so they were able to return to their normal life.

## KEYWORDS

animal model, external urethral sphincter, internal urethral sphincter, urinary incontinence

## 1 | INTRODUCTION

From time immemorial, humans have been familiar with the concept of urinary incontinence, with its definition first recorded in ancient Egyptian writings in 1500 BC. Various attempts at treating urinary incontinence ranging from Ambrose design portable urinals in 1564 to condoms with pig bladder and clamps to block the urethra in later years have been made. Moreover, Frederic provided the

definition for the first modern sphincter in 1926. Finally, in 1973, F. Brantley Scott introduced the first artificial multicomponent inflatable sphincter.<sup>1</sup> Other efforts such as physiotherapy (e.g., Kegel exercise), placement of supportive devices such as pessary,<sup>2</sup> use of chemical drugs and reconstructive surgery, and treatment with stem cells<sup>3,4</sup> have been made to treat urinary incontinence.

Today, large numbers of people suffer from many diseases related to the urinary system, such as urgency urinary incontinence (UUI),

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mixed incontinence, overactive bladder and neurogenic UUI, lower urinary tract symptoms, and complete urinary incontinence, costing countries huge sums of money annually.<sup>5,6</sup>

One of the most important causes of different models of urinary incontinence is internal or external urethral sphincter (or both) insufficiency; artificial urinary sphincter (AUS) implantation is the gold standard method for treatment.<sup>7</sup> Artificial sphincters are devices that replace biological sphincters by blocking the duct and play the role of these sphincters in the body.<sup>8</sup> Different artificial sphincters such as electromechanical, hydraulic, and magnetic sphincters are designed with different functional mechanisms.<sup>9</sup> One of the well-known and common artificial sphincters is AMS 800, which has been in use for ~40 years; the satisfaction rate of this sphincter has been about 80%.<sup>10</sup>

With the advancement of science and technology in modern times, new sphincters and methods for the treatment of urinary incontinence are introduced every day, for example, sphincters that are made using smart materials or operate based on magnetism.<sup>11,12</sup>

To evaluate the performance of new sphincters, we need a suitable animal model that is very similar to humans in physiology and anatomy. The characteristics of a suitable animal model are as follows: (1) reliability to maintain the feature for a long time, (2) ease of model development, (3) ability to evaluate the accuracy of performance, (4) minimal surgical intervention to reduce errors due to extensive surgery, (5) ability to repair and recover, and (6) ensuring complete health of the animal under study according to research ethics.<sup>13</sup>

Based on the criteria and the availability of urodynamic information in previous studies, canines are appropriate for developing a model to evaluate the performance of artificial sphincter.<sup>14–16</sup> Therefore, we designed a model of complete urinary incontinence with internal and external sphincter bypass that does not cause irreversible damage to the sphincters.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

This study was performed on seven male mixed-breed dogs aged 3 years and weighing  $26 \pm 5$  kg at the beginning of the study. Incontinence was induced by bypassing the dog's urinary sphincter by inserting a catheter into the sphincter site. Behavioral changes, vital signs, and changes in the animal's weight over 9 weeks were carefully evaluated. The animal underwent urination evaluations before surgery, and radiological and urinary evaluations were performed during the study. Finally, the animal was killed and subjected to histological analysis.

### 2.2 | ANATOMY AND SURGICAL TECHNIQUE

In dogs, various factors play a role in controlling urination, including the curvature of the bladder neck, the internal sphincter, and the external urethral sphincter.<sup>17–19</sup> The urethral sphincter is located between the

neck of the bladder and a few centimeters from the os penis (i.e., the part of the penis that is bony and specific to dogs; the urethra passes below it), which plays a major role in controlling urination.<sup>19,20</sup> We removed all these factors by bypassing to induce complete and reliable incontinence. All experimental procedures and measures of the seven dogs for the College of Veterinary Medicine were carried out in accordance with the laws of animal welfare and care of laboratory animals and under the supervision of the Ethics Committee of the Shahid Beheshti University of Medical Sciences, Tehran, Iran.

The animal was anesthetized by injecting ketamine and midazolam (1 mg/kg) intramuscularly, and the maintenance dose was 1.5% isoflurane. The dose of anesthesia and vital signs were constantly monitored during surgery. We used a Nelaton catheter, size 10 (white), and made the incision using a number 10 blade and an electronic biphasic cutter.

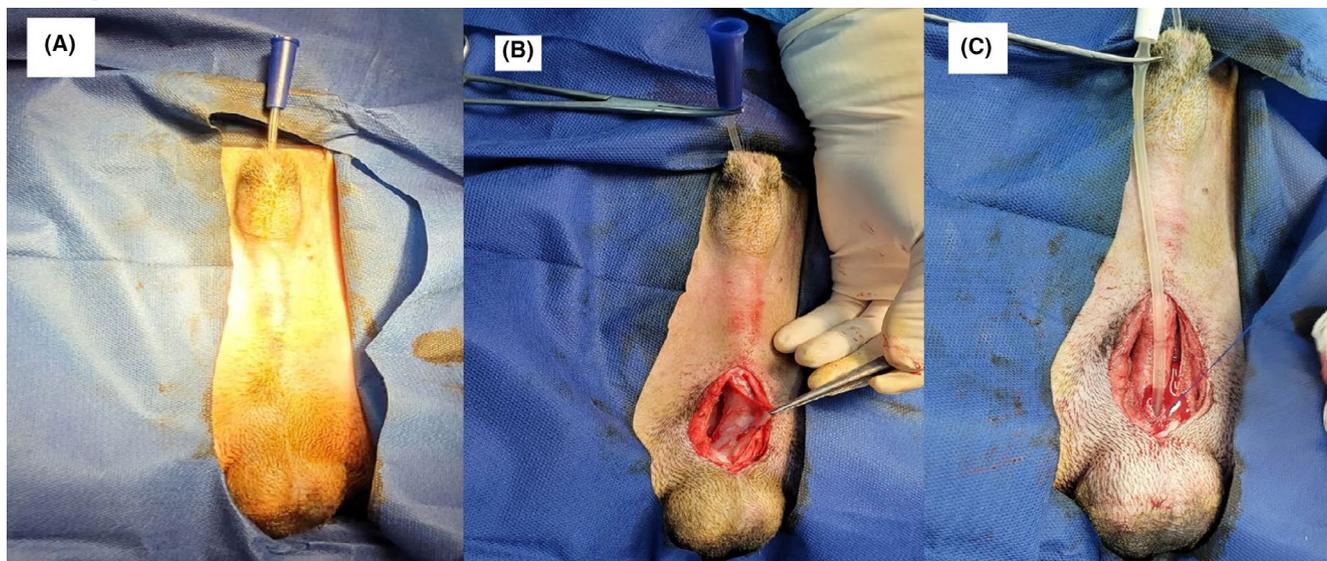
We first inserted a Nelaton catheter as a guide into the urethra to the bladder (Figure 1A). To access the urethra, we made a 3-cm longitudinal incision at the base of the penis starting just proximal to the os penis (Figure 1B), performed a urethrotomy in the distal region to the urethral sphincter, and removed the guide catheter that was inserted through the meatus; then we inserted a tube into the bladder from the urethrotomy to disrupt the function of the sphincters and bladder neck (Figure 1C). If the sphincter and bladder neck were bypassed, the urine in the bladder was drained through the tube, which confirms the correct placement of the tube; then the tube part of the tube, which is outside the urethrotomy, was cut an additional 5 mm. The tube was then completely guided to the bladder using forceps and inserted into the duct. Then, by maneuvering, the tube was pulled back slightly to bypass the distal area of the urethrotomy site and prevent the discharge of urine at the urethrotomy incision site. To prevent the tube from moving during dog activity or urination, the tube was sutured to the urethral wall through the urethrotomy. Then, the urethrotomy incision, which is 3 mm, and the perineal incision, which is 3 cm, were sutured.

### 2.3 | Urination assessment and radiologic evaluation

After surgery, the correct placement of the tube was ensured, and the residual volume of urine in the bladder was measured using sonography, which was equivalent to  $50 \pm 10$  cc. By applying pressure to the bladder by hand, we simulated abdominal pressure (Credé maneuver) to assess urine output and ensure complete urinary incontinence in the dog. After the animal was killed by injecting a contrast agent into the bladder and urethra, a graph of the lateral and anteroposterior views was obtained to evaluate the condition of the bladder and urethra.

### 2.4 | Histology

After the animal was killed, three transverse tissue samples were prepared to assess tissue changes, namely (1) bladder neck tissue, (2)



**FIGURE 1** (A) During the surgical procedure, a catheter was first placed as a guide in the urethra. (B) A 3-cm incision was made in the perineal area to access the urethra. (C) A catheter was inserted to bypass the sphincter by performing a ureterostomy.

urinary tissue at the site of contact with the catheter, and (3) urinary tissue at the site where the catheter was not present.

The third sample was prepared as a criterion of healthy tissue for evaluating changes in the second sample. The samples were placed in formaldehyde to be transferred to the pathology laboratory. Then, in the laboratory, the samples were fixed using paraffin dispenser (DS 4 LM, Did Sabz Co), and histological sections were prepared using a rotary microtome (RM2145, Leica) and a tissue processor (TP1020, Leica); finally, the Harris hematoxylin and eosin method was used for staining.

### 3 | RESULTS

During examination the general condition of the animal was good, and the weight changes were positive; no symptoms of infection, inflammation, perforation, obstruction, stone formation, and fibrosis in the bladder and urethra were observed.

Seven days after surgery, the incisions healed completely, and animal behavior was normal and did not indicate discomfort in the dogs. There were no severe weight changes in dogs, and during the study the mean weight increased from  $26 \pm 5$  to  $27.7 \pm 3$  kg (Figure 2). Urinary excretion was permanent and dropwise, which was monitored by a caregiver, and the results of sonography of the bladder during the study showed a residual volume of 50–70 ( $\pm 10$ ) cc of fluid in the bladder.

#### 3.1 | Cystourethrography

Radiographs were obtained from the anteroposterior and lateral views by contrast injection into the bladder using an ultrasound guide. They showed no signs of perforation, defect, diverticulum, and deformity in the bladder and urethra (Figure 3).



**FIGURE 2** Chart of weight changes of the model undergoing surgery; dogs were monitored for 9 weeks, which indicated normal behavior and dissatisfaction of the animals during the study, and the weight changes were evaluated as one of the factors of physical health.

### 3.2 | Histology

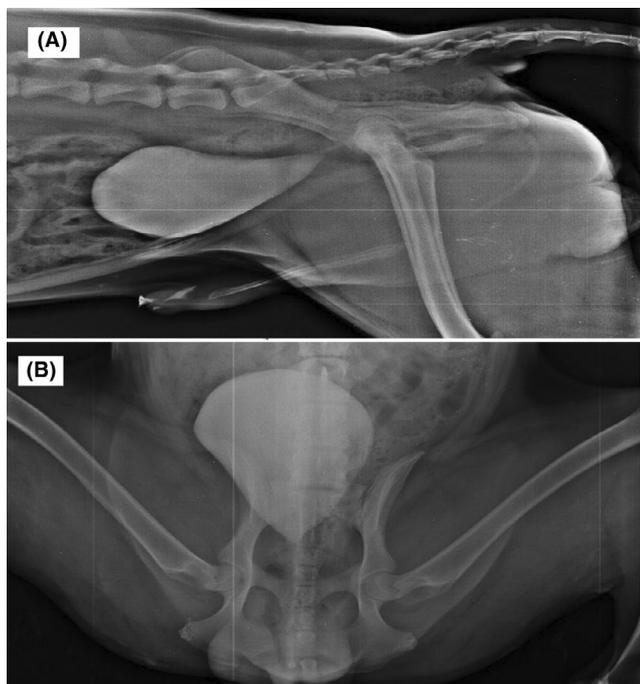
#### 3.2.1 | Urethra

Histopathological study showed the existence of some mononuclear inflammatory cells (lymphocytes, plasma cells, and macrophages) and scant neutrophils in the vascular lamina propria and a few infiltrated lymphocytes and neutrophils in the urothelium, accompanied by sporadic degenerated urothelial cells (Figure 4A).

#### 3.2.2 | Bladder neck

Histopathological examination showed sporadic infiltration of mononuclear inflammatory cells and eosinophils into the lamina propria, sporadic degenerated urothelial cells, and erosion (Figure 4B).

The submitted specimens exhibited a relatively ordinary histologic appearance with acceptable amounts of resident



**FIGURE 3** (A) Lateral and (B) anteroposterior images of the bladder and urethra with contrast injection show the health of the urethra and the absence of perforation and diverticula or abnormal protrusions due to catheter placement in the urethra.

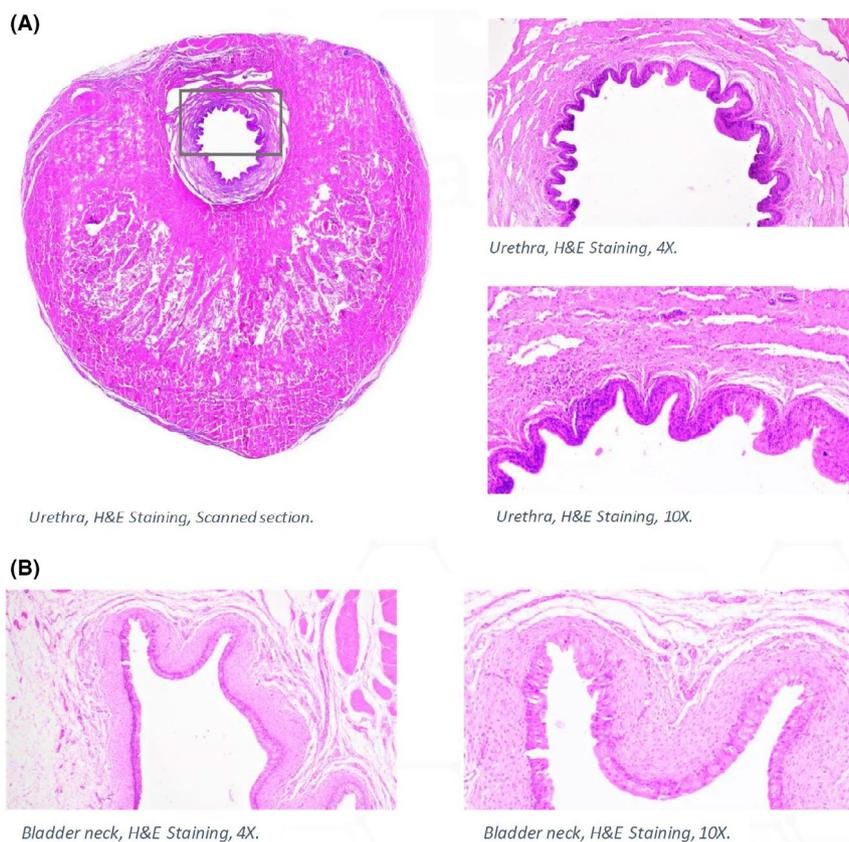
inflammatory cells, but mild and sporadic degenerative changes in urothelial cells and erosion due to movement of the catheter were observed.

Totally, no sign of significant damage due to experimental manipulation was detected.

#### 4 | DISCUSSION

According to the results, our animal model seems to meet the criteria for a suitable animal model, and an animal model with urinary incontinence that does not cause severe tissue damage in the animal with minimal aggression. It allows the animal to return to normal life after the end of the study process by removing the tube.

In this model, we completely removed the internal and external sphincters from the urinary control process by bypassing them, which makes it possible to use this model to evaluate urinary control devices such as artificial sphincters and smart catheters or in pharmacokinetic evaluation studies of drugs. Many methods have been previously introduced to develop a model of urinary incontinence, for example, permanent damage to the urethral sphincter through open surgery or microsurgery or the use of Botox injections to disable the sphincters.<sup>13,21</sup> However, in open surgical procedures, due to blood loss, long duration of surgery, and the possibility of adhesions between



**FIGURE 4** (A) Macroscopic and microscopic histological examination of the catheter in the urethra shows the absence of severe tissue damage and leukocyte infiltration in the normal range. (B) Histological evaluation of the bladder neck with 4- and 10-fold magnification showed no signs of pathological changes caused by tissue stimulation by the catheter in the duct.

different organs as well as iatrogenic injuries, the injury to the animal is severe, and the animal may not be in a condition to be used in the study. In microsurgery methods, there is a need for advanced techniques and tools. In both these methods, the animal can never return to normal life due to permanent anatomical damage. On the contrary, the sphincter may spontaneously improve and regain its function, which causes errors in the study's conclusions and requires animal specimens to be reoperated, which in many cases is not possible or is expensive. Botox injections are also possible. Due to the absence of the effect of botulinum toxin, the ability to control urine lies on the animal model, which reduces the reliability of this method.<sup>21,22</sup>

In our proposed method, there is minimal use of tissue and operation time is short; also this method does not require advanced facilities to perform and is highly reliable. It is also possible to implant an artificial sphincter and cause urinary incontinence in one stage of surgery and to assess the adequacy of urinary incontinence; it can be kept inactive for a few days. On the contrary, at the end of the study, the animal can return to normal life, which is confirmed by histological and radiographic results.

In this study, due to the anatomical similarity of dogs to humans (which develops the incontinence model used in many studies evaluating AUSs in the animal study phase), the incontinence model was developed using a male dog. However, as this method involves inducing urinary incontinence, it can be used in other species such as pigs, sheep, and monkeys.

One of the limitations of this study is the difficulty involved in housing and assessing large animals, such as dogs, within the confined environment of a laboratory, which naturally impacts the behavior and weight of the animals under study. Furthermore, the ethical considerations involved in performing surgeries on multiple subjects restrict the scope of the study. Overall, considering the possibility of inducing complete urinary incontinence with minimal side effects on the animal, this method becomes a standard approach for evaluating drugs or implants developed in this field that require animal models with complete urinary incontinence. Another limitations of the study include the small number of samples under surgery and the short duration of keeping the dog, which was due to limited resources and the difficulty of keeping and monitoring large animals, especially large breed dogs.

## 5 | CONCLUSIONS

This study demonstrates that consistent and reproducible urinary incontinence can be achieved by bypassing the urinary sphincter using a catheter. This method can be applied to dogs and even other species without the need for specialized facilities. The resulting animal models, with induced complete urinary incontinence, are suitable for evaluating the performance of artificial sphincters. Future studies should maintain the model over an extended period and increase the sample size, as well as explore the method in additional species to assess compatibility across animals with varying anatomical structures.

## AUTHOR CONTRIBUTIONS

**Pourya Shokri:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing – original draft; writing – review and editing. **Shahin Tabatabaei:** Conceptualization; data curation; formal analysis; funding acquisition; resources; software; validation; visualization; writing – original draft; writing – review and editing. **Seyed Amir Mohsen Ziaee:** Conceptualization; investigation; methodology; project administration; software; supervision; validation; visualization; writing – original draft; writing – review and editing. **Mir Sepehr Pedram:** Investigation; methodology; project administration; visualization; writing – original draft; writing – review and editing. **Mohammad Mehdi Dehghan:** Project administration; resources; software; supervision; validation; writing – original draft. **Nasser Shakhssalim:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; visualization; writing – original draft; writing – review and editing.

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## CONFLICT OF INTEREST STATEMENT

All authors declare that there is no conflict of interest related to this study.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All experimental procedure and measures were carried out in accordance with the laws of animal welfare and care of laboratory animals by approved number IR.SBMU.UNRC.REC.1401.008 of the ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran.

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