ASSESSMENT OF HEALTH RELATED QUALITY OF LIFE AND ADR IN DIABETIC FOOT PATIENTS UNDERGOING CEFTRIAXONE AND PIPERACILLIN/TAZOBACTAM TREATMENT IN TERTIARY CARE HOSPITAL

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ABSTRACT

Objectives: To conduct a comparative study based on HRQoL in diabetic foot patients treated with Ceftriaxone and with Piperacillin/Tazobactam, to identify ADRs associated with these antibiotics.

Methods: A cohort study was conducted in surgery department of KR hospital, Mysuru. SF-36 and Naranjo scale were used respectively to assess HRQOL and causality of ADRs in the study participants.

Results: In our study, patient who received Ceftriaxone showed greater improvement in 6 out of 9 domains, patients who received Piperacillin/Tazobactam showed greater improvement in 3 domains. Diarrhea, anemia and generalized weakness are the common ADRs seen in patients treated with Ceftriaxone. ADRs associated with piperacillin/Tazobactam therapy included anemia, generalized weakness and loss of appetite.

Interpretation and Conclusion: In our study, Ceftriaxone was found to be more effective than Piperacillin/Tazobactam in the aspect of HRQOL in patients with diabetic foot infection. We also observed the presence of significant amount of ADR associated with both drugs. Proper care and support should be provided to the Diabetic foot patients along with suitable medication care.

Keywords: Diabetic foot, HRQoL, Ceftriaxone, Piperacillin/Tazobactam.

INTRODUCTION

Diabetic foot infection is one of the most prevalent and significant complications of diabetes mellitus, which frequently results in hospitalization and disability. In India, 4.54% of people with type 2 diabetes mellitus were discovered to have diabetic foot ulcers. [1]

Poor foot care, peripheral vascular disease, underlying neuropathy, and poor glycemic control are the common causes of developing diabetic foot infection.[2] Microbial invasion into the tissue triggers a host reaction, which then impairs wound healing, leading to a wound infection in diabetic foot infection. can drastically alter innate immune activity, increasing susceptibility. The main risk factor for developing a diabetic foot infection (DFI) is continuing to have a foot wound.[3] The ulcers typically develop in parts of the foot that experience pressure and recurrent stress. The most prevalent infectious organism is Staphylococcus. Diabetic foot infection is also a frequent cause of foot osteomyelitis and lower extremity amputation.[2]

Diabetic foot ulcer is commonly classified according to Wagner's classification of diabetic foot ulcers. According to which the wound is classified as Grade

0, 1, 2, 3, 4, 5.[4] DFI is commonly diagnosed thorough history and physical examination, which is followed by a complete laboratory assessment, microbiology review, vascular assessment and diagnostic imaging. Clinical findings are used to make the diagnosis of a DFI.[5]

The initial treatment for diabetic foot ulcers(DFUs) involves several key approaches such as sharp debridement, offloading, local wound care etc.[6]

Common antibiotic therapy includes Oral cephalosporin, Amoxicillin-clavulanic acid combination, Piperacillin/Tazobactam[7], ampicillin/Sulbactam, if MRSA is suspected, then Linezolid, Clindamycin, Doxycycline, daptomycin. Other antibiotics such as Ciprofloxacin, Levofloxacin, Vancomycin, Linezolid, Daptomycin are also prescribed.[2] In patients with uncontrolled infections or wounds that are not healing, amputation, which is the removal of a nonviable limb, should be taken into consideration. There are numerous amputation levels, including those at the forefoot, midfoot, Syme, below-knee, and above-knee levels.[6]

Piperacillin/Tazobactam is a parenteral antibiotic and provides broad spectrum coverage and is used by clinicians in diabetic foot. A combination of piperacillin and tazobactam, a β-lactam/ β-lactamase inhibitor, has broad-spectrum antibacterial action against both Gramme-positive and negative aerobic and anaerobic bacteria.[7] Ceftriaxone is third-generation cephalosporin with strong activity against the majority of gram-negative bacteria, including the Enterobacteriaceae. Ceftriaxone is stable to betalactamases. It is the only third-generation cephalosporin with such a long half-life.[8]

Studies have shown that diabetic foot ulcers have a negative impact on health-related quality of life (HRQoL). Compared to patients with diabetes, DFU patients had significantly lower HRQoL. Severe HRQoL impairment affects both physical and mental health.[9]

In the Indian population, fluroquinolones, beta-lactam penicillin, and beta-lactam cephalosporin are widely used.[10] Since diabetic foot is commonly treated with empirical therapy, the occurrence of adverse reactions can be expected.

MATERIALS AND METHODS

Study design: Prospective Observational study

Site of the study: The study was conducted in Krishna Rajendra hospital, Mysuru.

Study population: Total 109 patients were included in the study.

Study period: The study was carried out for duration of six months from March 2023 to August 2023.

Department selected for the study: The study was conducted in the department of general surgery, which comprises 18 wards.

Sources of data: All the relevant data were collected from medical and medication record of patients, interviewing patient and caretaker, communicating with concerned physicians and health care professionals and also through telephonic contact with patients and/or physicians if necessary.

Ethical approval for the study: Ethical approval for the study is provided by institutional ethics committee of Mysore Medical College and Research Institute.

Inclusion criteria: Patients who are above 18 years old and suffering with diabetic foot infection, and are treated with ceftriaxone and Piperacillin/ Tazobactum and are willing to participate in the study were included.

Exclusion criteria: Pregnant and breastfeeding women and those diabetic foot patients who did not agree in participating in the study were excluded.

Experimental design: Patients who are suitable for the study were enrolled by obtaining their consent. Patient data inclusive of demographic information such as patient name, age, gender, contact information, other data like medical and medication history, diabetic foot details, DFU grade, treatment etc.. were collected in suitably designed data collection form. To evaluate the quality of life, SF-36 HRQoL questionnaire scale was employed. Patients were interviewed in the beginning of the therapy and later followed up after 10 days to assess the final HRQOL. During the period of the patient's hospital stay, ADR was assessed using causality assessment method-Naranjo scale.

Study tools:

a. Informed consent form: An appropriate ICF was created in both English and Kannada to obtain patient's consent to participate in the study. The patient was fully informed about the study in their regional languages, and their consent was obtained by taking their signature or thumb impression.

b. Data collection form: The form included demographic details of the patient and other data like medical history, medication history, diabetic foot details, relevant laboratory datas, treatment chart of the patient and ADR report.

c. SF-36 HRQOL questionnaire: it is a questionnaire that measures the HRQoL of the patient. It measures the quality of life in 8 scales. The score ranges from 0 to 100 while 0 being minimum and 100 being maximum quality of life.

d. Naranjo scale: Naranjo scale was used to determine the causality of an ADR.

Statistical analysis: Microsoft Excel 2010 was used to conduct the statistical analysis and to evaluate the data. Tables, graphs, means and percentages were used to represent the outcomes. Chi- square test and mean were used in our study.

RESULT

A total of 109 participants from surgery department, K
R hospital were included in the study.

Table 1: Demographics and clinical characteristics of study population

Demographics of the study population			
Demographics		**Number of patients**	**Percentage**
Age	Below 20y	0	0%
	20 – 30y	2	1.83%
	30 – 40y	5	4.58%
	40 – 50y	21	19.26%
	50 – 60y	32	29.35%
	60 – 70y	24	22.01%
	70 – 80y	16	14.67%
	Above 80y	9	8.25%
Gender	Male	86	78.89%
	Female	23	21.11%
Diet	Vegetarian	9	8%
	Mixed	100	92%
Habits	Alcoholic	26	23.85%
	Smoker	41	37.61%
	Pan masala	3	2.7%
	Gutka	2	1.83%
	Other	0	0%
	None	60	55.04%
Clinical characteristics of the participants			
Characteristics		**Number of patients**	**Percentage**
Diabetic history	Newly detected	93	85%
	K/c/o Diabetes	16	15%
Type of diabetes	Type-1 Diabetes mellitus	0	0%
	Type-2 Diabetes mellitus	109	100%
Ulcer grade	Grade – 0	0	0%
	Grade – 1	37	33.9%
	Grade – 2	39	35.7%
	Grade – 3	12	11%
	Grade – 4	9	8.2%
	Grade – 5	12	11%
Amputation	Yes	29	26.60%
	No	80	73.39%
Amputation details	Above knee amputation Below knee amputation Amputation of Foot Disarticulation of Toe/Toes	3 15 3 8	10% 52% 10% 28%

Quality Of Life In Diabetic Foot Patients

Among the 109 patients, 93 patients were interviewed about their quality of life. Among those, 39 were administered with ceftriaxone and 54 were administered with Piperacillin/Tazobactam.

The mean of quality of life in patients taking Ceftriaxone and Piperacillin/Tazobactam was given in the following table.

Table 2: Quality of Life in patients taking Ceftriaxone and Piperacillin/Tazobactam

Mean of quality of life in patients taking ceftriaxone (range= 0-100)	**Mean of quality of life in patients taking Piperacillin / Tazobactam (range= 0-100)**

Domain	Before	After	Domain	Before	After
Physical functioning	7.179	26.794	Physical functioning	8.703	28.71
Role limitations due to physical health	1.282	12.82	Role limitations due to physical health	1.85	11.11
Role limitations due to emotional problems	17.094	69.231	Role limitations due to emotional problems	16.67	65.43
Energy/fatigue	26.538	51.41	Energy/fatigue	28.796	51.85
Emotional well-being	42.153	63.076	Emotional well-being	43.11	64.96
Social functioning	45.512	68.589	Social functioning	47.41	71.06
Pain	16.538	55.833	Pain	20.83	54.26
General health	28.205	52.871	General health	28.15	52.203
Overall	17.948	42.307	Overall	16.67	33.796

The improvement in the quality of life in patients after the administration of drug, i.e., the difference in the before and after in each patient was calculated and their mean was obtained.

Table 3: Comparison of improvement in the health related quality of life (HRQoL) between patients taking Ceftriaxone and Piperacillin/ Tazobactam

Domain (range= 0-100)	Ceftriaxone	Piperacillin/ Tazobactam
Physical functioning	19.61	20.01
Role limitations due to physical health	11.54	11.11
Role limitations due to emotional problems	52.14	48.76
Energy/fatigue	25.51	23.7
Emotional well-being	20.92	21.85
Social functioning	23.07	23.67
Pain	39.29	33.24
General health	24.67	24.05
Overall	24.36	17.13

According to this study, patients who receive Ceftriaxone show greater improvement in 6 out of the total 9 domains. Piperacillin/ Tazobactam show greater improvement in 3 out of total 9 domains. Hence according to our study Ceftriaxone was found to be more effective than Piperacillin/ Tazobactam in the aspect of HRQOL (health related quality of life)of patients with diabetic foot infection.

Adverse Drug Reaction In Diabetic Foot Patients

Among the 109 patients, 41 patients developed ADR on treatment with either ceftriaxone or piperacillin/Tazobactam. In which, 18 patients (43.9%) who developed ADR were taking ceftriaxone and 23 patients (56.09%) who developed ADR were taking piperacillin/Tazobactam.

Table 4: ADR observed in patients taking Ceftriaxone and Piperacillin/Tazobactam

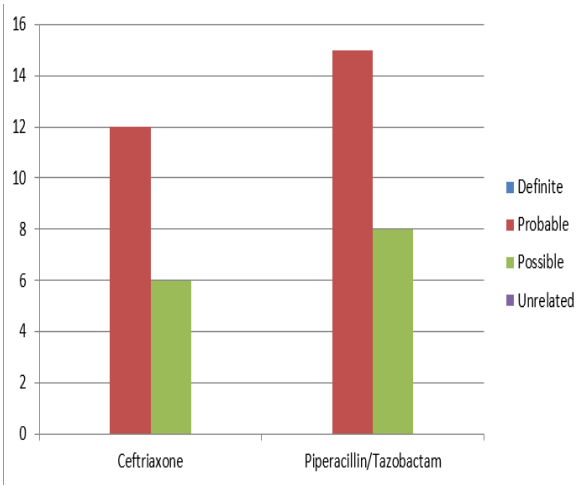
ADR observed in patients taking Ceftriaxone			ADR observed in patients taking Piperacillin/ Tazobactam		
ADR	**Number of Patients**	**Percentage**	**ADR**	**Number of Patients**	**Percentage**
Diarrhoea	5	27.7%	Anemia	14	60%
Anemia	7	38.8%	Generalized weakness	8	34.7%
Generalized weakness	4	22.2%	Loss of appetite	1	4.3%
Thrombocythemia	1	5.5%			
Acute Kidney Injury	1	5.5%			

Causality assessment

Using the Naranjo scale, the causality was assessed by providing a causality score. Among the 18 ADRs detected in ceftriaxone therapy, 12 ADRs were probable and 6 ADRs under possible category, no ADR were seen in definite and unrelated category of causation.

23 ADRs were detected in Piperacillin/ Tazobactam therapy out of which 15 ADRs are under probable category and 8 ADRs under possible category, ADR were not seen in definite and unrelated category of causation.

Figure 1: Causality assessment of ADR associated with Ceftriaxone and Piperacillin/Tazobactam



Association of Various Factors with ADR

Various factors that may affect the occurrence of ADR, such as age, gender, diet, habits and diabetic history were considered for the analysis.

Association of various factors influencing ADR in Piperacillin/ Tazobactam					
Factors		**ADRs**		**Chi-square value**	**p-value**
		Yes	**No**		
Age	20- 59	14	22	0.718	0.397
	59- 100	9	22		
Gender	Male	17	32	0.011	0.917
	Female	6	12		
Diet	Vegetarian	0	6	3.44	0.063
	Mixed	23	38		
Habits	With habits	9	14	0.358	0.549
	Without habits	14	30		
Diabetes history	K/C/O Diabetes mellitus	21	36	1.070	0.301
	Newly detected diabetes mellitus	2	8		

Significance was checked by using chi square test. No factors were found significant as the p value for all the factors were greater than 0.05. The result obtained was as the following table

Table 5: Association of various factors influencing ADR in Ceftriaxone

Association of various factors influencing ADR in Ceftriaxone					
Factors		**ADRs**		**Chi-square value**	**p-value**
		Yes	**No**		
Age	20- 59	8	16	2.074	0.15
	59- 100	10	8		
Gender	Male	16	21	0.019	0.89
	Female	2	3		
Diet	Vegetarian	2	1	0.75	0.387
	Mixed	16	23		
Habits	With habits	10	16	0.538	0.463
	Without habits	8	8		
Diabetes history	K/C/O Diabetes mellitus	16	20	0.259	0.61
	Newly detected diabetes mellitus	2	4		

Table 6: Association of various factors influencing ADR in Piperacillin/ Tazobactam

Note: Result is significant when significance level is ≤0.05.

DISCUSSION

Demographic details in our study showed that the mean age of the patients in our study was found to be 57.82 years. Most patients were falling into the age range of 50–60 years (n=32, 29.35%). Majority of the study population were male (78.89%, n= 86) female comprised of 21.11% (n=23). This is similar to a study conducted by **Ravisekhar Gadepalli, Benu Dhawan et al.,** named 'A Clinico-microbiological Study of Diabetic Foot Ulcers in an Indian Tertiary Care Hospital', according to which the mean age of patients in the study was found to be 53.9± 12.1 years. The percentage of male population was 85% in the study subjects.[11]

29 patients in our study had amputation (26.60%), among which below knee amputation was the most common category. Similar findings were found in an article by **Ghosh P, Valia R et al.,** which stated that about 20% of diabetic foot patients requires amputation.[12]

In our study it was found out that, a majority of patients had grade 2 ulcers (35.7%, n= 39). Grade 4 ulcers were found to be rare, affecting only 9 patients (8.2%). Similar results were found in the study conducted by **Jawed Mohammad Akther, Imran ali khan et al.,** According to their study, grade 2 was the commonest ulcer grade comprising 34.5% of the study population and grade 5 was the least common ulcer grade. [13]

In our study, significant improvement is seen in patients taking ceftriaxone and Piperacillin/ Tazobactam. Mean of results in the second observation in patients taking ceftriaxone and Piperacillin/ Tazobactam was found similar to the scores found in an earlier study conducted by **Maria Polikandrioti et al.,** named 'Quality of Life in Diabetic Foot Ulcer: Associated Factors and the Impact of Anxiety/Depression and Adherence to Self-Care'.[14]

In our study, among patients taking Piperacillin/ Tazobactam, a majority of patients developed anemia (n=14, 60%) and 8 patients had generalized weakness (34.7%). This is slightly contradicted to an earlier study conducted by **Will Fry et al.,** which stated that, hematological factors did not change much after the administration of Piperacillin/ Tazobactam, except that five patients developed mild pancytopenia.[15]

23 (34.33%) of the 67 individuals in our study who had taken piperacillin/Tazobactam experienced ADR. Slightly similar result was seen in an earlier study conducted by **Anneke M. Zeillimaker et al.**, on 'Piperacillin/Tazobactum therapy for diabetic foot infection', which stated that 56% of the study population has developed ADR which majorly comprised of nausea, diarrhea, exanthema etc.[16]

CONCLUSION

According to our study, Ceftriaxone was found to be more effective than Piperacillin/ Tazobactam in the aspect of HRQOL (health related quality of life) of patients with diabetic foot infection.

According to our study, the HRQOL of diabetic foot patient was found to be low in overall aspect, which has to be handled properly. Providing proper foot care, wound dressing, management of complication can help in improving the physical aspect of HRQOL of the patient. Doppler test and other vascular investigations play a crucial role in managing diabetic foot infection. Mental and emotional aspect of the quality of life can be improved by providing moral support, counselling and suitable assistance to the patient.

One of the common ADR found in both Ceftriaxone and Piperacillin/Tazobactam was Anemia. It can be managed by constant monitoring of haemoglobin level during treatment period as well as blood cell count. Other common ADRs of ceftriaxone include diarrhea, generalized weakness etc, which should be managed by proper monitoring of the patient along with symptomatic managements.

Along with medication therapy, the patients were advised about the significance of proper foot care and regular dressing. The patients were also advised about preventing the recurrence of diabetic foot by controlling modifiable risk factors like diet, lifestyle, habits (alcohol intake, smoking etc). Health care education and appropriate medication care should be provided to patients with diabetic foot. This study assisted in focusing on common empirically prescribed medications like ceftriaxone and piperacillin/tazobactam and how they affect the quality of life for people with diabetic foot. This study also helped to identify the common ADR associated with the administration of these drugs in the hospital setting.

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