



Original article

Long-term efficacy of fulguration of trigonitis for recurrent urinary tract infections in women



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ABSTRACT

Objective: Women with a longstanding history of recurrent urinary tract infections (RUTIs) represent a challenging population because of gradual development of antibiotic resistance and frequent antibiotic allergies. We report on the long-term results of women with RUTIs and trigonitis who were treated using endoscopic fulguration and were prospectively followed.

Materials and methods: Following institutional review board approval, charts of non-neurogenic women with RUTIs (defined as ≥ 3 UTIs/y), no voiding dysfunction or incontinence, and normal upper tracts by imaging, who underwent cystoscopy with fulguration of trigonitis (CFT) under anesthesia with 1 year minimum follow up after CFT, were reviewed. Trigonitis was defined as a condition of inflammation of the trigone region of the bladder. The primary outcome was complete resolution of trigonitis based on follow-up office cystoscopy 6 months after CFT. The secondary outcome was the total number of antibiotic courses (AC) prescribed for UTI-related symptoms and/or positive urine cultures (PUC) following CFT. We hypothesized that patients with complete trigonitis resolution after CFT fared best.

Results: From 2004 to 2008, 33 women met the inclusion criteria with a mean follow up of 48 ± 19 months (range, 14–82 months). Resolution of trigonitis at 6 months was noted in 25 (76%) patients. This group averaged 0.51 ± 0.5 total AC and/or PUC/y compared with 2.03 ± 1.1 total AC and/or PUC/y for women with persistent trigonitis following CFT ($p = 0.006$).

Conclusion: Patients with resolved trigonitis at 6 months after CFT did best; however, both groups benefited from the procedure over time.

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1. Introduction

Women with recurrent urinary tract infections (RUTIs) are increasingly frequent and difficult to treat, in part because of drug allergies, side effects, and resistant strains.^{1–3} There have been advances in the understanding of the pathogenesis of UTIs in recent years that may explain the difficulty in treating RUTIs. In addition to retrograde ascent of bacteria up the urethra,⁴ studies in animal models have indicated that other mechanisms may be at play, including formation of quiescent intracellular reservoirs.⁵ Trigonitis is a condition of inflammation of the trigone region of the bladder diagnosed visually during cystoscopy. We hypothesized that in women with RUTIs and trigonitis, the trigone may be the reservoir site for UTI reinfection. Therefore, starting in 2004,

we chose to eradicate these sites using a minimally invasive outpatient technique consisting of cystoscopy with fulguration of trigonitis (CFT). The feasibility of such an approach has already been tested by Costantini et al⁶ using laser therapy, albeit in a very different subset of women with irritative symptoms and negative urine cultures. As time progressed, additional studies were performed in association with our microbiology unit, including trigonal biopsies to isolate bacterial species⁷ and test their ability to form a biofilm. This was made possible by the fact that CFT was done under general anesthesia and the site of biopsy was treated as part of the fulguration procedure. Furthermore, since 2007, CFT has been performed with other procedures such as urethral dilation, anterior compartment prolapse repair, or during bulking agent injections, and those patients have been followed over time in an institutional review board-approved long-term prospective study.

In this report, we were interested to find out if the initial group of women with RUTIs treated with only CFT (and no additional

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procedures) benefited in the long term, implying that the eradication of these presumed chronic bacterial reservoir sites from the trigone had a durable impact. Therefore, the aim of this study was to review the long-term outcome of women with RUTIs treated with CFT alone, including the rate of UTI recurrences following CFT.

2. Materials and methods

Medical charts of women who underwent CFT for RUTIs were reviewed from a prospectively maintained, institutional review board-approved, database. Included in the study were non-neurogenic women with RUTIs who had failed multiple courses of antibiotic therapy, had normal upper tract imaging studies, had at least 1 year of follow up, and underwent an office cystoscopy at 6 months after their CFT procedure. RUTI was defined as three or more UTIs/y. Exclusion criteria included neurogenic bladder, incontinence or voiding dysfunction requiring additional procedures at the time of CFT, and uncontrolled diabetes. Men were excluded due to small sample size. Also, patients who did not undergo follow-up office cystoscopy at 6 months, or patients with complicating urological factors that predisposed them to RUTIs such as chronic intermittent catheterization or indwelling catheters, were excluded. Demographic information, clinical examination, laboratory data including urinalysis and urine culture results, pre- and postoperative cystoscopic findings, imaging studies, and subsequent treatment data were collected from an electronic medical record (EPIC) and reviewed by a neutral investigator not involved with patient care.

There is no single evidence-based, accepted definition of RUTI to date; however, most literature defines RUTIs as three episodes of UTIs in the past 12 months or two episodes in the past 6 months.^{1,8} For our study, RUTI was defined as three or more episodes of uncomplicated (symptomatic) UTIs/y, with at least one documented positive culture in the past year. Trigonitis was defined as a chronic mucosal inflammation of the trigone region (not pseudomembranous trigonitis) or squamous metaplasia of the trigone,⁹ and was diagnosed during flexible urethroscopy. Urethroscopy consisted of a methodical inspection of the urethra for areas of urethritis and bladder neck polyps along with the trigone, bladder, and bladder neck (including retroflexion). Fig. 1 provides a typical example of trigonitis with pus pockets, bullous lesions, and submucosal calcifications. All endoscopic procedures were documented with pictures and performed by the same experienced urologist and/or his trained physician assistants. Women with

normal imaging of their upper urinary tracts, trigonitis findings, and RUTIs refractory to multiple courses of antibiotic therapy underwent a CFT procedure. However, women with incidental trigonitis findings on cystoscopy, but no history of RUTI were not included in this study.

CFT was performed on an outpatient basis under anesthesia using a 17.5-French female urethroscope and a fine-tip Bugbee electrode on a low setting of 20 to cauterize all inflammatory areas involving the trigone, or any adjacent inflammatory lesions that have spread beyond the margins of the trigone (Fig. 2). All procedures were performed by the same surgeon. Patients were discharged home on the day of surgery without a urethral catheter.

At or near 6 months after CFT, patients routinely underwent office cystoscopy to assess trigonal healing. This procedure was done after documentation of a negative urinalysis. Therefore, all studied patients had no ongoing infection at the time of this follow-up office cystoscopy. A healed trigone has complete resolution of trigonitis with no new lesions over the confine of the trigone. This follow-up office procedure was performed by a variety of clinicians (fellow trainees, physician assistants, or urologists). Pictures obtained for documentation were reviewed and compared with pre-operative and intraoperative CFT photographs to objectively document persistence or resolution of trigonitis. Patients were monitored long-term for repeat episodes of UTIs as documented by positive urine cultures (PUC), and/or any antibiotic courses (AC) prescribed for lower urinary tract symptoms suggestive of UTI, whether accompanied by a urine culture or not. The independent reviewer tallied these two outcome measures (PUC and AC) from EPIC without the knowledge of the cystoscopic findings at 6 months after CFT to avoid interpretation bias.

The primary outcome measure was complete resolution of trigonitis on follow-up office cystoscopy (Fig. 2), with photographic documentation preserved in EPIC. Secondary outcomes, determined through querying EPIC, were the total number of AC prescribed for UTI-related symptoms and/or PUC in the years following CFT. Not all women with PUC were treated and vice versa, not all women who received AC obtained a urine culture before treatment. Therefore, one or both of these events (AC and/or PUC) was chosen to study the course of RUTIs after CFT. Because these patients experienced ≥ 3 UTIs/y pre CFT, patients with zero total AC and/or PUC over the follow-up period after CFT were defined as “cured” of RUTI. Those who averaged between 0 UTIs/y and 2 UTIs/y, and more than two AC and/or PUC per year were defined as “improved” and “no improvement”, respectively. Of note, in this study, it was

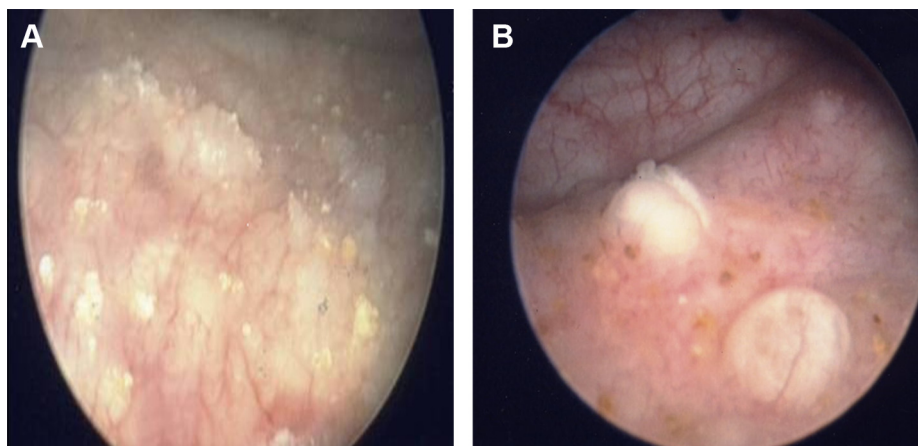


Fig. 1. (A) Flexible cystoscopy performed before fulguration reveals characteristic trigonitis with bullous edema and submucosal calcifications. (B) A closer view of trigonal inflammation shows two large mucosal pus containing pockets.

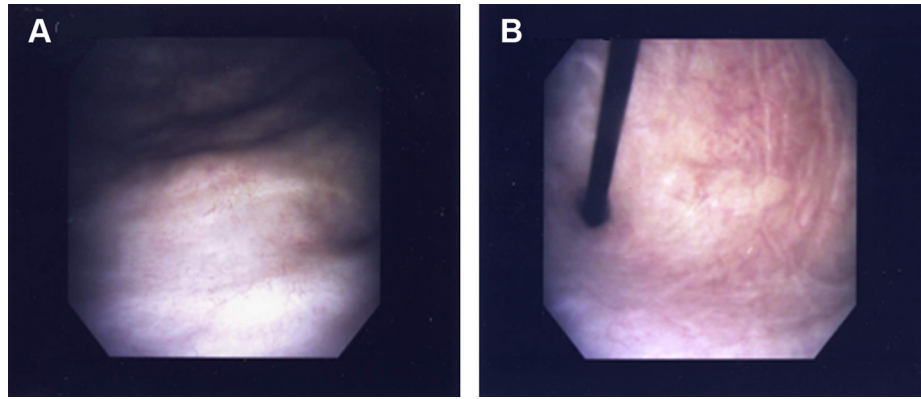


Fig. 2. At 6 months following cystoscopy with fulguration of trigonitis (A), office cystoscopy reveals a well healed trigone with no areas of residual trigonitis on retroflex view of the trigone (B).

verified based on office notes and review of the medication list that these patients were neither maintained on long-term antibiotic prophylaxis or coital prophylaxis, nor receiving cranberry supplements.

Data were analyzed using standard statistical software, SAS version 9.2 (SAS, Cary, North Carolina). The difference between the total number of AC and PUC over the total follow-up period for the two groups was compared using two-tailed paired *t* test for continuous variables and categorical values were compared using the Fisher's exact test. All results were evaluated at the $p < 0.05$ significance level.

3. Results

From 2004 to 2008, 33/92 women met strict study criteria with a mean follow up of 48 ± 19 months (range, 14–82 months). Excluded women were: neurogenic (5), had urethral dilation procedure (47), concurrent injectable agents (6), and were lost to follow up (1). Patient demographics are presented in Table 1. The majority were Caucasian, with a mean age of 70 ± 13 years (range, 37–92 years), and mean body mass index (BMI) of 25 ± 5 . Due to their fear of having another UTI between their office visit and the CFT procedure that could lead to a cancellation of the CFT procedure, 14/33 women (42%) elected to stay on a daily low dose antibiotic prophylaxis for a few days before their CFT procedure;

however, none stayed on long-term antibiotic prophylaxis after the CFT procedure.

Twenty five (76%) patients had a successful resolution of trigonitis after the CFT procedure, with a mean duration of follow up of 50 ± 19 months (range, 21–82 months), a mean age of 68 ± 14 years (range, 37–88 years), and mean BMI of 25 ± 6 . Among the eight patients with failed resolution of trigonitis based on office cystoscopy at 6 months, the mean duration of follow up was 41 ± 19 months (range, 14–63 months), with a mean age of 76 ± 11 years (range, 59–92 years), and mean BMI of 23 ± 3 . Baseline characteristics of both groups of patients are given in Table 1, and include the percentage of patients who were sexually active, had a hysterectomy, were incontinent, had diabetes, were on hormone replacement therapy, or were postmenopausal or had a bilateral oophorectomy. Overall, the baseline characteristics between both groups were statistically similar. Upper tract imaging was normal in all patients and no perioperative complications occurred. A comparison of preoperative versus postoperative urine cultures was of limited value in the success group, but was of greater value in the failure group, with six of eight women with similar bacterial strains; *Escherichia coli* (4), *Enterococcus* (2). The cystoscopically cured group averaged 0.51 ± 0.5 total AC and/or PUC/y compared with 2.03 ± 1.1 total AC and/or PUC/y for patients with some degree of persistent trigonitis by cystoscopy following CFT ($p = 0.006$; Table 2). Long-term outcomes, categorized as RUTI cure, improvement, or no improvement, are presented in Table 3. Thirty-two percent of the successful CFT group were completely cured. Overall, out of all patients treated with CFT, 30/33 (91%) patients were cured or improved following CFT.

Table 1

Baseline characteristics of women with successful and failed resolution of trigonitis based on office cystoscopy at 6 months after cystoscopy with fulguration of trigonitis (CFT).

	Successful CFT (<i>n</i> = 25)	Failed CFT (<i>n</i> = 8)	<i>p</i>
Follow up (mo)	50 ± 19 Range: 21–82 mo	41 ± 19 Range: 14–63 mo	0.19
Caucasian	96	100	> 0.99
Age (y)	68 ± 14	76 ± 11	0.13
BMI	25 ± 6	23 ± 3	0.37
Parity	2 ± 2	0.7 ± 1	0.09
Urinary	56	63	> 0.99
Hysterectomy	68	50	0.42
Menopause or oophorectomy	65	50	0.68
Hormonotherapy	24	25	> 0.99
Sexually active	36	50	0.68
Diabetes	12	0	0.56

Data are presented as mean \pm SD or %.
BMI = body mass index; SD = standard deviation.

4. Discussion

In this study we found that women who were cured of trigonitis lesions through CFT fared significantly better than those who had

Table 2

Mean number of antibiotic courses and/or positive urine cultures recorded for urinary tract infection-related symptoms during the follow-up period in both groups of patients.

	Follow up (mo), mean \pm SD	Average AC and/or PUC/y after CFT, mean \pm SD
Successful CFT (<i>n</i> = 25)	50 ± 19	0.51 ± 0.5
Failed CFT (<i>n</i> = 8)	41 ± 19	2.03 ± 1.1
		$p = 0.006$

AC = antibiotic courses; CFT = cystoscopy with fulguration of trigonitis; PUC = positive urine cultures; SD = standard deviation.

Table 3
Long-term outcomes, categorized as RUTI cured, improved, or no improvement.^a

	Successful CFT (n = 25)	Failed CFT (n = 8)
Cured	8 (32)	0 (0)
Improved	17 (68)	5 (63)
No improvement	0 (0)	3 (37)

Data are presented as n (%).

AC = antibiotic courses; CFT = cystoscopy with fulguration of trigonitis; PUC = positive urine cultures; RUTI = recurrent urinary tract infection; UTIs = urinary tract infections.

^a Patients who experienced ≥ 3 UTIs/y pre CFT, and patients with zero total AC and/or PUC over the follow-up period after CFT were defined as “cured” of RUTI. Patients who averaged between 0 UTIs/y and 2 UTIs/y, and those with two or more AC and/or PUC/y were defined as “improved” and “no improvement”, respectively.

remaining areas of trigonal infection on follow-up cystoscopy at 6 months after CFT. This finding (in addition to subsequent work on cultures of trigonal biopsies in these patients) supports the hypothesis that an infected trigone can serve as a reservoir for RUTIs. Moreover, both successful and failed groups showed improvement in UTI recurrence compared with pre CFT status.

There have been advances in the understanding of the pathogenesis of UTIs in recent years that may explain the link between an animal model for acute UTI and the findings of this study. A UTI is thought to begin with bacteria ascending into the bladder via the urethra.⁴ However, recent studies in a mouse model suggest that this is not always the case. Uropathogenic *E. coli* (UPEC) expresses type 1 pili, an adhesion that allows for attachment of UPEC to bladder epithelium.¹⁰ Once the UPEC have attached to the urothelium, they are internalized by the cells and rapidly multiply.¹¹ Following surface exfoliation, bacteria can invade deeper layers, resulting in quiescent intracellular reservoirs.^{5,12} Importantly, intracellular UPEC appears to be protected from a number of antibiotics, including mecillinam, cefuroxime, gentamicin, and trimethoprim-sulfamethoxazole.^{13–15} In fact, in one mouse model of UTI, a significant amount of UPEC could be found months after antibiotic treatment.¹⁶ Although not clearly established in humans, a similar cascade of events may result in RUTI, and could explain why these patients suffer from several bouts of infection despite multiple AC. Therefore, as supported by our results and significant long-term improvement in $>90\%$ of our patients treated with CFT, removal of these reservoirs in the trigone may have a superior benefit over prolonged and repeated antibiotic treatment courses.

Our results compare favorably with those of Costantini et al⁶ who prospectively analyzed 62 consecutive women who underwent laser diathermy of the trigone with either a side- or end-firing laser for refractory urethral syndrome consisting of urgency, frequency, and/or pain associated with negative urine cultures. At a mean follow up of 49 months, 68% of the patients who underwent side-firing laser had at least a 75% improvement in urinary symptoms. Although no patient had an active UTI, 61% had a history of UTIs, and the authors noted that these patients tended to improve more. They concluded that side-firing laser, which produced necrotic coagulation followed by reconstitution of normal functional epithelium, was significantly more successful and may destroy ‘bacterial factories’ in the bladder epithelium.⁶ Therefore, in their study, as in ours, removal of bacterial reservoirs in the trigone provided satisfactory results in the long run.

The clinical management of RUTIs includes, among others, vaginal estrogen therapy alone or in association with long-term prophylactic antibiotics.¹² In this contemporary series, the use of vaginal estrogen was relatively low, a finding tempered by a high rate of postmenopausal status in this cohort, the cost of oestrogen supplementation (which can be a deterrent), and the lack of sexual

activity in $>50\%$ of the participants. With regard to women with frequent UTIs who take prophylactic antimicrobial agents for extended periods, their rate of UTI will decrease while on prophylaxis, but will return to pretreatment rates once their prophylaxis is stopped.^{13,14} A Cochrane review of the literature indicated that such a prophylactic regimen can decrease the incidence of RUTIs in women.¹ However, that Cochrane meta-analysis determined that side effects are frequently seen in $>20\%$ of patients on antibiotic prophylaxis, and most commonly involve vaginal or oral candidiasis and digestive problems.¹ Therefore, enthusiasm for this prophylactic antibiotic-based approach can wane after patients experience adverse effects or when resistant bacteria arise. Lack of patient compliance and cost of medication are additional issues confronting patients on long-term prophylactic antibiotic treatment. Taken together, these multiple challenges related to vaginal estrogen supplementation and/or long-term antibiotic usage make CFT an appealing option, because it is a brief outpatient procedure with minimal side effects and clinical benefit as supported by our long-term results.

CFT as an alternative to long-term prophylactic antibiotic usage might also be viewed favorably as it could contribute to reducing the progression of antibiotic resistance. In the Antimicrobial Resistance Epidemiology in Females with Cystitis (ARESC) study, which consisted of nine European countries and Brazil, fosfomycin, mecillinam, and ciprofloxacin were found to have susceptibility rates of $>90\%$ for all countries, whereas antibiotics like ampicillin had a susceptibility rate of only 45%, cotrimoxazole of 70.5%, and amoxi-calvulanate of 82%.¹⁷ Therefore, lower susceptibility rates in conjunction with the frequent development of side effects in patients with a longstanding history of RUTIs increase treatment complexity and encourage the development of alternative therapies.

There are several strengths of this study: a single surgeon performed all CFT procedures; strict exclusion criteria were used so that women with additional voiding dysfunction requiring additional interventions (neurogenic bladder, urethral dilation, cystocele repair, etc.) were not studied as the pure benefit of the CFT procedure would have been harder to decipher; the primary outcome was based on cystoscopy at 6 months following CFT performed by various investigators and using photographic documentation pre- and postoperatively to allow neutral review of the CFT results; and long-term (mean 48 months) follow up was longitudinally collected. Therefore, the indication to proceed with CFT was very focused on women with RUTIs and extensive trigonitis with no additional procedure performed at the same setting. Additionally, the use of an electronic medical record facilitated the retrieval of UTI episodes by documenting the number of antibiotics prescribed for UTI-related symptoms and/or PUC results. Limitations included the limited cohort, the definition of trigonitis which is based on visual recognition (Fig. 1), and the possibility of patients receiving antibiotic therapy outside of our clinical setting or for a different condition. In addition, the numbers were too small to determine if sexual activity might have served as a contributory factor in the failure group. Other explanations for the failure group could be technical, suggesting the presence of bacteria already anchored to the bladder lining beyond the confines of the trigone and not visibly detectable or possibly liberated during the fulguration procedure itself. We have used gentamicin irrigation at the end of the procedure in some patients (since then and not in this series) but have not observed an additional benefit. Likewise, although the current trend favors a decrease in use of hormonal supplementation, the form of hormonal therapy (systemic or vaginal estrogen or both) might have fluctuated among participants over the course of the study follow up. Future studies with a larger patient population and the inclusion of subgroups that were

excluded in this study will be needed to corroborate this initial series.

5. Conclusion

In this retrospective study of a prospectively maintained database on non-neurogenic women with longstanding RUTIs refractory to multiple prior AC, fulguration of trigonitis resulted in a complete cystoscopic resolution of the trigonal lesions at 6 months postoperatively in 76% of the cohort. In this successful group, there was a significantly decreased need for antibiotic treatments for UTI-related symptoms and/or PUC results compared with the failure group with residual trigonitis. Therefore, CFT should be considered in the armamentarium of women with RUTI as growing antibiotic resistance, side effects, and cost, frequently complicate the care of these challenging patients.

Conflicts of interest

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

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