

Effects of multimodal environmental modification in crystal-related feline lower urinary tract diseases

[Efeitos da modificação ambiental multimodal em felinos com cristais
doenças do trato urinário inferior relacionadas a cristais]

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ABSTRACT

This study aims to analyze the effects of multimodal environmental modification (MEMO) of cats with recurrence of lower urinary tract signs (LUTS). Treatment of FLUTD included pharmacological treatment, dietary management, and multimodal environmental modification approaches. Twenty client-owned indoor-housed cats with recurrence of lower urinary tract signs had been covered in this observation. Diagnosis of lower urinary tract was made primarily based on the cat's clinical signs, results of laboratory parameters, urinalysis and ultrasonographic examination. Cats were divided into two groups as cefovecin (8 mg/kg sc, single time use) + meloxicam (0.1mg/kg q24h, 3 days) + dry food including l-tryptophan and milk protein hydrolysate to dissolve struvite stones (Group 1) and cefovecin + meloxicam + dry food including l-tryptophan and milk protein hydrolysate to dissolve struvite stones + multimodal environmental modification (Group 2). Clinical and urinary parameters are scored as 0, 1, 2, 3 or 4 points on initial, third, seventh days. Scores of clinical parameters were significantly different between ($p<0.05$) group 2 and group 1 on the third and seventh days and scores of urinary parameters are significantly different between ($p<0.05$) group 2 than group 1 on the seventh day. Clients who were contacted after 1 year reported that they did not see any clinical signs of urinary tract diseases.

Keywords: FLUTD, MEMO, cats, behavioral medicine, multiple treatment, cefovecin

RESUMO

Este estudo tem como objetivo avaliar os efeitos da modificação ambiental multimodal (MEMO) em gatos com recorrência de sinais do trato urinário inferior (LUTS). O tratamento da FLUTD incluiu tratamento farmacológico, controle dietético e abordagens de modificação ambiental multimodal. Vinte gatos de propriedade de clientes, alojados em ambientes fechados, com recorrência de sinais do trato urinário inferior foram incluídos nessa observação. O diagnóstico do trato urinário inferior foi feito principalmente com base nos sinais clínicos do gato, nos resultados dos parâmetros laboratoriais, na urinálise e no exame ultrassonográfico. Os gatos foram divididos em dois grupos: cefovecina (8 mg/kg sc, uso único) + meloxicam (0,1mg/kg q24h, 3 dias) + ração seca incluindo l-triptofano e hidrolisado de proteína do leite para dissolver cálculos de estruvita (Grupo 1) e cefovecina + meloxicam + ração seca incluindo l-triptofano e hidrolisado de proteína do leite para dissolver cálculos de estruvita + modificação ambiental multimodal (Grupo 2). Os parâmetros clínicos e urinários foram pontuados como 0, 1, 2, 3 ou 4 pontos no primeiro, terceiro e sétimo dias. As pontuações dos parâmetros clínicos foram significativamente diferentes entre ($p<0,05$) o grupo 2 e o grupo 1 no terceiro e sétimo dias, e as pontuações dos parâmetros urinários foram significativamente diferentes entre ($p<0,05$) o grupo 2 e o grupo 1 no sétimo dia. Os clientes que foram contatados após um ano relataram que não observaram nenhum sinal clínico de doenças do trato urinário.

Palavras-chave: FLUTD, MEMO, gatos, medicina comportamental, tratamento múltiplo, cefovecina

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INTRODUCTION

Feline lower urinary tract disease (FLUTD) is defined as different kinds of situations that could have an effect on the urinary bladder and urethra of cats (Grauer, 2013). Cats with FLUTD commonly present with signs of dysuria (straining), pollakiuria (increased frequency of urination), haematuria, urethral obstruction, periuria (inappropriate urination), and behavioral change (often aggression) and loss of litter-box training (Gun-Moore, 2003). FLUTD includes disorders such as feline idiopathic cystitis (FIC), cystolithiasis, urolithiasis, urethral plugs, urethral obstruction, bacterial infections, neoplasia, neurogenic causes, postsurgical iatrogenic injuries, congenital defects (Grauer, 2013; Gunn-Moore, 2008). In 55-69% of cats FIC is bound with FLUTD which is the major cause (Kruger *et al.*, 1991; Buffington *et al.*, 1997; Lekcharoensuk *et al.*, 2001). The pathophysiology of FIC is not clearly defined but the disease is seen mostly in young until middle of aged, over-weight cats which are less active in a day, using an indoor litter box and decreased access to the outside of the house, on a dry diet and living with multiple animal households (Cameron *et al.*, 2004; Gun-Moore and Shenoy, 2004; Buffington *et al.*, 2006a). The primary cause is unknown, but FIC is occurring when the action of the stress feedback system is accelerated with a reduced adrenocortical function in stressful situations (Westropp *et al.*, 2003; Buffington, 2004) leading to environmental stress; the final part of changes happens in the urinary bladder epithelium according to the cat's nervous and endocrine systems. Stress has an important role in triggering FIC and stressors including living in multiple households, litter box problems (access, position, type, hygiene, content), access to the outside, changes to environment and owner (Gun-Moore, 2008). Stress also affects a cat's drinking or eating habits that cause decreased water intake which has an important role in prevention from FIC and urolith formation (Lulich and Osborne, 2007; Buffington and Chew, 2007). A study shows that stress-associated alterations in urine pH were already suggested before present. The presence of hyperventilation and consequences of the sympathetic nervous system on the renal-tubular acid base balance causes the existence of alkaline urine and struvite crystalluria in a cat fed a diet that led to acidifying diet (Buffington and Chew,

1996; Lund and Eggertsdottir, 2018). Struvite crystalluria frequently was detected in feline idiopathic cystitis cases. Struvite crystals occur with magnesium, ammonium, and phosphate ions that dilute urine and pH play the most important role in their formation. Struvite crystals usually appear as colorless, three-dimensional, prism-like crystals (coffin lids) in microscopic evaluation. Urinary oversaturation with struvite may appear because of a urinary tract infection with a urease-producing bacteria or without the presence of infection as sterile struvite in cats (Bartges and Kirk, 2006). Specific nutritional management arranges to dissolve crystals and reduce the risk of recurrence later in their life (Queau, 2018). Urine pH is aimed to be generally between 6.0 to 6.4 to manage struvite while not developing the risk of occurring calcium oxalate crystal by using low-magnesium, urine acidifying dry diet. Studies show that there was at least a fifty percent reduction in struvite stone size by two weeks and total conversion by four weeks in most cases with using diet (Lulich *et al.*, 2013, Torres-Henderson *et al.*, 2017). Different new kinds of therapeutic diets were produced which do not intend to only protect the improvement of crystals, but also the management of the risk factors on occurring FIC. These diets are enriched with hydrolyzed casein and l-tryptophan ingredients are known to help manage stress and anxiolytic effects for cats (Landsberg *et al.*, 2017; Naarden and Corbee, 2019). A study about urinary stress diet (Hills Prescription Diet c/d Feline Urinary Stress) provides that diet develops both FLUTD signs and anxiety associated behaviors in cats shows FIC signs (Meyer and Becvarova, 2016). Additionally, FLUTD treatment contains several multipurpose choices. Cats with FLUTD have clinical signs of stranguria which is painful, particularly pain on abdominal palpation. A study has shown that between received orally administered meloxicam and placebo groups that treatment for obstructive FIC patients there were an important difference in pain on palpation of abdomen on the meloxicam administered group between day 1 and the re-examines (Dorsch *et al.*, 2016). Struvite crystals may occur with urinary tract infection (UTI) and asymptomatic bacterial cystitides are defined in cats. A study shows that live but unculturable bacteria are detected in the urine and DNA of bacteria has been identified in negative urine culture from cats (Lund *et al.*,

2015; Bartges and Kirk, 2006). Antimicrobial therapies are the key points of the treatment for urinary tract infections (UTI) and therapy which is commonly recommended for 10 to 14 days (Dunning, 2002; Passmore *et al.*, 2008). Clients complain during treatment and animals get more stress because many traditional antibiotics have a short life and need have repeated dosing. Cefovecin ingredient was founded to be an effective and safe treatment preference for UTI and useage is as follows single 8mg/kg subcutaneously injection effect expired to fourteen days can use for UTIs for cats (Passmore *et al.*, 2008). Effects of environmental stressors as an important trigger factor in the multifactorial etiology of FIC. Multimodal environment modification (MEMO) is defined as a system of changes in the cat's environment to try to reduce lower urinary tract disorder signs by reducing the possibility of activation of the stress feedback system in cats (Cameron *et al.*, 2004; Westropp and Eggertsdottir, 2004; Buffington *et al.*, 2006b). Avoiding punishing the cats when a client sees their unacceptable indoor elimination, diet changes, increasing water intake, litter box management (scent of litter, litter material, cleanliness of litter box, number of boxes, access to the box, location of the box, size of box), climbing structures, viewing and resting safe place, scratching posts, increased human-cat social interaction, different sensory stimulations when the client absent, an opportunity time for play and predatory behavior, administer multiple and separated environmental resources are approaches of decreasing the effect of environmental and social stressors (Buffington *et al.*, 2006b; Heath, 2019; Ellis *et al.*, 2013). The study evaluated with MEMO arrangements reduce the number and severity of the recurrent episodes of the LUTS and show significant reductions in fearfulness, nervousness, showing aggressive behavior (Buffington *et al.*, 2006a, Grauer, 2013). Pharmacological treatment, with a combination of environmental modification, is recorded to solve the problem of diseases and key points of the wellbeing of pets (Landsberg *et al.*, 2017).

MATERIAL AND METHODS

This study took place in the Department of Internal Medicine-Bursa Uludag University Animal Teaching Hospital with follow-up periods of 1 year. Ethical permission for this

study was given by the Animal Research Local Ethical Committee of Bursa Uludag University. Twenty client-owned indoor-housed cats aged from 2-6 years; 4 neutered females, 16 castrated males with at least 3 episodes of recurrence of lower urinary tract signs which naturally occur were included in this study. An episode of recurrence is described as showing at least 2 of these clinical signs: stranguria, haematuria, dysuria and pollakiuria. Diagnosis of the lower urinary tract was made based on the cat's clinical signs, results of hemogram (total blood counts), serum biochemistry levels (urea, creatinine), urinalysis (specific gravity, urine ph and microscopic evaluation of urine sediment as native and stained wet samples) and abdominal ultrasonographic examination of urinary bladder, urethra, and kidneys. Struvite crystals were defined by microscopic examination. Urine samples were collected with the cystocentesis method guided by USG each examination day. USG examination was completed for detection of patients who had visible struvite uroliths on their urinary bladders and urethras. Cats included groups who were diagnosed with crystal-related (struvite) feline lower urinary tract diseases and patients who only had microscopic struvite crystalluria were selected for groups. Cats were divided into two groups: treated with cefovecin (8mg/kg sc, single time use), meloxicam (0,1mg/kg q24h, orally, 3 days), urinary stress diet included l-tryptophan and milk protein hydrolysate alpha-casozepine to dissolve struvite stones (Group 1). Group 2 was treated with the combination of cefovecin (8mg/kg sc, single time use), meloxicam (0,1mg/kg q24h, orally, 3 days), urinary stress diet included l-tryptophan and milk protein hydrolysate to dissolve struvite stones and their owners applied our suggestions about multimodal environmental modification needs in their home (Buffington, 2006b; Naarden and Corbee, 2019; Dorsch, 2016; Passmore *et al.*, 2008). Participating animals were allotted to group 1 or group 2, build on the MEMO approaches they want to apply at home, this was based on the owner's choice. Owners apply to: create hiding/safe place; at least two fresh running water in a different accessible area for increasing water intake; water/food/litter box/resting place/play areas must be indifferent each other and easy-safe-quite- accessible areas; create playtime for predatory behavior; litter box number is 2 for each cat; both litter box locations must be in safe/ quite/ accessible place; litter

must be non-scented and cleaned every day; put scratching posts; open audio and video sensory if cat stays home alone as an environmental modification in their home condition (Buffington *et al.*, 2006b; Heath, 2019; Ellis *et al.*, 2013). We considered cats examination as clinical parameters (general demeanor, appetite, size of bladder, abdominal pain on palpation) are scored as 0, 1, 2, or 3 point and urinary parameters (hematuria, proteinuria, erythrocytes/hpf, leucocytes/hpf) are scored as 0, 1, 2, 3 or 4 points (Delille *et al.*, 2016). All scores that were determined and examinations were completed by the same veterinarians. Recheck examinations were completed in the initial (0 day), third, seventh and fourteenth days. Multimodal environmental modifications are followed on the initial day, and each recheck examination by videos and photos. Each case was followed for 1 year by client contact to define the effect of MEMO on lower urinary tract disorders signs.

STATISTICAL ANALYSIS

The results of daily clinical examinations and urinary parameter results were compared between groups on each day (day 3, 7, 14). Comparison of severity points within treatment groups between individual days and comparison of severity points between treatment groups on each day were achieved. Minitab16.1.0 (Minitab Inc., State College, PA, USA) software program was used for statistical analysis. Data were tested for normality using the Anderson-Darling model. Mann-Whitney U test was used for comparison of two groups in each day. Wilcoxon-T test completed for urinary and clinical parameter comparison between each examination day for each individual group. Values of $P < 0.05$ were considered significant in this statistical analysis.

RESULTS

We estimated both clinical and urinary score results of patients according to our scale. Separately two group urinary and clinical parameter scores were as observed statistically significant ($p < 0.05$) from with the day of diagnosis initial day to end of treatment (14.day). General condition and appetite scores were statistically significant ($p < 0.05$) between group 2 and group 1 on the seventh. Size of urinary bladder also had a significant difference ($p < 0.05$) between group 2 and group 1 in third and

seventh days. Scores of clinical parameters were significantly different between ($p < 0.05$) group 2 and group 1 on the third and seventh days and scores of urinary parameters are significantly different between ($p < 0.05$) group 2 and group 1 on the seventh day. There was no statistically significant difference between cats in group 1 and group 2 regarding hematuria dipstick, proteinuria dipstick, leukocytes in each day of treatment. Hemogram (total blood count), serum biochemistry levels (urea, creatinine) were detected in the normal range on first examination in all patients. The urinary pH levels were changed from alkaline to normal ranges at the end of treatment. Each client who was contacted after 1 year reported that any clinical signs of urinary tract diseases were not seen by them.

DISCUSSION

This research shows the positive effect of adding MEMO therapy on recurrence struvite crystal related to lower urinary tract disorders treatment in cats. Both treatment methods used in this study were effective and successful in healing the disorder both statistically and clinically. MEMO therapy has been observed to contribute to an earlier onset of recovery time. Environmental needs of animals are a fact of veterinary medicine and through that veterinarians must advise owners of the patient not only on preventive health care and medical situations, but also educate them about the importance of meeting the right environmental and behavioral requirements. Unwanted feline behaviors by owners and lots of diseases causes have been related to stressful environmental conditions (Westropp *et al.*, 2006; Tanaka *et al.*, 2012). One of those diseases, FIC, occurs primarily in combination with stress and neuroendocrine abnormalities (Buffington and Chew, 2007). Patients with FIC are commonly described as showing recurrent episodes and 39-65% of cats show recurrence within one to two years after the primary episode (Buffington, 2011; Kruger *et al.*, 2009). A study shows that cats were determined as having non-obstructive idiopathic cystitis at first onset; before detecting of uroliths or bacterial cystitis during later episodes of FLUTD (Lund and Eggertsdottir, 2018). Through that FIC can be a predisposing factor or underlying disorder as possible complications of other lower urinary disorders like urolithiasis, urethral plugs, bacterial cystitis.

Applying multimodal environmental modification as a behavior therapy to reduce potential stressors to cats with signs of FLUTD treatment independent of diagnosis should be recommended (Lund and Eggertsdottir, 2018; Buffington, 2006b; Seawright *et al.*, 2008). Clinical experiences show that the duration between the existence of a stressor and the appearance of clinical signs is forty-eight hours. In our study scores of clinical parameters decreased more in group 2 with MEMO than in group 1 on the third and seventh days after beginning the treatment combination. Stress also can affect changes in the drinking or eating arrangement of cats which has played an important role in the prevention of episodes of FIC and urolith formation. Hyperventilation or triggers of the sympathetic nervous system on the body affects renal tubular acid-base dynamics because alkaline urine causes struvite crystalluria even in cats fed an acidifying diet (Buffington and Chew, 1996, 2007; Lulich and Osborne, 2007; Lund and Eggertsdottir, 2018). Dietary management for the balance of urinary pH has an important role when treating a cat with crystalluria but it may not be enough to solve future recurrence problems of FIC occurrence. Stress diets were also effective to solve the risk causes related with idiopathic cystitis. These diets are enriched with alpha-casozepine and L-tryptophan which were determined to have anxiolytic effects on cats (Landsberg *et al.*, 2017; Kruger *et al.*, 2015; Naarden *et al.*, 2019). Total struvite cystolith dissolution was approximately two to five weeks with using the diet (Torres-Henderson, 2017). Both of our groups' scores of urinary parameters are significantly decreased and microscopic struvite crystals shape dissolution is complete at the end of the treatment. Many health conditions and medical procedures cause pain in cats. Loss of normal behavior (decreased appetite), expression of normal behavior (unacceptable elimination, vocalization, aggression), reaction to touch (palpation of regions likely to be painful), physiologic parameters create signs of pain. Painful conditions must be treated immediately which affects both the medical situation and welfare of the cats. FIC mostly appears to associate the pain of urination because of the release of substance P in the bladder wall due to stressors that trigger the sympathetic nervous system. Uroliths, ureterolysis, lower urinary tract disease, lower urinary tract infections are also

causes of pain. Pain during urination can also cause the cats to develop distress and show vocalization during urination (Seawright, 2007; Hellyer *et al.*, 2007). Meloxicam is a non-steroidal anti-inflammatory drug of the oxicam group with weak selectivity for cyclooxygenases-2 (COX-2) specialty that makes it more beneficial to use. The dose of oral meloxicam (Metacam 0.5 mg/ml) can use 0.1mg/kg initial dose and dose may be given once daily (at 24-hour intervals) for up to two days. The drug has a significant difference in pain in abdominal palpation on the first day of use in cats with FIC (Dorsch *et al.*, 2016). We continued to use meloxicam oral solution for both of our groups in the first 3 days and we observed both groups' abdominal palpation and bladder size scores are decreased in the third day. The cause of clinical parameters was significantly different between group 2 and group 1 on the third day and can be due to the effects of using both meloxicam and MEMO at the same time. It can be difficult to differentiate between a cat with asymptomatic bacteriuria or a cat with primary bacterial cystitis. Effective but unculturable bacteria and bacterial DNA positive bacteria but culture negative urines were detected in humans, mice, and cats (Anderson *et al.*, 2003; Dorsch *et al.*, 2016). Efficient and safe antibiotics were used in our groups. In vitro testing offers that bacterial species usually related to urinary tract infections which are sensitive to cefovecin usage. 8mg/kg single dose subcutaneous injection of cefovecin (Convenia 80 mg/ml) is used in cats and a single injection lasting up to fourteen days ensures compliance in this period (Passmore *et al.*, 2008). On the other hand, we know the multiple administration of drugs (tablets, subcutaneous or intramuscular injections) and veterinary clinic revisits causes stress in cats and their owners. Single-injection duration in 14 days may reduce stress in our groups too. The client who was contacted after 1 year reported that they did not see any clinical signs of urinary tract diseases so both treatments used in this study observed effective after 1 year.

CONCLUSION

Last of all, struvite crystals may occur because of stressful conditions besides many other factors. Multimodal environmental modifications are complementary therapy for indoor-housed cats that show lower urinary tract diseases signs and

provides shortened recovery time. Behavioral medicine is a big part of veterinary medicine science and an inseparable part of internal medicine. We must consider behavioral assessment of patients with any disorders that come to our clinics. Because if disorders being without stress and anxiety, recovery time can be shortened, life quality will be increased, clients are happier to learn to fix their cats problems and have more knowledge about cat's needs. Also, it is important to solve the cat's unacceptable urination problem quickly for us. Because the house soiling is one of the most common feline behavior problems accepted by cat owners and the biggest cause why owners abandon cats to animal shelters. Cats can be saved from this problem by veterinarians. So, adding behavioral preventive management to our patients' treatment list especially if they have any other internal diseases which have linked between stressors in underlying must be considered.

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