

Urethral sphincter mechanism incompetence in spayed bitches: new insights into the pathophysiology and options for treatment

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INTRODUCTION

Incidence of USMI after ovariectomy

Urinary incontinence is the involuntary loss of urine [1]. In intact bitches urinary incontinence is rare (0-1 %) [2], whereas in spayed bitches the incidence is up to 20% [3].

The underlying pathophysiological mechanism is mainly an acquired insufficient closure of the urethra after spaying [4]. Therefore urinary incontinence after spaying is called urethral sphincter mechanism incompetence (USMI). Within one year after spaying the urethral closure pressure is significantly reduced. Because many bitches may only become incontinent years after surgery it took a long time until the causal relationship between ovariectomy and the occurrence of incontinence was proven [5]. In one study, 83 of 412 (20%) bitches became incontinent 3 to 10 years after surgery [3].

As long as 40 years ago urinary incontinence was described as a rare side effect of spaying [6]. However, it took 20 years to verify the causal relationship between the removal of the ovaries and urinary incontinence [5]. The triggering mechanism is still unclear.

Neuronal damage can most likely be disregarded, as the risk of urinary incontinence is the same in ovariectomised and ovariohysterectomised bitches [3].

The role of oestrogen deficiency

It is generally assumed that USMI after spaying is due to an oestrogen deficiency [7, 8]. In view of other facts it appears unlikely that oestrogen deficiency alone accounts for USMI after spaying. For example, bitches treated with long acting gestagens to suppress the sexual cycle, have no increased risk for urinary incontinence, although this treatment leads to suppressed ovarian function [9] with a serum oestradiol concentration remaining at a basal level [10]. In addition, daily supplement of oestrogen only results in 61-65% of incontinent bitches

becoming continent [3, 11, 12]. Also, the plasma oestrogen concentration of spayed incontinent bitches is the same [13] or slightly lower [14] than that of intact, continent bitches.

Treatment of USMI

Dogs with USMI have a higher risk of urinary tract infection, that can result in polyuria and detrusor instability of the bladder. Urinary tract infection and other diseases causing polyuria such as decreased renal function, Cushing's disease, diabetes mellitus, or corticosteroid treatment can lead to overt urinary

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incontinence in dogs with USMI. Thus urinary tract infection and polyuric diseases should always be ruled out or treated adequately.

Medical treatment of USMI

Medical treatment of USMI is the method of choice and should always precede surgical therapy. The aim of medical treatment is to increase the urethral closure pressure.

Alpha-adrenergic drugs

In the first line alpha-adrenergic agonists are used. The effect of these sympathomimetic drugs is explained by the fact that 50% of the urethral closure pressure is generated by the sympathetic nervous system. Alpha-adrenergic agonists improve the urethral closure pressure by stimulation of the alpha-receptors of the smooth urethral musculature [13, 15-19]. The treatment with alpha-adrenergic agonists results in continence in 75% of incontinent bitches.

The alpha-receptors are divided into alpha-1 and alpha-2 subtypes. These receptor subtypes are distributed differently in each single effector. Alpha-1 receptors are found in many target organs of the sympathetic nervous system. With a few exceptions, alpha-2 receptors are not present in target organs of the sympathetic nervous system, but in neuronal synapses. It is now known, that the alpha-receptors at the bladder neck and proximal urethra of the bitch, which are responsible for continence, belong to the subtype 1 [20].

The side effects of alpha-adrenergic agonists is explained by the fact that alpha-1 receptors are not just found at the bladder neck, but also in other organs, especially in blood vessels. Phenylpropanolamine (PPA) acts selectively on alpha-1 receptors. The older substance Ephedrine is less selective than PPA. It also stimulates beta-receptors, and therefore has more side effects [21]. In contrast to PPA a habituation to Ephedrine occurs. Because of these reasons PPA is the therapy of first choice [21].

In humans treatment with PPA sometimes causes side effects, such as an increase in blood pressure and headache. It may occasionally trigger a stroke or a heart attack and is therefore no longer used. When PPA was used in dogs at the recommended dose of 1.5 mg/kg BW bid or tid, an increase in blood pressure was not observed [18, 22]. The side effects observed in dogs were never life threatening and usually were self-limiting; diarrhoea, vomiting, anorexia, apathy, nervousness and aggression [3, 19, 23].

Oestrogens

An alternative is the treatment with oestrogens, which is successful in 65% of the incontinent dogs [3, 12, 24]. However, with oestrogens unwanted side effects can occur such as swelling of the vulva and attraction of male dogs [12]. Nowadays only short-acting oestrogens (Estriol, Incurin®, Intervet, Netherlands) are used [11]. The depot preparations used in the past are obsolete, in part because they can potentially cause bone marrow depression [25]. Oestrogens indirectly increase the urethral closure pressure by sensitizing the alpha-receptors

to endogenous and exogenous catecholamines [26]. If therapy with alpha-adrenergic agonists is unsatisfactory, a combination with oestrogens may potentiate the effect.

GnRH depot analogues

As mentioned before not all the observations can be explained by oestrogen deficiency as being the sole underlying cause of urinary incontinence after spaying. In addition, it is not the only endocrine hormonal change after spaying. By removing the ovaries the feedback function of the gonadal hormones on the hypothalamic-pituitary system is abolished [27], which in turn results in a several fold increase of the initial plasma levels of the two gonadotropins (follicle stimulating hormone FSH, and luteinizing hormone, LH) [28, 29]. The question arises, if the elevated FSH and LH concentrations are responsible for the high incidence of urinary incontinence in spayed bitches. If this was the case suppression of the gonadotropin secretion would result in continence in affected bitches. GnRH depot preparations are suitable for the suppression of FSH and LH secretion. These are subcutaneously administered implants, which continuously secrete GnRH and, dependant on the preparation, result in an elevated blood concentration over weeks or months. This leads to a down-regulation of the GnRH-receptors in the pituitary gland and thereafter to a decrease of the FSH and LH concentrations to a low level.

Eighteen of thirtyfive bitches with USMI after spaying did indeed become continent, for an average period of 229 days [30, 31], after receiving depot preparations of GnRH-analogues. However, it is questionable if the therapeutic success is due to a decrease of the gonadotropin concentrations as there was no difference in concentrations between responders and non-responders [31]. It is possible that the success of the treatment is not based on a decrease in the FSH and LH, but instead on a direct effect of the GnRH on the lower urinary tract. This idea is quite conceivable as our working group has recently been able for the first time to prove the presence of LH, FSH and also GnRH receptors in the bladder and urethra of bitches [32]. Apart from that, it has been shown that the effect of GnRH is not limited to the regulation of pituitary hormones, but GnRH is also produced outside the hypothalamus and may have a direct effect on the target organs [33].

The fact that GnRH, FSH and LH receptors are expressed in the lower urinary tract and other organs supports the assumption that GnRH performs specific functions in the tissue and that a widely distributed paracrine or autocrine regulatory system exists.

In about 50% of bitches with urinary incontinence treatment with GnRH-analogues was successful [30, 31]. Based on the proposed pathophysiology of USMI, that after spaying the decrease in urethral closure pressure is the underlying cause for urinary incontinence, it seems reasonable to assume that the therapeutic success is due to a normalization of the urethral sphincter mechanism. However, this hypothesis was clearly disproved by the recording of urethral pressure profiles of incontinent bitches before and after GnRH treatment. The application of GnRH had no significant effect on the urodynamic

parameters, even in successfully treated bitches [31]. Recent studies in Beagle bitches may assume that GnRH modulates bladder function [34]. In 10 spayed Beagle bitches cystometric examinations were performed before and after treatment with depot formulations of GnRH analogues. The results showed a doubling of the difference between the medium and maximum bladder filling volume at the same bladder pressure after GnRH treatment.

Tricyclic antidepressant agents

Tricyclic antidepressant agents such as imipramine (0.5 to 1 mg/kg tid per os) increase bladder capacity, along with the urethral sphincter closure pressure [35]. These drugs may be beneficial to dogs with urinary incontinence due to USMI and detrusor instability or as postoperative treatment of USMI.

Surgical treatment of USMI

For refractory cases at least three different surgical therapies are available. However, before considering surgery, urinary tract infection should be ruled out or be initially treated. Polyuric diseases should also be evaluated and managed. Colposuspension [36], urethropexy [37] and endoscopic injection of collagen [38] are mainly used as surgical therapy, with a success rate of 50 – 75%. With all three techniques a deterioration in the response rate was seen over time. At our clinic, we prefer the endoscopic injection of collagen as this method is least invasive with a minimal rate of complications, and the results are as good as the more invasive techniques [39].

Colposuspension [36]

The bitch is placed in dorsal recumbency with the hind limbs flexed. A Foley catheter is used to empty the bladder. The catheter cuff is inflated with air and drawn into the neck of the bladder. A caudal midline, abdominal skin incision is made. The prepubic tendon is exposed on both sides of the mid-line. The external pudendal vessels are identified and avoided. Traction on the bladder allows the bladder neck to be identified due to the presence of the inflated Foley catheter cuff. An index finger is inserted through the vulva and used to displace the vagina cranially. The fat and fascia around the ventral bladder neck and proximal urethra are separated until the vaginal wall is exposed dorso-lateral to the urethra. The vaginal wall is grasped with Allis tissue forceps on each side of and approximately one centimetre away from the proximal urethra. The surgeon withdraws the finger from the vagina and changes his gloves. The vagina on each side of the proximal urethra is anchored to the prepubic tendon using two 0 or 1 monofilament nylon sutures. Sutures are taken through the full thickness of the vaginal wall and are pre-placed. Before tying, tension is placed on the sutures to determine that strangulation of the urethra between the vagina and pubis would not occur. Once the sutures are tied, a final examination is performed to confirm that the urethra is freely moveable between the vagina and pubis and is not compressed in any way. The beneficial effect of the operation may be the resultant re-location of the bladder, bladder neck and proximal urethra into an intra-abdominal position.

Urethropexy [37]

A caudal midline celiotomy is performed. Blunt dissection in the midline is used to visualise the ventral aspect of the urethra at the level of the cranial pubic brim. A suture of 2/0 or 0 polypropylene is placed caudal to one prepubic tendon so that it enters the caudal abdomen. While traction is applied to the bladder neck and urethra via the bladder neck stay suture, the polypropylene suture is passed transversely through the muscular layers of the adjacent urethra. Once placed through the urethra, the suture is passed caudal to the opposite prepubic tendon and out of the abdominal cavity. The suture ends are held together with a pair of haemostatic forceps. The procedure is repeated, with a second polypropylene suture being placed through the urethral wall approximately 3 to 5 mm cranial to the first. Both the polypropylene sutures are now tied. This results in the closure of the most caudal aspect of the celiotomy incision and fixation of the urethra to the ventral abdominal wall at the end of the cranial pubic brim. The mechanism of action remains uncertain, although re-location of the bladder neck into an intra-abdominal position and the production of a localised increase in urethral resistance are likely consequences of the procedure.

Urethral submucosal injection of collagen [38]

The goal of treatment is to enhance the closure of the proximal urethra. For endoscopic injection of collagen the dogs are placed under general anesthesia and positioned in dorsal recumbency with the hind limbs extended cranially. A human cystoscope is passed into the urethra via the external orifice. Approximately 1.5 cm caudal to the neck of the bladder, 3 injections of collagen are made into the submucosa at 2, 6 and 10 o'clock positions, respectively [38]. The procedure is considered complete when, on viewing through the cystoscope, the urethral lumen is closed by the collagen deposits.

Comparison of the surgical techniques for USMI

With the collagen injection, incontinence initially resolved in 83 % of 40 bitches, by injection alone in 68 % and with additional medication in the remaining 15 % [39]. Up to 12 months after the injection, there was a deterioration in the initial result in 16 dogs, thereafter the results remained unchanged. Among these 16 dogs, 13 dogs were reclassified from the continent group to one of the other 3 groups (continent with additional medication, incontinence improved by approximately 80 % after collagen injection and with additional medication, incontinence remained unchanged after collagen injection) up to 12 months after the injection. This corresponded to the period necessary for resorption of collagen deposits as seen in women [40]. However, the fact that the success rate categories stabilized 1 year after treatment suggested that the collagen deposits are not resorbed in dogs. Also, histologic examinations of collagen deposits 12 months after injection in dogs revealed that they were still in place as cell-free masses surrounded by a connective tissue capsule [38]. Flattening of the deposits was likely the cause of reoccurrence of incontinence.

Collagen injections compare well to the other established surgical methods for the treatment of canine USMI. After urethropexy, 56 % of affected dogs were continent and 27 % had an improvement in continence [37]. A similar success rate

was observed after colposuspension, with 53 % of the female dogs continent and a further 38 % experiencing a marked improvement (41). However, a serious complication with both these techniques is an increased risk of urinary retention, a post-operative condition not seen in dogs injected with collagen.

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