

Prazosin administration increases the rate of recurrent urethral obstruction in cats: 388 cases

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OBJECTIVE

To determine if prazosin administration decreased the rate of recurrent urethral obstruction (rUO) before hospital discharge and within 14 days.

ANIMALS

388 cats with urethral obstruction.

PROCEDURES

Veterinarians who either always or never prescribed prazosin (generally, 0.5 to 1 mg, PO, q 12 h for 14 days) were recruited to complete observational surveys. Patient data and characteristics of relieving the obstruction, including perception of a gritty feel within urethra or difficulty unobstructing the cat, were recorded. The rate of development of rUO before hospital discharge and by day 14 was compared between cats that received or did not receive prazosin with the Fisher exact test. Other variables were similarly compared between cats with and without rUO.

RESULTS

302 (78%) cats received prazosin, while 86 (22%) did not. There was no association between prazosin administration and risk of rUO prior to discharge, with 34 of 302 (11.3%) cats receiving prazosin and 5 or 86 (5.8%) not receiving prazosin developing rUO. Within 14 days, a significantly higher proportion of prazosin-treated cats (73/302 [24%]) developed an rUO, compared with the proportion of non-prazosin-treated cats (and 11/86 [13%]). The perception of a "gritty feeling urethra" or difficulty of performing the catheterization was associated with increased risk of rUO.

CLINICAL RELEVANCE

Prazosin administration increased the likelihood of rUO by 14 days; ongoing investigation of other therapies to decrease rUO in cats is warranted. Without specific indications, the use of prazosin for the prevention of rUO should be discouraged.

Urethral obstruction (UO) is a common condition in male cats.¹ The underlying cause of UO is often undetermined, with dietary factors, including urine pH and obesity, stress, and other environmental factors implicated.¹ Acute treatment of UO includes anesthesia or sedation, urethral catheterization, fluid therapy for correction of electrolyte disturbances, and pain relief.² While initial treatment is typically successful, recurrent UO (rUO) is a common complication, with up 11% to 58% of affected cats following initial treatment.²

A multitude of approaches have been examined as potential solutions to the problem of rUO. These solutions may include anxiolysis, pharmaceutically induced urethral relaxation, dietary management, and inhibitors of lower urinary tract inflammation. Anxiolysis has been targeted as a potential solution via the use of medication such as acepromazine, benzodiazepines, and gabapentin, as well as environmental modifications, such as quiet,

protected spaces that attempt to allow the cat to feel calmer.²⁻⁴ Urethral relaxation has largely been attempted pharmacologically with medications such as α_1 -adrenoceptor antagonists, acepromazine, and benzodiazepines. Inflammation, thought to be a key contributor to the pathophysiology of UO, has also been targeted via systemic NSAID administration and intravesicular glycosaminoglycan administration.^{5,6} However, none of these pharmaceutical strategies have been shown to be reliable in achieving reductions in rUO in smaller clinical studies, and a highly effective method to prevent rUO remains elusive. Short-term rUO remains a clinically important complication for cats treated for UO as rUO increases the risk of death and financially driven euthanasia, increased inflammation, and may result in urosepsis or the recommendation for a perineal urethrostomy.

Prazosin has frequently been recommended as a therapy to decrease rUO, via its potential action as a urethral smooth muscle relaxant. Prazosin is an

α_1 -adrenoceptor antagonist that selectively and competitively inhibits the postsynaptic α_1 -adrenoceptor, directly producing smooth muscle relaxation. Several studies have evaluated the utility of prazosin in prevention of rUO, although Lulich and Osborne⁷ have expressed concern surrounding this treatment due to lack of evidence of urethral spasm as a component of UO and the potential limited activity of prazosin in the distal urethra.

In 2013, Hetrick and Davidow⁸ retrospectively described a cumulative rate of rUO at 30 days in 20 of 110 (18.8%) cats that received prazosin as treatment for UO, which was significantly less than cats treated with phenoxybenzamine (16/41; 39%). In this study,⁸ only 6 cats did not receive an α_1 -adrenoceptor antagonist, of which 1 (17%) developed rUO; like many retrospective studies, this study was hampered by missing data and time points. In 2017, Reineke and colleagues⁹ reported a prospective evaluation of rUO in cats treated with prazosin versus placebo. In that study,⁹ 45 cats treated in hospital with prazosin had a rUO rate of 7% (2/26) while placebo-treated cats had a rUO rate of 5% (1/19). At 1 month, rUO had occurred in 15% (4/26) of cats treated with prazosin and 17% (3/18) of placebo-treated cats. No significant difference was identified between groups, although a post hoc sample size calculation indicated that a larger sample size would be required to definitively exclude any benefit of prazosin, with an estimated sample size of 1,915 cats required.⁹ More recently, in 2021, Hanson et al¹⁰ retrospectively evaluated 65 cats, with 11 of 37 (29%) cats developing rUO during treatment with prazosin, and 5 of 28 (18%) developing rUO with placebo; however, this study may have been underpowered to detect a difference in treatment groups.

Despite a lack of clinical and theoretical evidence of efficacy of prazosin, the use of prazosin remains common in veterinary medicine for treatment and prevention of rUO. Potential drawbacks of treating a cat with prazosin include lack of efficacy, cost of medication, time to administer the medication, and challenges in medicating cats. Additionally, hypotension, lethargy, gastrointestinal upset, and ptialism have been described.⁹ The goal of this study was to evaluate a large number of cats with UO that were treated either with or without prazosin to attempt to prevent rUO and determine the rate of rUO during hospitalization and within 14 days after discharge from the hospital.

Materials and Methods

Part 1

This study was designed as multicenter observational and retrospective cohort study. Veterinarians who self-reported that they either never or always prescribed prazosin to cats with UO were recruited via the American College of Veterinary Internal Medicine email list serve and American College of Veterinary Emergency Critical Care email list serve and Facebook page. Veterinarians or practices that

prescribed prazosin intermittently or on the basis of variable individual patient criteria were excluded to avoid biased prazosin administration based on perceived disease severity. One participating hospital reported that their clinicians had agreed to alternate months with either prescribing prazosin or not prescribing prazosin, but this was not a requirement for participation. Cat enrollment and data collection were performed via an electronic survey (Qualtrics), which included patient data including body condition score (1 to 9), treatment data (including prazosin use), difficulty of unblocking the cat (including the perception of intraurethral grit during urethral catheterization), color and bloodiness of the urine, and whether the cat developed rUO prior to being discharged from the hospital or within 14 days after discharge. Data were added both in real time and retrospectively via review of medical records. Participants could add data at any point although most appeared to wait until the 14-day point or later. More than 1 cat could be added at time.

Review of the records was performed locally, and the authors only had access to records from their own hospital. Cats were excluded if they had developed UO secondary to urolithiasis or lower urinary tract neoplasia, if they developed a urethral tear, or if the medical record contained insufficient patient data or treatment data for analysis. Due to the observational and retrospective nature of this study, the need for client consent was waived by the Clinical Science Review Committee.

Statistical analysis

Descriptive statistics were computed. The Fisher exact test was used to determine whether cats that received or did not receive prazosin differed in characteristics. The same test was also used to determine whether any of the variables evaluated were associated with a decreased risk of rUO, including prazosin administration, presence of crystalluria, subjectively reported difficulty of urethral catheterization, perceived grittiness of the urethra during catheterization, duration (hours) of indwelling urethral catheterization, and clarity of the urine at the time of catheter removal.

Part 2

To further evaluate prazosin's impact on the rate of rUO, we aggregated the data from this study with the 3 most recent published studies⁸⁻¹⁰ on prazosin administration and rUO in cats as well as the data from the 2 prospective studies,^{9,10} while excluding the data from the previous retrospective study.⁸

Results

The medical records of 485 male cats were reviewed. It was impossible to know the number of individual veterinarians, due to the nature of the survey. Of these cases, 97 were excluded due to the presence of urolithiasis (n = 33), the presence of a urethral tear (n = 5), or incomplete records (n = 59) leaving the records of 388 cats available for analysis (**Table 1**). Of the cats included, 354 (91%) were mixed

Table 1—Cat and urinary characteristics and attending veterinarian impressions during unobstruction between cats treated with or without prazosin.

Variable	Total no. of cats	Prazosin (n = 302)	No prazosin (n = 86)	P value
Age (y)				
< 2	39	25	14	0.04
2 to 5	205	163	42	0.46
6 to 9	106	83	23	1.00
> 9	38	31	7	0.68
BCS > 5	263	207	56	0.60
Crystalluria	193	149	44	0.81
Perception of a gritty urethra	126	99	27	0.90
Perceived as difficult to unblock	241	192	49	0.68

BCS = Body condition score.

Table 2—Number (%) of cats (n = 388) with various factors that developed a recurrent urethral obstruction (rUO).

Variable	Total affected cats	rUO prior to discharge	P value ^a	rUO within 14 days of discharge	P value ^a
Perceived as difficult to unblock	118 (30)	14 (12)	0.35	35 (30)	0.01
Perceived as a gritty urethra	126 (32)	8 (6)	0.12	28 (22)	0.01
Crystalluria	193 (50)	21 (11)	0.59	42 (22)	0.40
BCS > 5	263 (68)	23 (9)	0.36	55 (21)	0.61
> 48 hours of indwelling catheter	93 (24)	13 (14)	0.65	26 (28)	0.71
Hematuria resolved before catheter removed	225 (58)	21 (9)	0.82	49 (22)	0.63

^aIn comparisons, the referent group was cats without each factor (Fisher exact test used). See Table 2 for remainder key.

breed cats, and all but 11 cats were neutered males. The remaining 34 cats included 8 Siamese, 7 Maine Coons, 5 British shorthairs, 4 Himalayans, 3 Persians, 3 Siberian cats, 2 Scottish folds, 1 Abyssinian, and 1 Japanese Bobtail. Cats generally received 0.5 to 1 mg of prazosin, PO, once daily for 14 days, based on clinician preference. Compared with cats that did not receive prazosin, a greater proportion of cats that received the drug were < 2 years of age. No other difference in cat characteristics were identified between these 2 groups.

Of the 388 cats, 302 (78%) received prazosin, while 86 (22%) did not receive prazosin. Of the 302 cats receiving prazosin, 34 (11%) developed rUO before discharge and cumulatively, by 14 days, 72 cats (24%) developed rUO. Of the 86 cats not receiving prazosin, 5 (6%) reobstructed before discharge, and 11 (13%) reobstructed within 14 days. There was no significant association between prazosin administration and risk of rUO prior to discharge. However, the cumulative rate of reobstruction was significantly higher in cats that were prescribed prazosin by 14 days following discharge.

Other factors for potential associations were also evaluated for increased risk of rUO including the presence of crystalluria, the subjectively reported difficulty of urethral catheterization, a subjectively gritty feeling urethra during catheterization, hours of indwelling urethral catheterization, and clarity of the urine at the time of catheter removal (**Table 2**). The only significant associations identified with increased risk of rUO were a gritty feeling urethra during catheterization and subjective difficulty

of urethral catheter placement. Overall, 126 (32%) cats were reported by the attending veterinarian to have had a gritty-feeling urethra as the urethral catheter was placed. Of these cats, 8 (6%) experienced rUO prior to discharge and 20 (16%) experienced rUO within 14 days of discharge, resulting in a cumulative rUO rate of 22% of cats in this group. In contrast, the cats with no palpable urethral grit experienced rUO at a rate of 8% and 7% prior to discharge and within 14 days, respectively, resulting in a cumulative rUO rate of 15%. There was no significant association between grittiness and rUO prior to discharge, but there was an association between grittiness and increased risk of rUO within 14 days of discharge. There was no significant difference in rates of rUO between cats that did and did not receive prazosin in the group of cats with a gritty feel to the urethra.

Of the 359 cats that had a subjective difficulty of unblocking score included in their survey data, 241 (67%) were reported to be subjectively easy to unblock. Of these cats, 21 (9%) experienced rUO prior to discharge and 23 (10%) experienced rUO within 14 days of discharge for a cumulative rUO rate of 18% of cats in this group. Of the cats that were subjectively hard to unblock, 14 (12%) experienced rUO prior to discharge and 21 (18%) experienced rUO within 14 days of discharge, resulting in a cumulative rUO rate of 30%. There was no statistically significant difference between rates of rUO prior to discharge in cats that were subjectively easy or difficult to unblock, but there was a significant difference between rates of rUO for these groups within 14 days of discharge. There was no significant difference

in rates of rUO between cats that did and did not receive prazosin in the group of cats that were difficult to unblock.

Part 2

Collectively, the previous studies⁸⁻¹⁰ used in part 2 of the present study evaluated 700 cats with UO, 128 (18.3%) of which experienced rUO at some time point during their respective study, with 505 cats receiving prazosin and 195 not receiving prazosin. The rates of rUO in these populations were 19.4% and 15.4%, respectively, and there was no statistically significant difference in the rate of rUO between cats that did and did not receive prazosin in this aggregated data set. However, removing the retrospective study⁸ by Hetrick and Davidow, and using only the data presented here, combined with the prospective data from Hanson et al¹⁰ and Reineke et al⁹, revealed that 87 of 365 (24%) cats treated with prazosin developed rUO, while only 17 of 133 (13%) of cats not prescribed prazosin developed rUO.

Discussion

The results of this study failed to show a reduction in risk of rUO in cats with UO treated with prazosin at either evaluated time point and in fact showed that cats prescribed prazosin were more likely to reobstruct within 14 days of hospital discharge. Prior studies^{9,10} have supported that the risk of rUO is not lessened by prazosin treatment, but an increased risk of rUO has not previously been reported. Our findings, combined with all the previously published prospective data,^{9,10} provide even more robust evidence of the lack of efficacy of prazosin in preventing rUO.

Several potential explanations are considered for prazosin's failure to reduce risk of rUO. First, the feline urethra is only composed of smooth muscle along the proximal 28% to 37% of its length with the remainder of the urethral musculature being striated muscle, which is not relaxed by α_1 -adrenoceptor blockade.¹¹ The majority of urethral obstructions are thought to occur in the distal urethra, well out of reach of the pharmacological activity and potential smooth muscle relaxant effect of prazosin in the preprostatic and prostatic urethral segments. Additionally, there is limited documented evidence that spontaneous urethral spasm occurs in cats, let alone as a significant part of the pathophysiology of UO, which may render urethral muscle relaxation an ineffective management strategy.⁷ The nature of urethral obstruction, particularly the absence of a mucus plug or stone, remains to be elucidated. The present study supports that α_1 -adrenoceptor blockage is not beneficial in preventing rUO. It is still possible the urethral spasm, edema, or debris is the underlying cause and could benefit from more focused therapy.

It was not clear why cats prescribed prazosin were more likely to experience rUO within 14 days of discharge from the hospital, but consideration is given to the potential for the added stress to the cat

from receiving oral medications or potentially hypotension or gastrointestinal upset caused by prazosin. It is also possible that owners were not appropriately administering prazosin as prescribed. The possibility of a type 1 error cannot be excluded.

This study identified a statistically significant association of grittiness within the urethral lumen during catheterization and increased risk of rUO within 14 days of discharge. This may be explained by increased physical obstruction of the urethra in these cats, which was not completely ameliorated by the placement of the urethral catheter. The residual presence of this material after the catheter is removed may contribute to decreased functional urethral diameter and rUO. Potential management strategies for this problem could include flushing the urethra both during catheterization (hydropulsion) and when the urethral catheter is removed to attempt to dislodge as much of this material as possible. However, a study¹² by Dorsey et al failed to show a decreased rate of rUO associated with flushing. Additionally, increased difficulty of urethral catheterization was associated with increased risk of rUO within 14 days of discharge from the hospital. Potential explanations for this might include increased urethral inflammation and increased urethral trauma during attempts to unblock these cats.

Seitz et al¹³ identified that cats with discolored urine at the time of catheter removal were more likely to reobstruct. In the study reported here, there was not a difference in rate of rUO in cats that had discolored urine or normal colored urine at the time of catheter removal. The reason for this discrepancy is not clear but deserves further investigation.

There were several limitations to the present study. This study was limited by a disparity in the size of our cohorts, given that we enrolled more than 3.5 times as many cats that received prazosin than those that did not receive prazosin. Additionally, the observational study design and lack of a standardized clinical treatment protocol for UO cats inhibit the ability to draw extensive conclusions from this data set. Finally, this study's lack of a standardized follow up system and reliance on data electronically reported by a variety of clinicians result in the possibility of inaccurate or incomplete data. It is possible also more cats developed a rUO after hospital discharge, but this was not reported.

Our results further support existing evidence suggesting that prazosin is not beneficial in the prevention of feline rUO.^{9,10} Therefore, prazosin should be considered an ineffective treatment for the prevention of rUO in cats and other strategies should be considered clinically. We did identify that cats with a subjectively gritty urethra during catheterization or cats that were subjectively more challenging to unblock were more likely to experience rUO within 14 days of discharge. This population of cats warrants further study to identify interventions that may reduce their risk of rUO.

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