SHORT COMMUNICATION

Effectiveness and safety of intravesical Gentamicin therapy in patients with recurrent urinary tract infections caused by multidrug resistant organisms

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Abstract

A prospective study was conducted at the Liaquat National Hospital and Medical College, Karachi, to determine the effectiveness, feasibility, and safety of intravesical Gentamicin therapy among patients presenting with recurrent urinary tract infections (rUTIs). All patients aged ≥15 years, who presented with recurrent UTI, having ≥3 positive urine cultures, with neurogenic bladder, intermittent catheterisation, symptomatic UTIs, and multidrug resistant cultures, were included in the study. Data were compiled and analysed using SPSS version 26. An ethics committee approved the study. A total of 69 patients were enrolled. Most common organisms were *Klebsiella* (52.2%), *E. coli* (27.5%) and gram -ve *bacilli* (14.5%). Multi drug resistance was observed in 18 (26.1%) patients, while effectiveness and safety were reported in 62 (89.9%) and 65 (94.2%) patients, respectively. Intravesical Gentamicin may be helpful in reducing the frequency of episodes and need for oral antibiotics in patients with UTIs, and demonstrated effectiveness and safety in most patients.

Keywords: Intravesical Gentamicin therapy, Recurrent urinary tract infections, Multidrug resistance organisms.

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Introduction

[1]The treatment of recurrent urinary tract infections (rUTIs) is becoming difficult due to increasing antibiotic resistance.[1] In the light of evidence, after counselling and behavioural modification, and a non-antibiotic prophylaxis, an antimicrobial prophylaxis is recommended.[2] A systematic review reported that the use of prophylactic antimicrobial therapy was effective in preventing RUTI in young patients as compared to placebo.[3]

According to the World Health Organisation (WHO), resistance to antibiotics is one of the gravest threats to health worldwide in the current era. The improper use of broad-spectrum antibiotics is believed to have contributed to this era of anti-microbial resistance (AMR). This AMR would result in increased morbidity and mortality, longer hospitalisation, and increased cost of medicines. Since the infections would no longer be treated with the first line antibiotics, more expensive medicines would be required to treat resistant organisms that may require a longer treatment duration. This would increase the healthcare cost and be an economic burden for society.[4]

It can be said that increasing resistance to antibiotics would mean that the availability of antibiotics will be limited in future. Evidence suggests that an increased antibiotic resistance in *E. coli* is responsible for causing UTI. It is also reported that age, female gender, as well as resistance to antibiotics are risk factors for rUTIs.[5]

In such patients, evidence highlights that intravesical instillation of Gentamicin reduced UTI infections and the level of resistance.[6] This method of intravesical instillation is effective in prophylaxis and treatment of rUTIs and provides an option to treat such patients with a high-risk of UTIs after other treatment modalities have failed.[7] The use of intravesical antibiotics (IVAs) may be a potential way of treating rUTIs topically that avoids systemic absorption.[8] It also avoids associated side effects while reducing systemic absorption.

The aminoglycoside antibiotics, such as Gentamicin, have concentration-dependent antimicrobial activity. At the site of infection, a higher concentration, that is more than the minimum inhibitory concentration (MIC), may be achieved.[9] The development of antimicrobial resistance is unlikely due to high drug concentration, as a higher concentration of antibiotic would result in bacterial death or growth retardation.[10] Intravesical instillation of Gentamicin has been reported to be safe and tolerated by selected sample of patients.[11]

The aim of this study was to determine the effectiveness, feasibility, and safety of intravesical Gentamicin therapy among patients presenting with rUTIs.

Material and methods

This was a prospective study conducted at Liaquat National

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Hospital and Medical College, Karachi from September 2021 to November 2021. The sample size was calculated with the help of an online sample size calculator by considering a prevalence of 11.6% for patients having UTI episodes in a Pakistani tertiary care setting as noted by Ullah et al.[12] Our sample was 69 and the margin of error was 7.56%. The confidence level was considered at 95%.[13]

The eligibility criteria included patients with rUTIs, who presented in the urology OPD, aged ≥15 years, with ≥3 +ve urine cultures, neurogenic bladder, intermittent catheterisation, symptomatic UTIs, and multidrug resistant cultures. Pregnant women, patients with hypersensitivity to Gentamicin, upper urinary tract abnormalities including urinary incontinence, presence of urinary stones, permanent urinary catheter, positive urine culture for high levels of Gentamicin resistance Enterococci or Enterobacteriaceae and glomerular filtration rate <15ml/ minute were excluded from study.

Patients were registered and an implied/written consent was taken. The patient' clinical history was taken by the investigator. A positive urine culture was mandatory for every patient. All the patients were given Gentamicin 80mg through intravesical route, diluted in 20ml of normal saline on alternate day for 14 days instilled via urethral catheter. Treatment outcomes were defined as patients becoming asymptomatic and negative urine culture up to three months after the first intravesical injection.

Statistical package for social sciences (SPSS) version 26 was used for data compilation and analysis. Data normality was checked by applying formal Kolmogorov-Smirnov test, and through informal graphical visualisation method. For continuous variables, descriptive statistics, i.e. mean±SD, for normally distributed data, and median with IQR for non-normally distributed data were calculated. For categorical variables, descriptive statistics were presented in terms of frequencies and percentages. The effect modifiers were controlled through stratification. Post stratification was done where applicable. The Chi square test or Fisher exact test was used to assess association among categorical variables, while the student t-test or Mann Whitney U test was applied for continuous variables, considering p-value ≤0.05 as statistically significant. The Ethics Review Committee of Liaquat National Hospital and Medical College granted approval (Ref: APP # 0569-2020 LNH–ERC).

Results

A total of 69 patients were enrolled, including 31 (44.9%) male and 38 (55.1%) females, with the mean age of 41.69±15.89 years. The most common past medical history was C-section in 18 (26.1%) patients. It was observed that 14 (20.3%) patients had diabetes mellitus, 44 (63.8%) had hypertension, and 24 (34.8%) had ischaemic heart disease (IHD), while 11 (15.9%) had no known comorbidity (NKCM). Most common organisms reported were *Klebsiella* in 36 (52.2%) patients, *E. coli* in 19 (27.5%) patients, and gram-negative *bacilli in* 10 (14.5%) patients. The median pre-void residual was 280, median post-void residual (PVR) was 26, median maximum flow (Q Max) was 20, median average flow (Q Avg) was 11, and median voided volume (V.V) was reported at 172. Detailed descriptive statistics are presented in Table 1.

Inverted bladder wall thickness, seen in 11 (15.9%) patients, was the most common ultrasonic kidney ureter bladder (USG KUB) observation. Detailed frequency distribution of USG KUB is presented in Table 2.

Multi drug resistance (MDR) was noted among 18 (26.1%) patients. A borderline significant association of multi drug resistance was reported with hypertension (p=0.047). No significant association was noted between other patient

Table-1: Patients' characteristics (n = 69).

Characteristics	n (%)
Gender	
Male	31 (44.9)
Female	38 (55.1)
History	
Angioplasty	10 (14.5)
C-section	18 (26.1)
Chest Infection	14 (20.3)
ESWL (R)	12 (17.4)
N/S	2 (2.9)
TURP	13 (18.8)
Comorbid	
Diabetes	14 (20.3)
Hypertension	44 (63.8)
IHD	24 (34.8)
NKCM	11 (15.9)
Outcomes (↕Mean ± SD / Median (IQR))	
Mean Age(years)↕	41.69 ±15.89
Pre-void	280 (120)
PVR	26 (60)
Q Max	20 (8)
Q Avg	11 (3)
V.V	172 (36)
Organism	
E.coli	19 (27.5)
Enterococcus	4 (5.8)
Gram negative bacilli	10 (14.5)
Klebsiella	36 (52.2)
Outcomes	
Multi drug resistance	18 (26.1)
Effectiveness	62 (89.9)
Safety	65 (94.2)

ESWL: extracorporeal shockwave lithotripsy; : Normal saline; TURP: Transurethral resection of prostate; IHD: Ischemic heart disease; NKCM: no known co morbidity; PVR: post-void residual; Q Max = maximum flow; Q Avg: average flow; V.V: voided volume.

characteristics and MDR. The details are presented in Table 3. The effectiveness was noted among 62 (89.9%) patients. No significant association was reported between patient characteristics and effectiveness. The details are presented in Table 4.

Safety was reported in 65 (94.2%) patients. No significant association was observed between patient characteristics and safety. The details are presented in Table 5.

Table-2: Frequency distribution of ultrasonographic findings.

Ultrasonographic findings	n (%)
Both kidney normal UB trabeculated	4 (5.8)
Both kidney normal UB trabeculated+sacculated prostate 38 gm	9 (13)
Inverted bladder wall thickness	11 (15.9)
Normal , UB normal	10 (14.5)
Normal prostate 18 gm	10 (14.5)
Normal prostate 35 gm	1 (1.4)
Normal UB wall thickness	10 (14.5)
Right kidney mild hydronephrosis, left kidney normal ulerythema trabeculated	4 (5.8)
Ureteric stone (R) 4-month L kidney M	10 (14.5)

UB: Urinary Bladder

Table-3: Comparison of multi drug resistance based on patients' characteristics.

Characteristics	Multi drug resistance n (%) / (Mean ± SD/ Median (IQR))		
	Yes	No	*p*-value
Total patients	18 (26.1)	51 (73.9)	
Mean Age(years)↕	39.22±17.25	42.56±15.47	0.447*
Pre-void	280 (120)	280 (120)	0.818
PVR	80 (60)	26 (60)	0.422
Q Max	21 (8)	20 (8)	0.712
Q Avg	11.50 (4.25)	11.00 (3.00)	0.944
V.V	172 (19)	172 (60)	0.474
Gender			
Male	9 (50)	22 (43.1)	0.615⊥
Female	9 (50)	29 (56.9)	
History			
Angioplasty	3 (16.7)	7 (13.7)	0.275
C Section	3 (16.7)	15 (29.4)	
Chest Infection	2 (11.1)	12 (23.5)	
ESWL (R)	6 (33.3)	6 (11.8)	
N/S	1 (5.6)	1 (2)	
TURP	3 (16.7)	10 (19.6)	
Comorbid			
Diabetes	4 (22.2)	10 (19.6)	0.999
Hypertension	8 (44.4)	36 (70.6)	0.047⊥
IHD	6 (33.3)	18 (35.3)	0.881⊥
NKCM	5 (27.8)	6 (11.8)	0.140
Organism			
E.coli	7 (38.9)	12 (23.5)	0.221
Enterococcus	1 (5.6)	3 (5.9)	
Gram negative bacilli	4 (22.2)	6 (11.8)	
Klebsiella	6 (33.3)	30 (58.8)	

↕Mean±Standard Deviation, *Independent t-test was applied; Mann-Whitney U test applied; Fisher exact test applied; ⊥Chi-square test was applied; $p \leq 0.05$, considered as significant; ESWL=extracorporeal shockwave lithotripsy; N/S=Normal saline; TURP=Transurethral resection of prostate; IHD=Ischemic heart disease; NKCM=no known co morbidity; PVR= post-void residual; Q Max=maximum flow; Q Avg=average flow; V.V=voided volume.

Table-4: Comparison of effectiveness based on patients' characteristics.

Characteristics	Effectiveness n (%)/(Mean±SD/ Median (IQR))		
	Yes	No	*p*-value
Total patients	62 (89.9%)	7 (10.1%)	
Mean Age(years)↕	41.95 ± 16.29	39.42 ± 12.52	0.694*
Pre-void	280 (120)	280 (120)	0.378
PVR	26 (60)	20 (60)	0.436
Q Max	20 (8)	21 (12)	0.321
Q Avg	11 (3)	10 (26)	0.652
V.V	172 (60)	165 (12)	0.172
Gender			
Male	27 (43.5)	4 (57.1)	0.692
Female	35 (56.5)	3 (42.9)	
History			
Angioplasty	9 (14.5)	1 (14.3)	0.087
C Section	16 (22.6)	2 (28.6)	
Chest Infection	14 (22.6)	Nil	
ESWL (R)	12 (19.4)	Nil	
N/S	1 (1.6)	1 (14.3)	
TURP	10 (16.1)	3 (42.9)	
Comorbid			
Diabetes	14 (22.6)	Nil	0.330
Hypertension	39 (62.9)	5 (71.4)	0.999
IHD	22 (35.5)	2 (28.6)	0.999
NKCM	11 (17.7)	Nil	0.587
Organism			
E.coli	17 (27.4)	2 (28.6)	0.663
Enterococcus	4 (6.5)	Nil	
Gram negative bacilli	8 (12.9)	2 (28.6)	
Klebsiella	33 (53.2)	3 (42.9)	

↕Mean±Standard Deviation, *Independent t-test was applied; Mann-Whitney U test applied; Fisher exact test applied; $p \leq 0.05$, considered as significant; ESWL=extracorporeal shockwave lithotripsy; N/S=Normal saline; TURP=Transurethral resection of prostate; IHD=Ischemic heart disease; NKCM=no known co morbidity; PVR= ost-void residual; Q Max=maximum flow; Q Avg=average flow; V.V=voided volume.

Discussion

Urinary tract infections (UTIs) are among the most commonly occurring bacterial infections affecting roughly 150 million people globally.[12,14]

In a systematic review, it was reported that most patients who had antimicrobial agent instilled through the intravesical route demonstrated adequate response with reduced frequency of UTIs. Moreover, the short-term treatment success was >85%. Seven out of the total 11 studies reviewed systematically had used Gentamicin.[7]

The use of various prophylactic bladder instillations, including intravesical Gentamicin, Neomycin, etc., has been described in the literature.[7] Gentamicin has been the most evaluated antimicrobial candidate for the prevention of UTIs over the past few decades. Available evidence

Table-5: Comparison of safety based on patients' characteristics.

Characteristics	Safety n (%)/(Mean±SD/ Median (IQR))		
	Yes	No	*p*-value
Total patients	65 (94.2%)	4 (5.8%)	
Mean Age(years)↕	41.95±15.73	37.50±20.42	0.590*
Pre-void	280 (120)	340 (210)	0.829
PVR	26 (60)	50 (60)	0.801
Q Max	20 (8)	13 (8.33)	0.089
Q Avg	11 (3)	7.5 (5.75)	0.072
V.V	172 (36)	165 (120)	0.610
Gender			
Male	28 (43.1)	3 (75)	0.319
Female	37 (56.9)	1 (25)	
History			
Angioplasty	9 (13.8)	1 (25)	0.955
C Section	17 (26.2)	1 (25)	
Chest Infection	13 (20)	1 (25)	
ESWL (R)	12 (18.5)	Nil	
N/S	2 (3.1)	Nil	
TURP	12 (18.5)	1 (25)	
Comorbid			
Diabetes	13 (20)	1 (25)	0.999
Hypertension	42 (64.6)	2 (50)	0.617
IHD	23 (35.4)	1 (25)	0.999
NKCM	11 (16.9)	Nil	0.999
Organism			
E.coli	19 (29.2)	Nil	0.194
Enterococcus	4 (6.2)	Nil	
Gram negative bacilli	8 (12.3)	2 (50)	
Klebsiella	34 (52.3)	2 (50)	

↕Mean±Standard Deviation; *Independent t-test was applied; Mann-Whitney U test applied; Fisher exact test applied; $p \leq 0.05$, considered as significant; ESWL=extracorporeal shockwave lithotripsy; N/S=Normal saline; TURP=Transurethral resection of prostate; IHD=Ischemic heart disease; NKCM=no known co morbidity; PVR=post-void residual; Q Max=maximum flow; Q Avg=average flow; V.V=voided volume.

highlights that treatment with Gentamicin instillations was safe and effective in the prevention of bacteriuria and UTIs.[15] Most recent and updated evidence also supports the notion of intravesical instillation with aminoglycosides for safe and effective treatment of UTIs.[16]

The idea of intravesical drug administration lies in uroepithelium, the transitional epithelium that spreads through the inner surface of the bladder. This layer is known for a complex preventive action that allows the instillation of potentially toxic drugs to achieve a localised pharmacological effect while preventing systemic effects.[17]

It is evident that a high antimicrobial concentration can be achieved with intravesical administration of aminoglycosides. Due to the polar cationic nature, diffusion of aminoglycosides across the uroepithelium is even more limited. This concentration is achieved with minimal risk of side effects, such as nephrotoxicity or ototoxicity.[16] Most patients in this study were infected with MDR *E. coli*, therefore, it was decided to give intravesical aminoglycoside (IVA) treatment with comparatively high doses of Gentamicin for prevention of further emergence of resistance.

Compared to the previous studies, 80mg dose was considered significantly higher.[16,17] This may be termed as an over-treatment, but as it has been observed and reviewed in literature it can be concluded that optimal dosage remains unclear. However, in treatment with high doses, systemic absorption of Gentamicin was not observed because serum levels were repeatedly not determined. This is in support of the hypothesis that systemic side-effects should not be expected with IVA.

The results of this study confirm that resistance to antibiotics and adverse effects are minimal in patients using daily Gentamicin units. It can be hypothesised that the reduction in resistance to antibiotics after administration of Gentamicin lavage is due to the reduction in total oral/parenteral antibiotic use among these patients.

The treatment with Gentamicin instillations does not appear to alter the flora, at least in the urine at the time of culture. As this study did not use stool culture and more sensitive PCR to detect bacteria not cultured on standard media, it cannot be determined whether the microbiome has been altered. The frequency of adverse events in the current study was similar to that reported by other studies.[7,16]

The effectiveness of oral antibiotics for the treatment of UTIs may depend upon renal excretion, urinary concentration, etc.[18] It is known that changes occur in microbiome in urinary tract owing to oral antibiotic use.[19] However, it has been reported that IVA using Gentamicin do not alter the flora and, therefore, it is expected that AMR would be rare. Though, the evidence may be anecdotal. The duration of intravesical treatment with Gentamicin should be assessed based on an individual assessment of the risk-benefit ratio as there is a paucity of data pertaining to long-term follow-up of patients treated with intravesical aminoglycosides.

Conclusion

It can be concluded that treatment with IVA Gentamicin may be helpful in reducing the frequency of episodes and the need for oral antibiotics in patients with UTIs which shows its effectiveness, and safety. However, more studies are required to assess the long-term effectiveness of IVA Gentamicin treatment in the said patient group.

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Author Contribution:

ZM: Carried out all aspects of the research and preparing of the manuscript.