Gentamicin bladder instillations decrease symptomatic urinary tract infections in neurogenic bladder patients on intermittent catheterization

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Abstract

Introduction: This study aimed to determine if gentamicin bladder instillations reduce the rate of symptomatic urinary tract infection (UTI) in neurogenic bladder (NGB) patients on intermittent self-catheterization (ISC) who have recurrent UTIs. Secondary aims were to examine the effects of intravesical gentamicin on the organism resistance patterns.

Methods: We retrospectively reviewed our prospective NGB database. Inclusion criteria were NGB patients performing ISC exclusively for bladder drainage with clinical data available for six months before and six months after initiating prophylactic intravesical gentamicin instillations. Symptomatic UTIs were defined as symptoms consistent with UTI plus the need for antibiotic treatment.

Results: Twenty-two patients met inclusion criteria; etiology of NGB was 63.6% spinal cord injury, 13.6% multiple sclerosis. Median time since injury/diagnosis was 14 years and 6/22 (27.3%) had undergone urological reconstruction. Patients had fewer symptomatic UTI's (median 4 vs. 1 episodes; p<0.004) and underwent fewer courses of oral antibiotics after initiating gentamicin (median 3.5 vs. 1; p<0.01). Days of oral antibiotic therapy decreased from 15 before to five after gentamicin, but this did not reach significance. There were fewer telephone encounters for UTI concerns per patient (median 3 vs. 0; p=0.03). The proportion of multi-drug-resistant organisms in urine cultures decreased from 58.3% to 47.1% (p=0.04) and the rate of gentamicin resistance did not increase. Adverse events were mild and rare.

Conclusions: Gentamicin bladder instillations decrease symptomatic UTI episodes and reduce oral antibiotics in patients with NGB on ISC who were suffering from recurrent UTIs. Antibiotic resistance decreased while on gentamicin instillations.

Introduction

Urinary tract infections (UTI) are a common and morbid clinical problem in patients with neurogenic bladder (NGB), with cystitis diagnosed in 29.2–36.4% and pyelonephritis in 1.4–2.2% of NGB patients annually.[1] Urological conditions, including urosepsis and renal failure, were a leading cause of mortality among patients with spinal cord injury in the past. Modern urological care has decreased urological- related mortality significantly; however it still remains one of the eight leading causes of death in this population.[2]

Risk factors for UTI in the NGB population are poorly understood; however, decreased bacterial washout due to inefficient voiding, vesicoureteral reflux, and altered hydrokinetics, as well as alterations in protective flora or the urothelium itself are potential contributors to increased rates of infection.[3] Non-sterile intermittent self-catheterization (ISC), unfortunately does violate the main defense mechanisms of the bladder by introducing bacteria into the system, but is the standard of care for bladder management in NGB with chronic retention, with advantages over indwelling catheters and no proven disadvantages when compared to sterile catheterization.[4]

Strategies for preventing UTI in NGB patients on ISC are lacking in evidence.[5] Oral prophylactic antibiotics have been shown to delay the onset of bacteriuria,[6,7] but rarely have shown a decrease in symptomatic UTI.[8] Furthermore, many of these studies were conducted in an institutional setting in patients with acute spinal cord injuries, with varying endpoints and definitions of UTI,[9] and therefore may not be generalizable to community-dwelling individuals. Significant side effects of daily oral suppressive antibiotics can occur[8] and along with changing the genitourinary flora,[10] antibiotics can also affect the oral, pulmonary, skin, vaginal, and bowel commensals, and lead to increased findings of antibiotic-resistant organisms. Methenamine hippurate has also been trialed as an oral therapy to prevent UTI in NGB patients. Methenamine hippurate has fewer described side effects and organism resistance, but has not been shown to be effective in community-dwelling NGB patients.[11-13]

The use of daily intravesical gentamicin instillations for the prevention of UTI is a common clinical strategy in our institution for patients with NGB on ISC who have a history of very frequent symptomatic UTI. It is not used for patients

with asymptomatic bacteriuria since this does not require treatment. Also, only patients with a high number of recurrent UTIs are offered this treatment since a handful of UTIs in a year is not difficult to manage with oral antibiotics during infections. Animal models, in vitro studies, and human case series of patients with intact and surgically reconstructed bladders have indicated that gentamicin instillation are safe, with low or undetectable blood levels.[14-16] The effectiveness of intravesical gentamicin instillations to prevent UTIs in a clinical population performing ISC has been incompletely studied and is not in widespread use.

This study aimed to determine if gentamicin bladder instillations reduce the rate of symptomatic UTI and/or reduce the use of oral and intravenous antibiotics in NGB patients on ISC who had a high rate of recurrent UTIs. Secondary aims were to examine the effects of intravesical gentamicin on the bladder organisms and their resistance patterns detected on urine culture in this population. We hypothesize that this treatment does reduce the rate of symptomatic UTI and that the gastrointestinal and cutaneous organisms that are introduced with catheterization will remain susceptible to the gentamicin since the antibiotic is not systemically absorbed from the bladder.

Methods

The data source for this study is our prospective institutional review board-approved neurogenic bladder database. Inclusion criteria for this study were NGB of any etiology with bladder drainage exclusively managed with ISC for six months before and six months after initiating prophylactic intravesical gentamicin instillations. Providers used a compounded formulation of 480 mg gentamicin diluted in 1 L normal saline. A gravity instilled dose of 30–60 ml (14.4–28.8 mg) of the solution is instilled into the bladder (depending on bladder capacity) after drainage of urine is complete at the patient's last evening catheterization and left indwelling until the next catheterization. Nurse-lead teaching of patients and caregivers on instillation administration was based on a standardized institutional education protocol.

Exclusion criteria included patients receiving short-term instillations for treatment of an acute UTI only (≤14 days), <6 months followup, and discontinuation of ISC (due to placement of an indwelling catheter or urinary diversion). Symptomatic UTIs were defined by patient complaint of symptoms consistent with UTI (cloudy/foul-smelling urine, fevers, chills, increase in bladder spasms, pain, or leakage) combined with urine testing and antibiotic treatment. Urine smell and cloudiness alone (i.e., without other symptoms), given their high prevalence in this catheterizing population, were not considered UTI symptoms. Urinalysis and culture were routinely requested and UTI was defined as a positive leucocyte esterase and or nitrites on dipstick urinalysis or a urine microscopy with >10 WBC/hpf with a urine culture with $>10^5$ bacteria/ml. Occasionally, patients were not able to provide urine samples due to transportation issues; to avoid under-reporting UTI events, we included those calls with classic symptoms that were treated with antibiotics as UTI events. Multidrug-resistant organisms were defined as any organism with resistance to two or more antibiotics of different classes (penicillins, cephalosporins, fluoroquinolones, carbapenem, macrolide, tetracyclines, etc.).

Descriptive statistics were used to evaluate demographic characteristics and paired variables were evaluated before and after gentamicin instillations. For comparisons between included and excluded patients, Wilcoxon rank sum test and chi-square test or Fisher exact test were used for continuous and categorical variables, respectively. For pre-/post-gentamicin comparisons on symptomatic UTI, use of antibiotics, telephone encounters, and emergency department visits for UTI, Wilcoxon signed-rank test and McNemar test were used for continuous and categorical variables, respectively. For organism comparisons, considering the dependence between organisms belonging to the same culture or the same patient, Generalized Estimating Equations (GEE) model was used in order to take unknown correlation into account. All analyses were performed using SAS statistical software (version 9.3; SAS Institute Inc, Cary, NC, U.S.) and all testing was two-sided. The probability of type I error was set at 0.05.

Results

During the time period of 2010–2015, 50 subjects were identified who received intravesical gentamicin, and 22 met inclusion criteria. Of the 28 excluded subjects, 11 were excluded due to having less than six months followup, 11 due to short-term use of gentamicin for UTI treatment only, five due to use of indwelling catheters, and one due to a urinary diversion. Included subjects were a median of 37.5 years of age and were 59.1% male. The etiology of NGB was primarily spinal cord injury (63.6%), with 13.6% having multiple sclerosis, 9.1% myelodysplasia, and 9.1% tranverse myelitis. Median time since injury or diagnosis was 14 years (Table 1). Six of the 22 patients (27.3 %) had undergone prior urological reconstruction (bladder augmentation, ureteral reimplantation, catheterizable channel formation).

Before initiation of gentamicin irrigation, patients had a mean of four UTIs in the preceding six-month period. Patients had fewer symptomatic UTI's (median 4 vs. 1 episodes; $p<0.004$) and underwent fewer courses of treatment with oral antibiotics after initiating gentamicin (median 3.5 vs. 1; $p<0.01$). Median days of oral antibiotic therapy decreased from 15 days before gentamicin to five days after gentamicin, but this did not reach significance. Emergency department visits, hospitalizations, and courses of intravenous or intramuscular antibiotics were infrequent and no

Table 1. Patient demographics

Age (median)	37.5 years (range 18–75)
Gender	
Male	13 (59.1%)
Female	9 (40.9%)
Race	
White	19 (86.4%)
African-American	3 (13.6%)
Neurological condition	
Spinal cord injury	14 (63.6%)
Cervical	9 (64.3%)
Thoracic	5 (35.7%)
Lumbar	0 (0%)
Multiple sclerosis	3 (13.6%)
Myelodysplasia	2 (9.1%)
Transverse myelitis	2 (9.1%)
Other	1 (4.6%)
Time since injury or diagnosis (median)	14 years (range 1–45)
Comorbidities	
Diabetes mellitus	3 (13.6%)
Hypertension	4 (18.2%)
Mobility	
Ambulates	2 (9.5%)
Ambulates with assistive device	2 (9.5%)
Self-powered wheelchair	8 (38.1%)
Motorized wheelchair	9 (42.9%)

statistical difference was seen before and after gentamicin instillations. There were also fewer telephone encounters for UTI concerns per patient (median 3 vs. 0; p=0.03) after starting gentamicin instillations (Table 2).

Fewer patients used oral antibiotic prophylaxis after gentamicin instillations were initiated (6 vs. 1; p=0.03). The use of methenamine hippurate and oral cranberry supplements were similar before and after gentamicin instillations were initiated (Table 3).

With chronic antibiotic use, antibiotic resistance can develop; therefore, resistance patterns in urine cultures of patients receiving intravesical gentamicin were assessed. The proportion of multidrug-resistant organisms in urine cultures actually decreased significantly from 58.3% to 47.1% (p=0.04) after gentamicin was initiated, and the rate of gentamicin resistance overall in urine culture did not increase (Table 2). Two antibiotic-related adverse events were reported in patients in the six months before starting gentamicin: one episode of diarrhea and one patient requiring treatment for thrush. There were two adverse events reported post-gentamicin: one vaginal yeast infection and one episode of diarrhea.

Discussion

This is the largest reported series of adult NGB patients using intravesical gentamicin instillations for management of recurrent UTIs. Symptomatic UTIs decreased significantly in our subjects, from four episodes to one in a six-month period.

The prevention of UTIs among patients with NGB is

Table 2. Use of antibiotics, telephone encounters, and UTI characteristics before and after initiation of gentamicin instillations

	Before gentamicin	After gentamicin	p
Symptomatic UTI median (range)	4 (1–5) Interquartile 2–5	1 (0–2) Interquartile 1–1	0.004
Courses of oral antibiotics	3.5 (1–5) Interquartile 3–4	1 (0–5) Interquartile 1–2	0.01
Courses of IM or IV antibiotics	3 (27.3%)	1 (10.0%)	0.16
Days of antibiotic therapy	15 (1–34) Interquartile 7–24	5 (0–30) Interquartile 1–10	0.06
ED/Hospital visits for UTI	3 (27.3%)	1 (10.0%)	0.32
Telephone encounters for UTI	3 (0–6) Interquartile 1–5	0 (0–3) Interquartile 0–1	0.03
Multidrug-resistant organisms	21/36 (58.3%)	8/17 (47.1%)	0.04 OR 2.83 95% CI (1.03–7.79)
Gentamicin resistant organisms	2/33 (6.1%)	0/11 (0.0%)	NA
Organisms on all cultures* (number):			
Pseudomonas aeruginosa	3	1	NA
Klebsiella pneumonia	9	5	
E. coli	10	1	
Enterococcus	3	3	
Enterobacter	3	0	
Other organisms	2	1	
Multiple organisms	2	2	

*Not all UTIs had culture data available. IM: intramuscular; IV: intravenous; UTI: urinary tract infection.

Table 3. Other UTI prevention strategies used by patients for 6 months before and 6 months after initiation gentamicin instillations

	Before gentamicin	After gentamicin	p
Use of oral prophylaxis	6 (54.6%)	1 (10.0%)	0.03
Use of methenamine hippurate	3 (27.3%)	4 (40.0%)	0.32
Use of cranberry extract	1 (9.1%)	1 (10.0%)	>0.99

UTI: urinary tract infection.

vitally important to this vulnerable patient population, but has thus far fallen short.[17,18] A meta-analysis of oral antibiotic prophylaxis in acute and non-acute spinal cord injured patients showed no decrease in symptomatic UTI in non-acute patients.[19] The pooled data showed that in eight controlled studies of the effect of nitrofurantoin, methenamine, and trimethoprim/sulfamethoxazole, no agent was able to achieve a difference in weekly infection rates vs. controls.

The use of a variety of prophylactic bladder instillations, including intravesical gentamicin, is described in the literature, but only in small cohorts.[20] Chlorhexidine (trisdine), povidone-iodine, bacitracin, polymixin B, and colistin (polymixin E), have all been trialed for UTI prevention over the past several decades.[19] Other aminoglycosides, neomycin and kanamycin, have been studied as an intravesical agent since the 1970s.[9,21-23] Two contemporary series by DeFoor (80 children) and Wan (10 children) in the pediatric population included patients with vesicoureteral reflux, bladder augmentation and renal transplantation, and gentamicin instillations were found to be safe and effective at preventing bacteruiuria and UTIs.[14,16] McGuire and Savastono[15] (four women) and more recently Van Nieuwkoop[20] (two women) describe using intravesical gentamicin as effective treatment for non-neurogenic patients with difficult-to-manage, frequent UTIs.

This series of patients represents a difficult clinical problem of recurrent UTI in NGB patients on ISC. The 75% improvement in symptomatic UTI and telephone encounters for UTI over six months indicates that daily gentamicin instillation is an excellent option for prevention of UTI while actually decreasing antibiotic resistance patterns. Anecdotally, patients and their families also report a decrease in cloudy urine, foul odour, and caregiver concern for UTI. In addition, the therapy is minimally burdensome in that patients only add an additional step to one daily catheterization and the medication is easily stored and shelf-stable for at least two months.[14]

Our study subjects had a high rate of UTI, as well as a high rate of prior reconstruction and were selected by their provider to receive this intervention, which is a limitation of this observational, retrospective study that could impact the generalizability of the results. Another limitation is the lack of culture data on all patient infections due to geographic distance. The limitations of observational data collection also include the inability to compare gentamicin to placebo, to determine if the drug itself is having the effect, or if similar results would be obtained with daily saline irrigation. Irrigation with saline, ascetic acid, and neomycin-polymixin have been compared and found to have similar effects on bacteriuria in the community-dwelling spinal cord injured patient, but not in a population on intermittent catheterization as represented in our study.[24] A large-scale, randomized, placebo-controlled trial would help to answer this question.

Our results are reassuring in that antibiotic resistance and adverse events are rare in patients using daily gentamicin installations. We postulate that the observed decrease in antibiotic resistances after gentamicin washes are initiated is due to the decrease in overall oral antibiotic use by these patients. Waites et al demonstrated that oral antibiotics change the urinary, perineal, and urethral flora of neurogenic bladder patients.[10,24] The use of gentamicin instillations appears not to alter the flora, at least in the urine at the time of culture obtained for symptoms. Since stool cultures and the more sensitive PCR to detect bacteria not cultivable on standard media were not used in this study we cannot determine if the microbiome was altered. Our rate of adverse events is similar to those reported in other series.[9,14-16,20,22,23]

Oral antibiotic effectiveness for treatment of UTI is dependent on gastrointestinal absorption, renal excretion, and concentration in the urine. A threshold concentration is required for bactericidal effectiveness of any antibiotic, but it may not be possible to safely achieve adequate urine concentrations via oral or IV administration. The gentamicin concentration of this regimen is approximately 10-fold the typical urine concentration of gentamicin administered by the IV route,[25] which may explain the effectiveness of this treatment regardless of bacterial species or resistance patterns. Because the bowel and perineal flora that are introduced with each catheterization are gentamicin-naive, resistance should be expected to be infrequent. Prospectively studying the microbiome within and outside of the genitourinary tract of patients on gentamicin irrigations compared with patients receiving placebo could verify these assumptions.

Conclusion

Gentamicin bladder instillations decrease symptomatic UTI episodes by 75% and reduce the need for oral antibiotics in patients with NGB on ISC in this retrospective study without a placebo arm. Antibiotic resistance actually decreased while on gentamicin instillations, likely due to decreases in oral antibiotic needs. Larger, prospective, placebo-controlled (saline instillations) trials should be conducted to confirm these effects.

Competing interests: Dr. Cameron has received grants/honoraria from Allergan; and has been a primary investigator for a clinical trial supported by Medtronic. The remaining authors report no competing personal or financial interests.

This paper has been peer-reviewed.

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