The Effect of Oral Co-trimoxazole on Decreasing Bacterial Adherence and Biofilm Formation on Ureteral Stents Surfaces

Mohammed S. Abdel-Kader [a], Omar Mohamed [a], Mohamed Alemam[b], Mohamed El-Gelany[a], Mostafa AbdelRazek[a]

[a]Urology Department, Faculty of Medicine, South Valley University, Qena, Egypt.
[b]Clinical and Chemical Pathology Department, Faculty of Medicine, South Valley University, Qena, Egypt.

Background: Double J ureteral stents have been widely used in urological practice. They are liable to biofilm formation on their outer or inner surfaces.

Objectives: To assess the effect of oral co-trimoxazole on decreasing bacterial adherence and biofilm formation on double J ureteral stent surfaces and subsequent post-operative urinary tract infection.

Patients and methods: 109 patients undergoing double J ureteral stent insertion in our department randomized into two groups group A (55 patients) not taking any antibiotics during the indwelling time "control group" and group B (54 patients) on oral co-trimoxazole (2 TMP mg/kg/day) during the indwelling time. Two weeks post double J stent insertion, urine analysis was done for all patients and urine culture was done for patients with significant pyuria (WBCs => 20 by high power field). One-month post-operative, double J stent was removed anda segment of about 3-5 cm is sent for culture. All results recorded and analyzed with Statistical Package for Social Science® (SPSS) and Microsoft Excel 2010.

Results: 63.6% of group A (35 patients) were positive stent culture, while 37% of group B (20 patients) were positive stent culture. Escherichia coli was the organism most commonly isolated from the stent culture in both groups.

Conclusion: This study shows that oral co-trimoxazole has a role on decreasing bacterial adherence and biofilm formation on double J ureteral stent surfaces.

Key words: Double J ureteral stents, Biofilm, Co-trimoxazole.

Introduction

Ureteric stents are commonly used in urological practice **(Mohan-Pillai et al., 1999)**. They were first described in 1967 by Zimskind et al. **(Zimskind et al., 1967)**. Ureteric stents are used after treatment of kidney and ureteric stones, for relieving renal obstructions and after urological procedures such as kidney transplantation, ureteric stricture **(Soylu et al., 2007)**. However, complications such as stent obstruction, migration and encrustation, biofilm and stone formation may occur **(Lojanapiwat, 2005)**.

Biofilm is a population of cells which are growing on the stent surface and are enclosed in an exopolysaccharide matrix that may result in blocking of the lumen **(Desgrandchamps et al., 1997)**. Biofilm development occurs when bacteria transfer from a planktonic (free) existence to a lifestyle in which micro-organisms are firmly attached to the surfaces of the ureteral

stents. Then, exopolysaccharideglycocalyx polymers produced, a matrix in which microcolonies grow to form biofilms (**Costerton et al., 1987**).

Co-trimoxazole is a combination of trimethoprim and Sulfamethoxazole which has good activity against the common urinary tract pathogens including S. saprophyticus(**Marrie and Kwan, 1982**).

Patients and Methods:

Study design:

This study is prospective randomized clinical study for patients underwent double J ureteral stent insertion inurology department, Qena university hospital from May 2018 to October 2019.

Sample size:

109 patients underwent double J ureteral stent insertion.

Patient grouping:

We planned to have two groups each group with at least 50 cases using closed envelope method.

Group A:55 patientswith double J ureteral stent without taking any antibiotics during the indwelling time.

Group B:54 patientswith double J ureteral stent on oral co-trimoxazole during the indwelling time. The dose is 2 (TMP) mg/kg/day (prophylactic dose).

Patient selection:

Inclusion criteria:

All patients underwent double J ureteral stent insertion (Polyurethane double J stent), with indwelling time of 4 weeks.

Exclusion criteria:

1. Patients with preoperative urinary tract infection.
2. Patients underwent long term double J ureteral stent insertion.
3. Patients with hypersensitivity to sulpha drugs.
4. Pregnant and lactating women.
5. Children less than 3 months.
6. Patients with megaloblastic or folate deficiency anemia.
7. Patients with significant renal or hepatic impairment.

Preoperative evaluation protocol:

1. History and clinical examination.
2. Pre-operative urine analysis: to exclude urinary tract infection; as patients with urinary tract infection are excluded from the study.

Intra-operative:

Selective urine sample it is obtained intraoperative from the ureter through the ureteroscope before Polyurethane double J stent insertion and then urine sample is sent to the laboratory to be analysed to exclude urinary tract infection.

Post-operative follows up:

1. After two weeks: Urine analysis is done and urine culture in cases with significant pyuria (=>20 WBCs per high power field).
2. At double J stent removal after 4 weeks: Under complete aseptic conditions in the operating theatre; the double J stent is removed by the cystoscope, a segment of about 3-5 cm from the double J ureteral stent is obtained in a previously prepared sterile cup and sent to the laboratory for culture.

Results:

This study was conducted at Urology department;Qena University Hospital with about 109 patients underwent double J

ureteral stent insertion, randomized into two groups.

The mean age of each group compared, shows no statistically significant difference between two groups in **Table 1** group A ± 41.73 years while in group B ± 39.52 years.

Sex distribution in**Table 2** shows no statistically significant difference between two groups.

Two-weeks post double J stent insertion, urine analysis was done for all patients. Significant was detected in the urine analysis of 40 cases (72.7%) in group A and 22 cases (40.7%) in group B. There is statistically significant difference in pyuria between two groups in **Table 3**.

Urine culture was done for the patients with significant pyuria. It shows no statistically significant difference the between two groups in **Table 4**. Escherichia coli was the organism most commonly isolated from the urine culture in both groups.

After double J stent removal, a segment of 3-5 cm of the double J stent was sent for culture. The results of culture of the indwelling ureteral stents showsstatistically significant difference between the two groups in**Table 5**. Escherichia coli was the organism most commonly isolated from the stent culture in both groups.

Table 1 Age distributionof the studied groups

	Group A	Group B	P value
Number	55	54	
Age (years) Mean	41.73	39.52	0.527
Standard deviation	14.83	20.91	

Table 2 Sex distribution of the studied groups

	Group A	Group B	P value
Male	37 (67.3%)	31 (57.4%)	0.288
Female	18 (32.7%)	23 (42.6%)	
Total	55 (100%)	54 (100%)	

Table 3Frequency and percentage of significant pyuria in the urine analysis of the studied groups

	Group A	Group B	P value
Positive	40 (72.7%)	22 (40.7%)	0.001*

Table 4 Data of urine culture of the patients with significant pyuria in the studied groups

	Group A (N=40)	Group B (N=22)	P value
E-coli	4 (10%)	3 (13.6%)	0.669
Klebsiella	2 (5%)	0 (0%)	0 .29
Pseudomonas	1 (2.5%)	1 (4.6%)	0.665
Staph.	1 (2.5%)	0 (0%)	0.458
Candida	1 (2.5%)	0 (0%)	0.458
Patients with positive urine culture	9 (22.5%)	4 (18.2%)	0.692
Patients with negative urine culture	31 (77.5%)	18 (81.8%)	0.692

Table 5 Data of double J ureteral stent culture of the studied groups

	Group A (N=55)	Group B (N=54)	P value
E-coli	19 (34.5%)	8 (14.7%)	0.017*
Klebsiella	8 (14.6%)	7 (13%)	0.81
Pseudomonas	4 (7.3%)	3 (5.6%)	0.714
Staph.	2 (3.6%)	0 (0%)	0.159
Candida	2 (3.6%)	2 (3.7%)	0.985
Patients with positive urine culture	35 (63.6%)	20 (37%)	0.005*
Patients with negative urine culture	20 (36.4%)	34 (63%)	0.005*

Discussion:

In recent years, the use of ureteral stents has increased in urological practice. However, Ureteral stents lead to the formation of foreign bodies such as biofilms. Studies have shown that biofilms formed by microorganisms are responsible for approximately 65% of nosocomial infections. As the use of ureteral stent increased, the incidence of complicated urinary tract infection, which is one of the most complications of ureteral stent, also increased **(Tenke et al., 2012)**. Infection associated with urinary stents can lead to significant morbidity such as acute pyelonephritis, bacteremia, renal failure and even death **(Paick et al., 2003)**.

Bacterial colonization on the ureteral stent plays an important role in the pathogenesis of stent-associated infections **(Liaw and Knudsen, 2016)**. In addition, biofilms provide foci of infection for other parts of the body through biofilm sloughing and bacterial detachment **(Marshall, 1992)**. Thus, prevention of bacterial adherence to indwelling catheters or host cells themselves may reduce biofilm-associated infections **(Elves and Feneley, 1997)**.

Reid et al. found that oral administration of ciprofloxacin and ofloxacin in 40 patients with ureteric stents led to drug levels on the device surfaces that were higher than MIC of E. coli, P. aeruginosa, E. faecalis and S. aureus. Also, no bacteria were isolated from patients' urine and no biofilm were detected **(Reid et al., 2001)**.

In this study, we discussed the effect of oral co-trimoxazole on decreasing bacterial adherence and biofilm formation on double J ureteral stent surfaces and subsequent postoperative urinary tract infection.

We preferred the use of co-trimoxazole as an antibiotic because it is a combination of trimethoprim and sulfamethoxazole; which are two drugs acting on sequential steps in the pathway of an obligate enzymatic reaction in bacteria; thus, having synergistic effect **(Hitchings, 1961)**.

109 underwent double J ureteral stent insertion inour urology department, randomly divided into two groups using closed envelope method group A (55 patients 50.49%) with double J ureteral stent without taking any antibiotics during the indwelling time and group B (54 patients 49.54%) with double J ureteral stent on oral co-trimoxazole during the indwelling time. The mean age in our study is41.73 in group A (range 1-69) which not differ from that of group B 39.52 (range 2-68).

In our study, there was no statistically significant difference in gender in both groups as group A males 37 (67.3%) females 18 (32.7%) while in group B males 31 (57.4%) females 23 (42.6%)**.**

After two-weeks urine analysis revealed that 72.7% in group A have significant pyuria (=>20 WBCs per high power field); this matches the results of Pooli et al. (2016)**(Pooli et al., 2016)**.

This percentage decreased to 40.7% in group B. There is statistically significant difference (p= 0.001).

Urine culture for the patients with significant pyuria revealed that 9 out of the 40 (22.5%) of group A were positive urine culture. There is poor correlation between positive findings on urine analysis and positive urine culture in patients with indwelling ureteral stent and therefore the use of urine culture to diagnose urinary tract infection is necessary. This matches the results of Pooli et al. (2016)**(Pooli et al., 2016)**. In group B this percentage decreased to 18.2%. There is no statistically significant difference after the use of co-trimoxazole as urine culture was done only for patients with significant pyuria (small sample size) (p= 0.692). Escherichia coli was the organism most commonly isolated from the culture in both groups.

Stent culture revealed that 63.6% of the patients of group A were positive culture. This is close to the results of Kehinde et al. (2004) **(Kehinde et al., 2004)**. The most common organisms were E. coli, Klebsiella and Pseudomonas. This is also close to the results of Kehinde et al. (2004) **(Kehinde et al., 2004)**. In group B this percentage decreased to 37%. There is statistically significant difference between both groups (p= 0.001).

Limitation of the study:

The number of patients was not high enough to reduce the impact of statistical error during analysis. Urine culture was done only for patients with pyuria not all the study groups, thus comparison between the results of urine culture and stent culture was not possible, also patient co-morbidities should have been taken in consideration and these are the limitations of our study.

Conclusion:

Oral co-trimoxazole has a role on decreasing bacterial adherence and biofilm formation on double J ureteral stent surfaces.

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