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Comparative Study of Efficacy of Piperacillin/ Tazobactam and Cefoperazone/ Sulbactam Combinations in Hospitalised Patients of Complicated Urinary Tract Infections

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Abstract: Complicated UTIs (cUTIs) are one of the leading causes of the gram negative bacteraemia which occur in patients who have a functionally, metabolically, or anatomically abnormal urinary tract. The primary objective of this study was to compare efficacy of Piperacillin/Tazobactam (PT) and Cefoperazone/Sulbactam (CPS) combinations in complicated Urinary Tract Infections. At entry, total 92 patients admitted in the hospital due to cUTI were enrolled. Among of 92 patients, 49 patients were given PT while 43 patients were given CPS combinations. Clinical symptoms were registered and scored as mild (1) moderate (2) or severe (3). The follow-up were done daily till the patient is discharged. Thereafter, one follow up visit was done within 4 to 9 days of after discharge, termed as test of cure (TOC). Furthermore, one late follow up visit after 6 to 8 weeks was done, known as late follow up visit (LFU). Clinical assessments and microbiological analysis were done at the time of TOC and LFU. The mean baseline clinical score for PT and CPS were 10.89 ± 2.23 and 10.28 ± 2.33, respectively. At TOC visit, PT and CPS groups, clinical scores were 0.86 ± 2.35 and 1.36 ± 3.48, respectively; suggesting significant improvement from baseline ($p< 0.001$). Rate of clinical improvement at TOC visit was 92.68% and 87.50%, while microbiological cure rate was 87.80% and 93.75% with PT and CPS groups respectively. While, at LFU visit, clinical scores in PT and CPS groups were 1.32 ± 3.37 and 1.65 ± 3.56, respectively, suggesting significant improvement from baseline ($p < 0.001$). Clinical cure rate at LFU visit was 87.80% and 87.75% while microbiological cure rate at LFU visit was 82.92 and 77.00% in PT and CPS groups, respectively. These results suggest that both regimens have no significant difference for the treatment of cUTI. PT and CPS, both the combinations, are equally efficacious in treatment of cUTI.

Keywords: UTI, Piperacillin, Tazobactam, Cefoperazone, Sulbactam, Complicated UTI.

INTRODUCTION

After respiratory tract infections and gastro-intestinal infections, urinary tract infections (UTI) are the third most common infections, In fact, bacterial infections of the urinary tract are the most common cause of both community acquired and nosocomial infections for patients admitted to hospitals. A complicated urinary tract (cUTI) infection is a urinary infection occurring in a patient with a structural or functional abnormality of the genitourinary tract. Complicated urinary tract infection (cUTI) is defined in various ways by different authors. It can be defined as that which occurs in a patient with anatomically abnormal urinary tract or significant medical or surgical comorbidities [1]. It is also defined as that occurring in individuals with functional or structural abnormalities of the genitourinary tract [2]. The most common uropathogen causing cUTI are the Gram negative organisms [3] *E. coli* is the most common organism causing cUTI [4]. The most common determinant of infection is interference with normal voiding, leading to impaired flushing of bacteria from the genitourinary tract. Mechanisms of infection include obstruction with incomplete urinary drainage, persistence of bacteria in biofilm on stones or indwelling devices or increased introduction of organisms into the genitourinary tract through instrumentation [5].

Identification of patients with Complicated Urinary Tract Infections [6]

1. Men
2. Children
3. Nosocomial infection
4. Women

- Known lesion on prior diagnosis
- Functional or structural urinary tract anomaly
- Obstruction (e.g. Stone, Uretero-Pelvic Junction obstruction)

- Pregnancy
- Diabetes
- Spinal cord injury
- Neurological disorders (e.g. Multiple sclerosis) that affects bladder function
- Indwelling catheter
- Co morbidities that predispose to papillary necrosis (e.g. Sickle cell disease, severe diabetes, analgesic abuse, pseudomonas species infection)
- Infection with an unusual organism (e.g. tuberculosis)

5. Suspected lesion based on history
- Unresolved Urinary Tract Infections -failed response to antimicrobial therapy
- Bacterial persistence (recurrent Urinary Tract Infections with the same organism)
- Infection with urea splitting organism
- Recurrent febrile Urinary Tract Infections as a child

6. Suspected lesion based on symptoms
- Febrile Urinary Tract Infections (especially > 3 days)
- Renal colic
- Gross hematuria

A wide variety of genitourinary abnormalities may be associated with complicated urinary infection [2].

Obstruction

Ureteric or urethral strictures, Tumours of the urinary tract, Urolithiasis, Prostatic hypertrophy, Diverticulae, Pelvicalyceal obstruction, renal cysts, and congenital abnormalities.

Instrumentation

Indwelling urethral catheter, Intermittent Catheterization, Ureteric stent, Nephrostomy tube, Urological procedures

Impaired voiding

Neurogenic bladder, Cystocele, Vesicoureteral reflux, Ileal conduit

Metabolic abnormalities

Nephrocalcinosis, Medullary sponge kidney, Renal failure, Diabetes Mellitus.

Immunocompromised

Renal transplant

The purpose of this study was to evaluate efficacy of Piperacillin/Tazobactam and Cefoperazone/Sulbactam combinations used in the treatment of complicated UTI. The study can help in selecting correct antimicrobial combination treatment of complicated UTI in future. The primary objective of this study was to compare efficacy of Piperacillin/ Tazobactam and Cefoperazone/Sulbactam combinations in complicated Urinary Tract Infections. While, secondary objectives of this study were to evaluate sensitivity of causative organisms and to generate guidelines to the prescriber

MATERIALS AND METHODS

The study was continuous, longitudinal, prospective, single centre, cohort study which consist the cases of complicated urinary tract infections only, without blinding. Male and female patients of all ages, admitted in the wards Institute of Kidney Disease & Research Centre, Ahmedabad were enrolled. Institutional ethics committee approval was taken. No healthy volunteers were allowed to participate in study. However, Patients with the following conditions were excluded: 1) Treatment with another antimicrobial due to any other condition. 2) Uncomplicated UTI. 3) Renal transplantation. 4) Immunocompromised status. 5) Prostatitis. 6) Severely ill patients requiring prolong dialysis. 7) History of allergy.

The study had included total 92 patients admitted in the hospital due to cUTI. Among of 92 patients, 49 patients were given Piperacillin/ Tazobactam, while 43 patients were given Cefoperazone/ Sulbactam combinations. Patients were classified as having cUTI based on the criteria defined by Rubenstein and Schaeffer [5]. Informed consents were obtained from all patients. At the time of admission detailed clinical history was taken including chief complaints, physical examinations, laboratory investigations regarding the case and data regarding the drugs prescribed and adverse drug reactions was recorded in the Case Record Form (CRF). Five clinical symptoms (e.g., dysuria, frequency, suprapubic pain, back and/or flank pain) were registered and scored as mild (1), i.e., no significant interference with normal daily activities, moderate (2), i.e., significant interference with normal daily activities, or severe (3), i.e., preventing normal daily activities.

The follow-up of the Indoor patient was done every day till the patient is discharged. Thereafter one follow up visit was done within 4 to 9 days of after discharge, which was to be termed as test of cure (TOC). Furthermore, one late follow up visit was done after 6 to 8 weeks of discharge, known as late follow up visit (LFU). Clinical assessments and microbiological analysis were done at the time of TOC and LFU.

Efficacy assessments were performed during treatment, at the time of discharge, at 1st and late follow up visit. The data was collected over a period of 18 months and at the end of this period, the data were analysed as following:

Clinical outcome

1) Clinical cure—resolution of all symptoms of patient at the TOC visit and no further use of additional antimicrobial therapy. 2) Improvement—each clinical symptom is decreased by at least one score between visits. 3) Failure— No change / increase in score of each symptom at the test-of-cure visit, or use of additional antimicrobial therapy for the current infection. 4) Recurrence (at LFU only)—increase in score after clinical cure at TOC visit.

Microbiological Outcome

1) Eradication: A urine culture, taken within the 5 to 9-day post-therapy window, shows that all uropathogens found at entry at are reduced to < 10^4CFU/mL. 2) Persistence: A urine culture, taken any time after the completion of therapy, grows > 10^4CFU/mL of the original uropathogen. 3) Superinfection: A urine culture grows > 10^5 CFU/mL of a uropathogen other than the baseline pathogen during the course of active therapy. 4) New Infection: A pathogen, other than the original microorganism found at baseline at a level > 10^5 CFU/mL, is present at a level > 10^5 CFU/mL anytime after treatment is finished. 4) Recurrence: A urine culture grows > 10^4 CFU/mL of the original uropathogen taken any time after documented eradication at the 5 to 9 day post-treatment visit, up to and including the 4 to 6 week post-therapy visit.

Recorded information of patients were coded and entered in SPSS and Microsoft Excel Worksheet. Statistical tests were carried out in order to test each of the stated hypotheses. Depend on type of numbers of groups and paired or unpaired, data were analysed with the help of appropriate statistical tests. The data were analysed as follows for demographic analysis (age, gender), coexisting condition, and comparison of drug combination therapy in terms of clinical and microbiological outcomes.

RESULTS

A total of 92 patients were recruited during the study period of eighteen months. Out of these patients, 49 patients received Piperacillin/Tazobactam (PT), and, 43 patients received Cefoperazone/Sulbactam (CPS). A total number of 73 patients completed the study, of which 41 and 32 patients belonged to PT and CPS group respectively. A total of 19 patients did not complete the study. Out of these 19 patients, 13 patients were lost to follow up, 3 patients had required additional antibacterial drug and 1 patient was died. While in 2 patients culture sensitivity reports were not found.

Demographics and baseline characteristics

As shown in Table-1 the mean age was 46.22 $\pm$ 17.81 (CI 40.59 to 51.84), 44.78 $\pm$ 17.21 (38.57 to 50.98) years for PT and CPS respectively, there was no significant difference. Both treatment regimens were well matched with respect to age characteristics of the patients. These patients belonged to the age ranging from 1 to 69 years. Most common age group was 50 to 59 years of age. Table 2 shows the distribution of study population on the bases of gender. Male participants were 51.12%, 53.13% respectively for PT and CPS. While 48.78% and 46.87% were females in PT and CPS groups respectively. Thus, both groups had almost equal distribution of male and female population.

Table-1: Age wise distribution of patients in study population

Age (year)	Piperacillin + Tazobactam (n = 41)	Cefoperazone + Sulbactam (n = 32)
Mean (SD)	46.22 (17.81)	44.78 (17.21)
Range	1 to 69	1 to 67

Table -2: Gender wise distribution of patients in study population (Values are expressed as absolute numbers and percentage in parenthesis)

Gender	Piperacillin + Tazobactam (n = 41)	Cefoperazone + Sulbactam (n = 32)
Male (%)	21 (51.12)	17(53.12)
Female (%)	20 (48.78)	15 (46.87)

Clinical presentation

It was observed that lower cUTI (78.04%) was more common clinical presentation than pyelonephritis (21.52%) in both treatment group. Amongst the patients suffering from lower cUTI, majority of the patients were symptomatic [79.16% and 78.94% in PT and CPS, respectively]. It was observed that dysuria (44 patients) was the most common presenting symptom for the patient with cUTI, followed by suprapubic pain (35 patients), fever (34 patients) and vomiting (19 patients). Other symptoms like oliguria, back-pain, heamaturia, anemia were also reported. Among both the treatment group, dysuria was the most common presenting symptom observed in PT group (24 patients) and CPS group (20 patients).

Complicating factors

Male gender was found to be the most common complicating factor in PT (65.71%) and CPS (66.76%) group. Diabetes mellitus and instrumentation were the second most common factor complicating the

UTI in PT group, and CPS group respectively. Complicating factors are shown in Table 3.

Table-3: Complicating factors in study population (Values are expressed as absolute numbers and percentage in parenthesis)

Complicating factors	Piperacillin+ Tazobactam (n = 41)	Cefoperazone+ Sulbactam (n = 32)
Male gender	21 (65.71)	17(66.66)
Diabetes mellitus	18 (56.25)	15 (62.50)
Instrumentation	10 (24.39)	16 (66.66)
Obstructive uropathy	14 (43.75)	15 (62.66)
Urogenital surgery	3 (09.37)	02 (08.33)
Functional/ anatomical abnormality	5 (15.62)	07(29.16)
Pregnancy	2 (06.25)	0

Baseline characteristics

Clinical evaluation

At first visit, before starting the therapy, a clinical score was calculated according to the intensity of each symptom (presented by the patient. 1 - mild, 2 - moderate, 3 - severe. The sum of score of all presenting symptoms is considered as total clinical score. The mean baseline clinical score for PT and CPS were 10.89 ± 2.23 and 10.28 ± 2.33, respectively. When mean baseline clinical score of both treatment groups was compared using ANOVA test, it was found that there was no significant difference between the both the groups.

Microbiological evaluation

It was observed that gram negative organisms were the most common pathogens in both treatment groups. Amongst the organisms, *E-coli* and *P. aeruginosa* were the two most common organisms found in both treatment groups. Other pathogens were also isolated as shown in table 4.

Drug therapy

The mean duration of drug therapy was 11.65 days in for Piperacillin + Tazobactam and 10.81 days for Cefoperazone + Sulbactam. Hence, the duration of drug therapy in all treatment group was found almost similar.

Table-4: Organisms isolated from urine samples of patients with cUTI. (Values are expressed in percentage) [Patient may have more than one uropathogens.]

Pathogen	Piperacillin + Tazobactam (n = 41)	Cefoperazone+ Sulbactam (n = 32)
Gram negative		
Escherichia coli	41.46%	43.75 %
Klebsiella pneumoniae	12.19%	12.50 %
Pseudomonas aeruginosa	14.63 %	15.62%
CUrobacterfreundii	02.43 %	0%
Proteus Vulgaris	07.31 %	06.25 %
Morganelle	02.43 %	0% •
Enterobacter cloacae	02.43 %	0%
Gram positive		
Staphylococcus aureus	07.31 %	12.50%
Staphylococcus Saprophyticus	02.43 %	0
Streptococcus agalactiae	02.43 %	06.25 %
Enterococcus Faecalis	04.87 %	03.12 %

At TOC visit

Clinical evaluation

After starting the therapy, each patient was evaluated for clinical score at TOC visit. The mean clinical score was found to be 0.86 ± 2.30, 1.36 ± 3.48 in PT, CPS respectively. When mean clinical score at TOC was compared to baseline clinical score using paired t-test significant difference ($p<0.0001$) was found in both treatment groups. However, when compared both the groups for total clinical score at TOC visit by using ANOVA test, there was no significant difference between both treatment groups. Mean reduction in clinical scores between TOC visit and baseline were 9.95 ± 2.44 and 9.75 ± 2.16 in PT and CPS group respectively. However no significant difference, when compared the both treatment groups for mean reduction in clinical score between two visits by using paired t test, was observed.

Microbiological evaluation

At TOC visit, urine samples were also investigated for culture and sensitivity test, it was observed that urine samples were negative from 87.80% and 93.75% of samples in PT and CPS group, respectively. In PT group, urine samples from 3 patients were positive for the presence of microorganisms including *E. coli* (2 samples), *K. pneumoniae* (1 samples). They were resistant to PT. There were 6 cases of new infection (3 cases each for PT and CPS) at the TOC visit. Majority of the pathogens (*E. coli, S. agalactie, K. pneumoniae and P. aeruginosa)* were resistant to respective treatment regimen. Prolong catheterization and diabetes mellitus were the predominant reasons for the growth of new uropathogens.

Table-5: Comparison of the clinical score between baseline and TOC (Test of Cure) visit. [Values are expressed as mean (SD)] [*p < 0.0001 (paired t-test) significantly difference as compared to baseline]

Clinical Evaluation	Piperacillin + Tazobactam(n = 41)	Cefoperazone+ Sulbactam (n = 32)
BASELINE	10.89 (2.23)	10.28 (2.33)
TOC	0.86 (2.35)*	1.36 (3.48)*
Reduction in clinical Score	9.95 ± 2.44	9.75 ± 2.16

Table-6: Microbiological evaluation at TOC in both treatment groups

Pathogen	Piperacillin + Tazobactam (n = 41)			Cefoperazone + Sulbactam (n = 32)		
Gram negative	Base line C/S +ve	TOC C/S -ve	Conversion % (+ve to -ve)	Base line C/S +ve	TOC C/S-ve	Conversion % (+ve to -ve)
Escherichia coli	17	15	88.23	14	13	92.85
Klebsiella pneumoniae	5	40	80.00	4	3	75.00
Pseudomonas aeruginosa	6	5	94.44	5	4	80.00
Citrobacter freundii	1	1	100	0	0	-
Proteus Vulgaris	3	3	100	2	1	50.00
Morganelle	1	1	100	0	0	
Enterobacter cloacae	1	1	100	0	0	-
Gram positive						
Staphylococcus aureus	3	1	33.33	4	2	50.00
Staphylococcus Saprophyticus	1	1	100	0	0	-
Streptococcus agalactiae	1	1	100	2	2	100
Enterococcus Faecalis	2	2	100	1	1	50.00

At LFU visit

Clinical evaluation

At LFU visit, mean clinical score was found to be 1.32 (3.37), 1.65 (3.56) in PT, CPS treatment groups respectively. When compared mean clinical score at LFU visit using paired t-test, significant difference *(p <* 0.0001) was found between baseline and LFU visit in both treatment group. However, when compared the mean clinical score of both treatment groups using ANOVA test, there was no significant difference between both treatment groups. The mean reduction in clinical score in both treatment group were 9.65 and 9.48. When compared the mean reduction score of both treatment groups using ANOVA TEST, there was no significant difference between both treatment groups.

Microbiological evaluation

When urine samples were investigated at LFU visit, 88.91% and 77% samples were negative from patients of PT and CPS, respectively. At LFU visit, culture sensitivity reports of 4 patients showed the presence of microorganism in PT group. The organisms were *E. coli* [2 samples], *K. pneumoniae* [1 sample] *and p. aeruginosa* [1 sample]. Similarly 5 patients treated with CPS were positive for presence of microorganisms including *E. coli [2* samples] one sample each for *P. vulgaris, E.faecalis and k. pneumoniae*; suggesting resistance of these organisms. There were 8 cases of new infection (4 with PT and 4 with CPS) at the LFU. Majority of the pathogens *(E. coli and P. aeruginosa)* were resistant to respective treatment regimen.

Table-7: Comparison of the clinical score between baseline and LFU visit [values are expressed as mean (SD)]

Clinical score	Piperacillin + Tazobactam	Cefoperazone + Sulbactam
Baseline	10.89(2.23)	10.28 (2.33)
LFU	1.32(3.37)*	1.65 (3.56)*
Reduction in clinical score	9.65	9.48

Table-8: Evaluation of clinical and microbiological response at TOC and LFU visit, [values are expressed in percentage]

Treatment group	PT (n=41)	CPS (n=32)	PT (n=32)	CPS (n=32)
Clinical Improvement	92.68%	87.50%	87.80%	87.75%
Microbiological cure	87.80%	93.75%	82.92%	77.00%

DISCUSSION

Urinary tract infection is a term applied to a variety of clinical conditions ranging from asymptomatic presence of bacteria in the urine to severe infection of the kidney with resultant sepsis. It is an inflammatory response of the urothelium to microorganism. One study concluded that in entire world more than 150 million cases of UTIs occur, reflecting 6 billion dollars in health care expenditures. [7] In USA, in 1997, only UTI, more than 7 million cases of OPD and 1 million cases of emergency department visits, resulted in 10,000 hospitalisations. Furthermore, the direct and indirect costs associated with community-acquired UTIs in the USA alone exceed an estimated US $1.6 billion.[9] The clinical symptoms of cUTI usually include frequency, dysuria, pyuria, abdominal pain, back pain, fever or urgency. It is very important to view the urinary tract infection seriously because of the high morbidity and emergency of antibiotic resistant organisms. Antimicrobial agents are prescribed to almost all patients with cUTI. There is lack of data about drug pattern of antimicrobial agents for cUTI. The objective of this study was to provide a summary of the existing efficacy data pertaining to the use of antimicrobial combinations for the treatment of cUTI. While our search of the literature revealed that there are only few publications meeting the criteria for microbiological and clinical cure rates in patients of cUTI. Hence the present study was carried out with the aim to compare the efficacy and safety of antimicrobial combinations in patients with cUTI.

In this study, a total of 73 patients were enrolled. Patients were divided in two groups: 1) Piperacillin + Tazobactam (PT, n = 41) 2) Cefoperazone + Sulbactam (CPS, n = 32). The mean age for patients was 46.22 ± 17.81 and 44.78 ± 17.21 years for PT and CPS. Male patents were 51.12% and 53.13%, while female patients were 48.78% and 46.87% in PT and CPS, respectively. In all patients with cUTI, Symptomatic UTIs (77.70%) were commoner than asymptomatic UTI (22.30%). Male gender was the most common complicating factor for cUTI. Dysuria was the commonest presenting symptom followed by suprapubic pain.

The baseline clinical scores in PT group had mean value of 10.89 ± 2.23, while CPS was having mean value of 10.28 ± 2.33. Most common organisms in both groups were E. coli (41.46% and 43.75% in PT and group respectively) followed by *P. aeruginosa* (14.63% and 15.62% in PT and CPS group respectively).

At TOC visit clinical score in both the groups were 0.86 ± 2.35 and 1.36 ± 3.48 suggesting significant improvement from baseline ($p<0.0001$). Rate of clinical improvement at TOC visit was 92.68% and 87.50% while microbiological cure rate was 87.80% and 93.75% with PT and CPS groups respectively. These results suggest both regimens have no significant difference for the treatment of cUTI and thus they are equally effective for the treatment of cUTI.

At LFU visit, clinical scores in both groups were 1.32 ± 3.37 and 1.65 ± 4.10, in PT and CPS, respectively; suggesting significant improvement from baseline ($p < 0.0001$). Clinical cure rate at LFU visit was 87.80% and 87.85% while microbiological cure rate at LFU visit was 82.91% and 77.00% with PT and CPS groups respectively. These results suggest that both regimens have no significant difference for the treatment of cUTI and thus they are equally effective for the treatment of cUTI.

Demographic characteristics (Age and gender)

The demographic results of our study revealed that the mean age of patient was 46.22 ± 17.81 and 44.78 ± 17.21 years for PT and CPS, respectively. Study carried out in New Jersey, USA had mean value 51.2 ± 21.1 and 51.1 ± 21.0 for the doripenam and levofloxacin group with cUTI which was higher as compared to mean age of our study [10]. The reason for higher mean age value is they excluded patients lesser than 18 years of age, while in our study we included all the patients suffering from cUTI irrespective of their age. Eight patients less than 10 years of were included in present study. Complicated UTI is very common in age group of 45-50 years because the complicating factors like DM, prostate hypertrophy are very common in these age groups [10].

In our study male patients were higher than female. Male to female ratio were 1.05:1, and 1.13 in PT and CPS group respectively. Similar outcome was seen in study conducted in Orlando clinical research center, Florida showed ratio of 1.27:1 and 1.38:1 in cUTI patients treated with gatifloxacin and ciprofloxacin respectively [11]. Any UTI present in male is to be considered as cUTI. The other reason behind high male female ratio in our study is many patients were having benign prostatic hypertrophy. Male gender is one of the complicating factors in

cUTI[12]. Our study also observed the male patients (52%) were more common than female (48%) patients.

In our study majority of patient population had Symptomatic UTIs (77.70%). While only 22.30% patient had asymptomatic UTI. Study conducted in USA revealed that 90% patients were symptomatic [13]. These results show that majority of patients with cUTI are symptomatic. The reason behind less symptomatic patients compared to other studies 1) we have enrolled those patients who are positive for organisms with culture and sensitivity irrespective of their clinical features. 2) Sample size was quite small as compared to other multi-centre study.

E. coli (41.73%) was the most frequently isolated baseline uropathogen and was identified in samples from nearly half of the population. The second most common organisms causing cUTI followed by was *p. aeruginosa* (14.08%). A review by Lindsay Nicolle reported *E.coli* as the most common uropathogen with a worldwide Prevalence rate of 21-54%[14]. The results from worldwide review are similar to the present study. Similar findings were obtained in one Tunisian hospital to determine the prevalence of hospital-acquired infection; they reported the most frequently isolated organisms were Gram-negative rods (80.8%) [15]. All these data suggests that gram negative bacteria are the most common organisms causing cUTI and among all these gram negative organisms *E.coli*, Proteus mirabilis and Pseudomonas aeruginosa are the most common organisms. Though *E.coli* was the most frequently isolated organisms, percentage of *E.coli* positive were less in our study as compared to other studies. In our study the number of female patients was less as compared to other studies and females are likely to have more *E.coli* induced cUTI female patients. This could be due to the close proximity of the urethral catheter to the anal passage. If the patient is not cleaned properly, then the bacteria are likely to colonize the entry site of the catheter. It was also established that the female patients showed more susceptibility to getting the infection than their male counterparts although the difference is not statistically significant.

It is also observed that there is significant difference between the clinical score of first visit and TOC visit showing the efficacy of both treatment groups. The microbiological cure rate observed was negative from 87.80% and 93.75% of samples in PT and CPS group respectively.

Many comparative clinical trials of treatment of complicated urinary infection have been reported. Evaluation of these studies is frequently compromised by variability in study subjects, small sample size, lack of blinding or placebo control, variable follow-up and exclusion of patients with resistant isolates. Published reports describing comparative studies of adequate sample size with at least short-term follow-up (five to nine days post-therapy) are summarised in Table 9.

[bid Twice a day; Clin Clinical; d Days;; IV Intravenous; Micro Microbiological; NS Not stated; od Once daily; po per oral; q6h Every six hours; q8h Every eight hours; ql2h Every 12 hours;]

Table-9: Comparative clinical trials of complicated urinary tract infection (cUTI)

		Outcomes (% cure rate)			
		Short-term 5-9 days post therapy		Long-term 4-6 weeks post therapy	
Clinical Trial	Regimen	Micro biological	Clinical	Micro biological	Clinical
Cox *et al.* [11]	Ceftriaxone 1 g od x 3 d oral	84.90	84.90	NS	NS
Naber *et al.* [10]	Piperacillin/tazobactam 2 g/0.5 g q8h, 5d - 14d (161);	57.80	83.00	49.10	65.20
Horowitz *et al.* [17]	Ceftazidime 500 mg ql2h, 7 d - 12 d (27);	74.00	NS	42	NS
Nishiura *et al.* [18]	Cefoperazone 1 g bid, 5 d (116);	68.20	59.50	NS	NS
Nishiura *et al.* [18]	Carbenicillin 2 g bid, 5 d (116)	50.00	30.20	NS	NS

In our study, 4 patients were resistant to PT group including E. coli (2 samples), K. pneumoniae (1 sample) and *p. aeruginosa* (1 sample). Similarly 5 patients were resistant to CPS including E. coli (2 patients), and one patient each for P. vulgaris, E. faecalis and k. pneumoniae. There were total 4 cases of new infection with PT and 4 cases with CPS group, at the LFU. Majority of the pathogens (E. coli and P. aeruginosa) were resistant to respective treatment regimen. All these results were similar to or better than those reported in previous studies of patients with cUTI [11,16].

CONCLUSION

Complicated UTIs are highly prevalent but data regarding their treatment and adherence to available guidelines are lacking, especially in India. Our study has tried to assess the clinical and antimicrobial activity of piperacillin + tazobactam and cefoperazone + sulbactam combination therapy for the cUTI. Our study concluded that, both the combination therapies are equally efficacious in treatment of cUTI. Selection of drug in accordance with urine culture sensitivity, and, instead of using single agent use of antimicrobial combinations improved the clinical and antimicrobial efficacy. Long follow up, involvement of all age groups, measurement of clinical scoring system were the main pillars of our study which strengthen our study. The study population was quite small which limited our study. Furthermore the study was observational study and decision of drug selection was taken by clinicians in nephrology unit. Management of cUTI especially in Indian setup (limited resources, lack of laboratory investigations, and sensitivity of organisms) should be outlined in a clear manner. Emphasis on proper diagnosis and treatment, continuous medical education and availability of locally effective guidelines may lead to better and judicious use of drugs. We recommend further extensive study involving parameters like tolerability of drugs and pharmacoeconomics evaluation.

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