ISSN 2708-5651 ISSN e 2708-566X

JAMDC

Quarterly

Journal of
Akhtar Saeed Medical & Dental College,
Lahore, Pakistan.

Registered With

"Y" Category

Jul- Sep 2024 Volume 06 Issue 03

JAMDC
Journal of Akhtar Saeed Medical & Dental College, Lahore, Pakistan.

July – Sep 2024 Volume 06 Issue 03

Editorial Board

JAMDC

July - September 2024 Volume 06 Issue 03

Editorial

Original Article

Case Report

Editorial

CARDIOTOXICITY: A MAJOR CONCERN IN CANCER THERAPY

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doi: https://doi.org/10.51127/JAMDCV06I03editorial

How to cite this:
Abid S. Cardiotoxicity: A Major Concern in Cancer Therapy. JAMDC. 2024;6(3): 85-86
doi: https://doi.org/10.51127/JAMDCV06I03editorial

In recent times, the scenario of patients suffering from cancer has greatly improved owing to the evolution of cancer treatments. As a result, the number of cancer survivors has greatly increased. This achievement, however, comes with a high burden of short and long term cardiovascular (CV) toxicity. Anti-cancer therapies cause various cardiovascular toxicities which make the management of patients on long-term follow up, very challenging. Such events call for multidisciplinary care that entails skills in oncology, cardiology, and other related fields, hence the development of the cardio-oncology subspecialty. The growing number and types of anticancer drugs have added to the intrinsic complexity of the care and treatment of patients facing oncology today. Overcoming cardiotoxicity of the treatment necessitates the participation of several specialists in various disciplines such as clinical oncology, cardiology, and clinical pharmacology.[1]

Anthracyclines are widely used pharmaceutical agents, which have been noted to present certain adverse cardiovascular effects including left ventricular systolic dysfunction (LVSD) and heart failure (HF). In brief, all of the guidelines suggest emphasizing screening and optimal management of cardiovascular diseases and risk factors before, during, and after the therapy with anthracyclines. They underlie the importance of evaluating the patients for the presence of cardiotoxicity at the earliest stage possible to be able to suggest cardioprotective measures aimed at preventing the overt manifestations of LVSD and HF from developing. Nonetheless, there are numerous variations in concepts concerning the assessment and monitoring before the therapy (with the inclusion of some cardiac biomarkers such as troponin) as well as drug prevention indications in the primary prevention of cardiotoxicity.[2]

With the termination of therapy, LV dysfunction due to trastuzumab, can in many cases be restored to normalcy. Furthermore, the majority of patients can withstand the re-challenge, after heart failure was managed by the use of neurohormonal antagonists. For instance, it is possible to administer anthracyclines and trastuzumab but one of the two is given after the other, increasing the risk of cardiotoxicity significantly.[3] Statins, or, hydroxymethyl glutaryl coenzyme A reductase (HMG-CoA) inhibitors, are recognized for cardiovascular disease prevention due to their anti-inflammatory, oxidative, and cholesterol lowering properties.[4] In addition to these, statins also act through the inhibition of small Ras homologous (Rho) GTPases, due to which their function is called pleiotropic. These effects are relevant as they attenuate topoisomerase II inhibition, which is involved in the generation of reactive oxygen species. Both HMG-CoA inhibitors & Rho GTPases inhibition are thought to be pathways that contribute to the toxic cardiomyopathy associated with anthracycline and/or trastuzumab treatment. Treatment with statins may help prevent the cardiotoxic effects of these drugs.[5]

Clinical molecular biomarkers that are gaining popularity include cardiac troponins and

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natriuretic peptides (BNPs). Their applications in cardiovascular toxin evaluation, during and post cancer treatments are becoming part of recent discussions. Cardiac troponins are ideal biomarkers when determining cardiotoxicity in patients and assessment of cardiac tissue necrosis. BNP and N-terminal pro-B-type natriuretic peptides (NT-pro BNP) are often used to assess long-standing cardiovascular disorders with no obvious symptoms. However, these biomarkers are not applicable in all instances producing encouraging results. Therefore, there is a need for the exploration of novel biomarkers.[6] The emphasis of the studies has been on understanding the effects of exogenous molecular markers on the heart before or immediately after treatment to identify the patients who are likely to experience cardiotoxicity. However, cancer drugs may lead to cardiovascular effects even after remission.[7]

Provided the complex situation characterized by a constant discourse between the oncological condition and cardiovascular comorbidity, the clinician needs to get sufficient knowledge to duly fulfill the requirements of the oncological case under cardiotoxic treatment. Cancer patients, who require cardiotoxicity treatment should be closely monitored for any cardiotoxic effects before it becomes clinically apparent. Echocardiography is a useful tool to assess parameters similar to LV ejection fraction (LVEF) and global longitudinal strain (GLS), ultimately to detect heart damage. Cardiac biomarkers, natriuretic peptides, and high-perceptivity (hs) troponins are gaining interest as these offer the possibility to descry cardiotoxicity in an early phase.[8]

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Original Article

ANTIBIOTICS RESISTANCE PATTERNS IN GRAM POSITIVE UROPATHOGENS IN CHILDREN

Madiha Tahir[1], Huma Anwar[2], Hareem Khalid[3], Afsheen Batool Raza[4], Saadia Choudhary[5]

Abstract:

Background: Children and infants are commonly infected with UTIs due to several anatomical reasons and hygiene measures. The most common organisms causing UTI in children are gram-negative pathogens but some gram-positive pathogens. The objective of study was to see antibiotic-resistant patterns in Gram Positive Uropathogens in children in Children's Hospital, Lahore.

Materials & Methods: Urine samples obtained from 200 children taken with non-probability, convenient method presenting with UTI were cultured on CLED agar and then drug sensitivity testing of isolated gram positive bacteria (n=25) was performed using Disk diffusion (Kirby Bauer) method on Muller Hinton agar plates as per standard laboratory guidelines. A descriptive study (cross-sectional) was conducted to assess sensitivity against Ampicillin, Cotrimoxazole, amoxicillin, cefotaxime, Ceftriaxone, tobramycin, amikacin, Sulbactam, Nitrofurantoin, and Polymixin B.

Results: The mean age of children in this study was 2.4 years from 0 to 5 years. Among Gram positive uropathogens Staphylococcus aureus (65%) was the commonest organism isolated. Enterococci were isolated in 25% of cases. Coagulase-negative staphylococci were 10%. Gram positive cocci included Methicillin Sensitive Staphylococcus Aureus (MSSA) (50%) and Methicillin Resistant Staphylococci (MRSA) (50%). The highest resistance was noted against Ampicillin (68%). The lowest resistance was noted against tobramycin (24%).

Conclusion: Emerging antibiotic resistance has rendered many first-line drugs ineffective against UTI-causing organisms and treatment regimens need to be revised.

Keywords: Urinary Tract Infection, Urinalysis, Gram Positive Uropathogens, Antibiotic sensitivity, Resistance

doi: https://doi.org/10.51127/JAMDCV06I03OA01

How to site this:
Tahir M., Anwar H., Khalid H., Raza A. B., Choudhary S., Antibiotics Resistance Patterns in Gram Positive Uropathogens in Children. JAMDC, 2024: 6(3): 87-90
doi: https://doi.org/10.51127/JAMDCV06I03OA01

INTRODUCTION

Urinary tract infections (UTIs) in children are an extremely common clinical condition, with millions of young sufferers globally every year.[1] UTIs have, therefore, been an important health concern not only in developing countries but also in developed countries where they impose a heavy burden on the healthcare system.[2] UTIs in children are resource-intensive, all the way from the clinical diagnosis by a very experienced physician to the exact identification of the causative microorganism in the laboratory through culture and sensitivity testing.[3] Beginning from the collection of the specimen to the isolation and identification of the microorganism, it

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Date of 1st Review: 22-07-2024
Date of 2nd Review: 29-07-2024
Date of Acceptance: 20-08-2024

includes thorough steps. This calls for proper observation of guidelines and fair utilization of resources at its disposal in the course of the same process.[4]

A timely diagnosis and proper therapy of UTI are crucial in children, as untreated infection may lead to complications like acute and chronic pyelonephritis, renal scarring, and hypertension later in life.[5] Historically, Gram-negative bacteria comprised the preponderance of UTIs in children, with Escherichia coli accounting for the vast majority.[6] However, UTIs caused by Gram-positive pathogens, although relatively rare, do occur and pose a different challenge because of increased resistance to normally used antibiotics.

Several studies document the growing trend in antibiotic resistance of Gram-positive bacteria, including Enterococcus spp. and Staphylococcus saprophyticus.[5] Continued surveillance and development of further antimicrobial strategies are therefore needed. Taking into account that a host of host-related or other factors influence the epidemiology of UTIs in children, which may range from age, sex, genetic predisposition, and underlying health conditions, this could misleadingly complicate the diagnosis and treatment protocols of UTI infection.[6]

Recent advances in the development of diagnostic technologies, such as rapid molecular assay and enhanced culture methods, enabled the identification of causative agents of UTI with much accuracy and speed, thus providing an avenue for early effective treatment.[7,8] However, the rising prevalence of antibiotic-resistant strains in circulating pathogens mandates continued research efforts and even more robust implementation of antimicrobial stewardship programs if UTIs are going to be managed effectively in children.[9]

MATERIAL AND METHODS

Research was conducted after approval from IRB Children's Hospital & ICH , Lahore IRB no: 2021-259-CHICH dated 26-03-2021.

In this study, focus was on the isolation of gram positive bacteria in urine samples of children suffering from UTI. In a time, duration of six months, a total of 200 urine samples were received in the laboratory of Children's Hospital, Lahore. Out of these 200 urine samples from children, 25 samples yielded the growth of gram-positive bacteria which were gram-positive cocci, coagulase-negative staph, and enterococci. The disc diffusion (Kirby Bauer) method was used for the drug sensitivity testing using Muller Hinton agar. Data was analyzed using SPSS 23.

RESULTS

The age range in this study was from 0 to 5 years with a mean age of 2.424±1.14 years. Female patients were 70.7% and males were 29.3%. Percentage of sensitivity / Resistance of Gram Positive bacteria Against following Anti-microbials. (n=25) (Table 1)

Table 1:

Ampicillin		
	Frequency	**%age**
Yes	8	32%
No	17	68%
Cotrimoxazole		
	Frequency	**%age**
Yes	7	28%
No	18	72%
Cefotaxime		
	Frequency	**%age**
Yes	12	48%
No	13	52%
Ciprofloxacin		
	Frequency	**%age**
Yes	11	44%
No	14	56%
Amikacin		
	Frequency	**%age**
Yes	8	32%
No	17	68%
Sulbactam/Cefoprazone		
	Frequency	**%age**
Yes	10	40%
No	15	60%
	Frequency	**%age**
Yes	15	60%
No	10	40%
Polymixin B		
	Frequency	**%age**
Yes	16	64%
No	9	36%
Tobramycin		
	Frequency	**%age**
Yes	19	76%
No	6	24%

DISCUSSION

In this current research, there has been an increased resistance of Gram-positive bacteria isolated from UTIs in children to antimicrobial agents. This presents a serious challenge to the treatment strategies. The finding presented agrees with studies performed on the emerging trend of antibiotic resistance.[1,2] Despite developments in antibiotic therapy, limited therapeutic options are available in events of UTIs as a result of limited effective options available. Empirical therapy with broad-spectrum agents is often practiced, but resistance rates of over 20% undermine their effectiveness.[2,4] In our study, we found quite alarmingly that the resistance was very high, specifically against Cotrimoxazole of 72%, while with tobramycin it was the lowest, that is, 24%. These figures are much higher in comparison with rates of resistance reported previously.[13] Broad-spectrum coverage and the frequent indication of Cotrimoxazole in pediatric UTIs make it challengeable as a result of rising levels of resistance and underscore the importance of prudent antibiotic selection given local resistance patterns.

Comparative studies showed variable sensitivity and resistance patterns across different regions and also proved regional disparities in antibiotic resistance. For example, in our study, it had higher resistance to amikacin 68%, ciprofloxacin 56%, and cefoperazone 60% compared with European and African data.[14] Such variations bring out the salient need for tailored antibiotic stewardship programs and continuous surveillance to take up the challenge posed by resistance effectively.

Among children, the emergence of obesity as a risk factor for UTIs portrays a different pattern of epidemiology and management of the infection.[3] In this case, individualization of therapy should be involved in the management of the complex relationship between obesity and susceptibility to UTI.

CONCLUSION

The growing antibiogram of resistance to gram-positive bacteria causing UTIs in children is a major therapeutic concern. Highest resistance is noted with Tobramycin, Polymixin B and Nitrofurantoin. Effective management requires a tailored selection of antibiotics based on local resistance profiles, coupled with stringent antibiotic stewardship practices.

CONFLICT OF INTEREST

None

SOURCE OF FUNDING

None

ACKNOWLEDGEMENTS

1. Asadullah Yousaf, Postgraduate Resident General Surgery, KEMU, Lahore, who has done SPSS Analysis & Data Entry.

AUTHOR'S CONTRIBUTION

MT: Manuscript writing, Data collection
HA: Critical Review, Data Collection
HK: Manuscript writing
ABR: Manuscript writing
SC: Manuscript writing, Critical Review

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Original Article

RELATIONSHIP OF PERIPHERAL BLOOD LYMPHOCYTE/ MONOCYTE RATIO WITH CLASSICAL HODGKIN'S LYMPHOMA STAGE AT THE TIME OF DIAGNOSIS AND ITS UTILITY AS PROGNOSTIC FACTOR

Umera Saleem[1], Rafeeda Maab[2], Hajrah Syndeed Pal[3], Muhammad Asif Naveed[4]

Abstract:

Introduction: Hodgkin lymphoma, a prevalent neoplasm in our part of the world requires the simplest investigations that can overview prognostic features. The objective of this study is to examine the lymphocyte-monocyte ratio (LMR) in various stages of classical Hodgkin's lymphoma (cHL) as defined by Ann Arbor Staging System and to study the relationship of LMR with the overall survival of the patients.

Materials & Methods: A prospective cohort study was done at the Department of Pathology, King Edward Medical University, Lahore from June 2019 to June 2024. Eighty patients were enrolled after informed consent. Clinical parameters included age, gender, and clinical stage. Laboratory parameters included histology, serum albumin, Hemoglobin (Hb), Total leukocyte count, ALC, and AMC with 3-year overall survival. LMR was calculated from the EDTA sample taken and overall survival in each stage was recorded.

Results: Out of eighty patients, 78.8% were males. The mean age was 40.9±14.8 years. LMR was highest in stage I and lowest in stage IV. Lower LMR was associated with inferior overall survival.

Conclusion: LMR at diagnosis is inversely related to disease stage in cHL and patients with low LMR have a poor disease outcome. This relationship with stage can be used to predict the clinical outcome in patients with cHL in resource limited countries.

Keywords: Classical Hodgkin lymphoma, absolute lymphocyte count, absolute monocyte count, lymphocyte/monocyte ratio, and survival rate.

doi: https://doi.org/10.51127/JAMDCV06I03OA02

How to site this:

Saleem U., Maab R., Pal H. S., Naveed M. A., Relationship of Peripheral Blood Lymphocyte/Monocyte Ratio with Classical Hodgkin's Lymphoma Stage at The Time of Diagnosis and Its Utility as Prognostic Factor. JAMDC, 2024: 6(3): 91-97
doi: https://doi.org/10.51127/JAMDCV06I03OA02

INTRODUCTION

The tumor microenvironment plays a pivotal role in the growth and survival of malignant cells.[1]

Classical Hodgkin lymphoma (cHL) is characterized by the presence of neoplastic Reed Sternberg cells in an inflammatory background which represents tumor microenvironment.[2] Of these, lymphocytes and macrophages are associated with clinical outcomes in cHL. Recently, the peripheral blood LMR has gained attention as a predictor of disease outcome in cHL.[3] There is a variation in cut offs of LMR from <1.1 to 1.5 and 2.9 as independent prognostic indicators in quoted literature.[4,5] Moreover, consensus is lacking to incorporate this biological marker (LMR) into currently

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Date of Submission: 07-07-2024
Date of 1st Review: 20-07-2024
Date of 2nd Review: 30-07-2024
Date of Acceptance: 15-08-2024

validated prognostic scoring systems along with acceptable risk factors for disease monitoring.

According to a collective cancer registry report from Shaukat Khanum Memorial Cancer Hospital and Research Center 1994-2023, Hodgkin lymphoma is the 6th most common tumor in Pakistan and the commonest malignancy in the pediatric population constituting about 21.6% of all malignancies in the age group < 18 years.[6,7] So far, there has not been any study that has solely explored LMR and its relationship with prognostic factors in cases of classic Hodgkin lymphoma in the setting of our country. Considering this fact, the study was designed and conducted to examine LMR in various stages of Hodgkin's disease and to study its relationship with overall disease survival. The LMR prognostic score, obtained from a globally available test such as complete blood count (CBC) at diagnosis combines an estimate of host immune status and tumor microenvironment. This is one of the easiest and most inexpensive tests ever used in any predictive model.[8] The objective of this study was to examine the lymphocyte monocyte ratio (LMR) in various stages of classical Hodgkin's lymphoma (cHL) as defined by Ann Arbor Staging System and to study the relationship of LMR with the overall survival of the patients.

MATERIALS & METHODS

This prospective cohort study was conducted in the Department of Pathology at King Edward Medical University, Lahore, after IRB approval no; 458 RC/KEMU dated 13-06-2023. Purposive sampling of included cases was done from June 2019 to June 2022. No patients refused their authorization to use their medical records for research and none was lost to follow up. The inclusion criteria was newly diagnosed cases of cHL were enrolled and followed for 3 years. The exclusion criteria was the patients who had received any chemotherapy in the past, history of malignancy or immunosuppression, HIV positivity, or those diagnosed as nodular lymphocyte predominant Hodgkin lymphoma were excluded to minimize selection bias.

Patients were treated with ABVD chemotherapy according to the standard protocol: 2-4 cycles for the early stage and 4-6 cycles for the advanced stage.

The clinical parameters including age, gender, clinical stage, and laboratory parameters including histology, serum albumin, Hemoglobin (Hb), Total Leucocyte Count, (TLC), ALC, AMC, and disease stage were evaluated. The ALC and AMC were obtained from CBC performed at the time of diagnosis and LMR was calculated. The overall survival in each group of the disease was recorded and analyzed. The prognostic factors assessed were age >45 years, male gender, Hb <10.5 g/dL, TLC ≥15 x 109/L, ALC <600 x 109/L, serum albumin <4 g/dL and stage IV (Blombery P and Linch D, 2016) Statistical analysis was done using SPSS version 23.

Frequencies and percentages were calculated for categorical data while mean with standard deviation and median (IQR: Q1-Q3) for quantitative data. Shapiro- Wilk and Kolmogrov Smirnov test was used to assess the normality of quantitative variables. The overall survival (OS) time was defined as the time between the first day of diagnosis and the date of death from any cause.[7] The follow-up period was 3 years. Kaplan and Meier's method was employed for overall survival analysis. Log-rank test was used to analyze the differences between survival curves. The prognostic factors for survival were analyzed through univariate and multivariate Cox proportional hazard models.

Chi-squared tests Fisher's exact test or likelihood ratio test were used to determine relationships between categorical variables as appropriate. Independent sample t-test or Mann-Whitney U test was used to determine the difference between continuous variables. All P values are two sided and a P value of

less than 0.05 is considered statistically significant. Receiver Operating Curves (ROC) were generated for LMR. The 1.7 cut off value having the highest AUC (0.77) with a significant P value (0.011) was chosen.

RESULTS

A total of 80 patients were enrolled, 63 (78.8%) were males. The mean age was 40.9± 14.8 years (range 15-75 years). Stage I was seen in 3 (3.8%), stage II in 37 (46.3%), stage III and stage IV each in 20 (25%). Mixed Cellularity was the most common histology 64 (80%), followed by Nodular Sclerosis 12 (15%), Lymphocyte Rich 3 (3.8%) and Lymphocyte Depleted 1 (1.3%). Mean was calculated for CBC parameters with normal distribution whereas median were calculated for the parameters not following normal distribution. The mean Hb was 11±3.5 g/dL. Median TLC was 8.4(6.7-12.7x10^9/L, median platelet count was 222.9(220.4-232.8x10^9/L, median ALC was 1.8(1.2-2.7) x10^9/L, median AMC was 0.4(0.2-0.6) x10^9/Land median serum albumin was 3.7(2.3-6.5g/dL. Mean Hb, TLC and LMR differed significantly between early and advanced-stage disease (p<0.05). (Table 1)

Table 1: Difference in mean Hb, TLC, serum albumin and LMR between early and advanced stage disease

Characteristics	Stage I/II	Stage III/IV	P value
Age (years)	41.2±16.3	40.7±13.4	0.881
Gender			
Male	26 (65%)	37 (92.5%)	0.003
Female	14 (35%)	3 (7.5%)	
Median serum albumin (g/dL)	4.1 (2.3-6.8)	3.3 (2.3-6.3)	0.365
Mean Hb (g/dL)	11.9±3.1	10.2±3.7	0.035
Median TLC	8.4 (7.6-13.2)	7.5 (5.8-10.5)	0.025
Mean LMR difference	9.9±1.1	5.6±1.3	<0.001

The characteristics of study population summarized according to LMR ≥1.7versus <1.7 are presented in Table 2. (Table 2)

Table 2: IQR according to LMR

Characteristics	LMR ≥1.7 (N=72)	LMR ≤1.7 (N=8)	P value
Age			
Median (IQR)	38.0 (25.3-50.0)	27.0 (22.8-32.3)	0.170

A higher number of patients in the group with LMR ≥1.7 had ALC ≥ 600x10^9/L (p=0.042) and AMC <900x10^9/L (p=0.001).

No difference was observed regarding age (p=0.674), male gender (p=0.192), Hb (p=0.068), histology (p=0.107), stage IV disease (p=0.085), TLC (p=0.143), platelet count (p+0.640), limited vs advanced stage disease (p=0.712) and IPS score≥3 (p=0.197). The median survival time was 5.1 years with a range of 3.0 to 5.6 years. In univariate analysis, Hb ≤10.5g/dL, ALC <600 X 10^9/L, AMC ≥ 900 x 10^9/L, LMR ≥ 1.7, and stage IV and IPS index >3 were independent risk factors of poor OS. In multivariate analysis, Hb ≤10.5g/dL, AMC ≥900 X 109/L, stage IV and IPS index ≥3 were independently associated with poor OS. (Table 3)

Table 3: Evaluation of clinic-pathological variations between different stages of Hodgkin's Lymphoma and their relationship in IPSS scoring.

Gender			
Male	55 (76.4%)	8 (100%)	0.192
Female	17 (23.6%)	0 (0%)	
Histology			
Lymphocyte Dominant	01 (1.4%)	1 (12.5%)	0.17
Lymphocyte Rich	03 (4.2%)	0 (0%)	
Mixed Cellularity	59 (81.9%)	5 (62.5%)	
Nodular Sclerosis	09 (12.5%)	2 (25%)	

Hb			
Mean SD	10.8±2.7	9.0±1.4	0.068
Stage			
I	3 (4.2%)	0 (0%)	0.357
II	35 (48.6%)	3 (37.5%)	
III	19 (26.4%)	1 (12.5%)	
IV	15 (20.8%)	4 (50%)	
Limited vs. advanced Disease			
I & II (limited)	37 (51.4%)	3 (37.5%)	0.712
III & IV (advanced)	35 (48.6%)	5 (62.5%)	
TLC			
Median	7.5 (5.7-10)	9.6 (07-17.1)	0.138
Platelets			
Median	220 (146.3-356.8)	344.5 (166.3-459.8)	0.262
IPS			
Age			
>45 years	20 (27.8%)	1 (12.5%)	0.674
<45 years	52 (72.2%)	7 (87.5%)	
Hb g/dL			
≥ 10.5	44 (61.1%)	2 (25%)	0.066
≤ 10.5	28 (38.9%)	6 (75%)	
TLC x 109			
≥ 15	5 (6.9%)	2 (25%)	0.143
≤ 15	67 (93.1%)	6 (75%)	
Platelets x 10^9			
≤ 150	13 (18.1%)	2 (25%)	0.640
≥150	59 (81.9%)	6 (75%)	
ALC x 10^9			
≥ 600	66 (91.7%)	5 (62.5%)	0.042
≤ 600	6 (8.3%)	3 (37.5%)	
AMC x 10^9			
≥ 900	70 (97.2%)	4 (50%)	0.001
≤ 900	2 (2.8%)	4 (50%)	
Stage IV	16 (22.2%)	04 (50%)	0.085
IPS factor index	≥ 3 ≤3	17(23.6%) 55 (76.4%)	0.197

Five patients died of causes other than disease or its treatment. Overall survival (OS) at 5 years for stage I was 91% (88- 95%), stage II; 88% (83-90%), in Stage III;
71% (68-75%) and in stage IV; 64% (58-69%).

The LMR correlated significantly with overall survival (p< 0.001). However, there was no significant variation of LMR between different histological subtypes of cHL (p 0.656). Of the studied variables, female gender, early stage of the disease, those with Hb >10.5g/dL, ALC>600 x 10^9/L, AMC<900 x 10^9/L, IPS sore<3 and LMR ≥1.7 had a superior overall survival. (Figure 1).

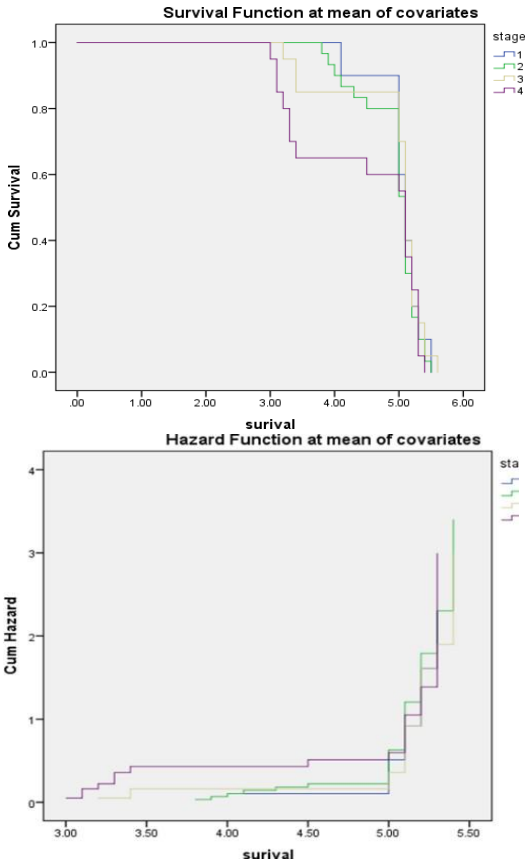

Figure 1: Overall survival in different stages of Hodgkin Lymphoma.

DISCUSSION

The mean age of our patient population was 40.9 years in comparison with 32 years Bolukbasi et al[9] and 36.4 years.[5] This slight difference may be attributed to the late access of the patients to the tertiary care centers in

developing countries either due to lack of awareness, mishandling by quacks or Hakeem, or financial constraints. The majority of our patients were males (78.8%) in contrast to females in the study of Mexico by Perez R et al[10] who found 59% of females and 41% of males to be affected. Male patients were found to be 50% more suffering from cHL (following data from USA.[11] UK cancer registry[12] highlights 58% affected males and 42% affected females. The most common histological pattern in the present study was mixed cellularity (80%) followed by nodular sclerosis (15%). This is similar to another study from Pakistan which mentions 63.8% mixed cellularity followed by 19% nodular sclerosis.[13] While according to another study[14] the most frequent histological pattern was nodular sclerosis (77.4%). This variability is consistent with WHO data on developing vs developed countries. Fifty percent of our patients were at an advanced stage at diagnosis; a pattern consistent with Pakistani data from another study.[15]

B symptoms were seen in 40% and bone marrow was involved in 25% of our patients. According to an Australian study, 44% and 11% had B symptoms and bone marrow involvement respectively.[16]

Serum albumin <4g/dL was seen in 71% of our patients in whereas in a previous study it was 58%.[16]

Bulky disease was seen in 11.3% and LDH was elevated in 15% of our patients. These levels were different from similar previous studies.[17,18]

Our study showed that patients with higher LMR scores were younger and had higher levels of Hb and serum albumin; very similar to a previous study.[20] The findings of study reported Porrata LF et al[20] are similar in terms of younger age and high serum albumin levels; however, they didn't report much difference in Hb values among their patients. A previous study[16] stated that the prognostic value of LMR is particularly significant in nodular sclerosis subtype histology. However, we could not find any statistical difference in LMR between different histological subtypes (p=0.820).

Our study showed that LMR varies inversely with disease stage i-e. LMR decreases as disease advances consistent with the evading of anti-tumor immunity by malignant cells. We found a statistically significant difference in LMR values between early and advanced stage disease (p <0.001). Our study also showed that a lower LMR at diagnosis is an independent prognostic marker associated with overall inferior survival.

Our findings are in consistent with a meta-analysis of eight studies done in 2019.[19] As LMR is associated with the stage of the disease, this can reflect upon prognostic sub grouping of cHL patients even before the results of time consuming staging investigations have been received. This association becomes relevant to predict clinical sequelae in cHL patients in countries such as Pakistan where financial constraints and unequal distribution of standardized diagnostic facilities pose a big hurdle in the delivery of healthcare services across different areas.

CONCLUSION

LMR is inversely related with disease stage at the time of the diagnosis and patients with low LMR have an inferior overall survival. This association can be useful to predict disease course in cHL by utilizing a routinely available and simple test such as CBC without extra financial burden on the patient and compromised health resources in developing countries like Pakistan.

CONFLICT OF INTEREST

None

SOURCE OF FUNDING

None

AUTHOR'S CONTRIBUTION

US: Conceptualization
RM: Conceptualization, Formulation of Data Collection Forms
HSP: Data Collection, Manuscript Writing

MNK: Review, Manuscript Writing
MTR: Data Collection, Manuscript Writing
MAN: Data Collection, Statical Analysis Assistance

ACKNOWLEDGEMENTS

1. Muhammad Naeem Khattak MSc, Epidemiologist Alberta health services, Edmonton, Alberta Canada.
2. Muhammad Tariq Roshan MD, PhD, FRCPC, Department of Pathology and Laboratory Medicine, University of Calgary, Alberta, Canada
3. Muhammad Haadi Ashal Pal, Student, Aitchison College, Lahore, Pakistan.

We are thankful to all above fellows for their help in statistical analysis and data collection.

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Original Article

EFFECTS OF GENETIC & ENVIRONMENTAL FACTORS ON THE PHARMACOKINETICS OF CEFUROXIME FOLLOWING INTRAMUSCULAR ADMINISTRATION IN HEALTHY ADULT MALES FROM PAKISTAN

Saima Shouket[1], Memoona Rashid[2], Muhammad Haseeb Ur Rehman[3], Sulaman Yaqub[4], Qazi Amir Ijaz[5], Shahzad Rasheed[6]

Abstract:

Background: Cefuroxime is an extensively prescribed broad-spectrum beta-lactam antibiotic employed to treat a wide range of bacterial infections. The objective of this research is to study variability in drug response and pharmacokinetics due to genetic and environmental variations among the male population in Pakistan.

Materials & Methods: The pharmacokinetic study was carried out on eight adult male healthy volunteers at the dose of 10.7 mg/kg/intramuscular. Samples of blood were taken at predetermined time intervals 0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours. High performance liquid chromatography (HPLC) was used to measure the cefuroxime concentration in plasma. Pharmacokinetics of cefuroxime, in the Pakistani population, were determined by plasma concentration time curve using two compartment open model without lag time.

Results: Pharmacokinetic parameters (mean±SD) were calculated and came out to be; maximum plasma concentration (Cmax) 31.35±0.90µg/ml, time to reach maximum plasma concentration (Tmax) 0.75±0.02h, volume of distribution (Vd) (0.28±0.02l/kg, half-life (t1/2) 1.4±0.1h, area under curve (AUC) 78.7±3.56µg h/mL.

Conclusion: In the Pakistani population it is suggested that minimum inhibitory concentration can be achieved by 1.5µg/mL of plasma level. The optimum dosage regimen of 7.31 mg/kg of body weight for the primary dose, and 7.16 mg/kg of body weight as the maintenance dose, to be repeated every 8 hours.

Keywords: Cefuroxime, Pharmacokinetics, Metabolism, Genetic Polymorphism, Environmental Factors

doi: https://doi.org/10.51127/JAMDCV06I03OA03

How to site this:

Shouket S., Rashid M., Rehman M. H. U., Yaqub S., Ijaz Q. A., Rasheed S., Effects of Genetic and Environmental Factors on The Pharmacokinetics of Cefuroxime Following Intramuscular Administration in Healthy Adult Males from Pakistan. JAMDC 2024;6(3):98-106 https://doi.org/10.51127/JAMDCV06I03OA03

INTRODUCTION:

The reliability of drug treatment in various genetic subsets of patients is the main goal of clinical trials during which a limited number of patients and lack of variability in genetic groups are the prime reasons for the failure to achieve this objective in clinical trials.[1] Lack of

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Date of Submission: 03-06-2024
Date of 1st Review: 22-07-2024
Date of 2nd Review: 29-07-2024
Date of Acceptance: 20-08-2024

clinical trial programs in developing countries due to various barriers such as limited research and development (R&D) facilities, and other operational barriers lead to inadequacy of literature describing therapeutic efficacy of developing country population.[2] Similarly, in Pakistan R&D of medicines is only limited to the development of pharmaceutical formulations and new lead compounds.[3] Several internal and external factors contribute to the variability in the response of drugs, including sex, race, age group, ethnic background, the status of liver and kidney functions, polymorphic isoforms of cytochrome-P 450 enzymes, and expressions of drug-membrane transporters. External factors include drug-food interactions, drug-drug interactions, and environmental factors such as xenobiotics.[4] Literature illustrates that almost 25–50% of patients show either inadequate or exaggerated responses to the drug due to these factors.[5] Genetic polymorphism causes phenotypic differences within individuals that not only cause variability in drug transport, distribution, and metabolism but also in observed pharmacodynamics. The inter-individual variability due to polymorphism in drug-metabolizing enzymes in different ethnicities is apparent even if equivalent doses of the same drug are administered. Therefore, this enzymatic polymorphism results in varied drug metabolism, which in turn is related to the unpredictability of drug response in a given population.[6] As a result of genetic and environmental factors and subsequent differences, the optimum therapeutic dosage regimen of imported drugs should be evaluated in the local population.[7]

Cefuroxime is a 2nd generation broad spectrum cephalosporin antibiotic that is resistant to β-lactamases. It can be administered via the intravenous, oral, or intramuscular routes. It is used to treat infections mainly caused by Gram-positive bacteria and a few Gram-negative bacteria. Cefuroxime is a bactericidal antibiotic, and its mechanism of action involves inhibition of the bacterial cell wall by binding to penicillin-binding proteins (PBPs).[8,9] Cefuroxime exhibits plasma protein binding ranging from 33-50% with a volume of distribution between 19.3 and 15.8 L per 1.73 m^2 of body surface area.[10] After administration, the drug is distributed across various body tissues, including the eye, gallbladder, kidneys, bones, and inflamed meninges. Effective concentrations are also attained in the amniotic fluid, umbilical cord blood, and the central nervous system. The oral dosage form was found to be less bioavailable due to the hampered absorption of the administered dose that has confined its use by the parenteral route compared to oral dosage forms.[11,12,13] As discussed earlier, the pharmacokinetic parameters of cefuroxime with various factors that ultimately affect the dosage regimen and may affect the prognosis of the disease for which it is being employed.

According to the analysis of unsuccessful antibiotic treatment, insufficient tissue concentrations of antibiotics were identified as the primary cause of their ineffectiveness.[34] The minimum inhibitory concentration of cefuroxime was reported to be between 0.5-2μg/mL, and ≥ 1μg/mL for the majority of susceptible pathogens.[35,36] In the current study, the recommended dose of cefuroxime (10.7 mg/kg) was insufficient to sustain therapeutic concentrations for 12 hours in healthy adult male subjects. The dosage regimen should be defined based on the pharmacokinetic parameters of drugs investigated in local populations where they are employed clinically Thus, to achieve maximum efficacy of a given drug, it is imperative to assess it in the local population and then modify the dosage regimen according to the obtained results.[14,15] This way, the dosage regimen and drug therapy can be tailored according to the indigenous population.

Therefore, the objective of the present study was to assess and evaluate the pharmacokinetic parameters of cefuroxime sodium in healthy local Pakistani volunteers. Furthermore, the study also evaluated whether genetic and/or

environmental factors had any effect on cefuroxime in the Pakistani population.

MATERIALS AND METHODS:

Eight healthy young male volunteers were included in this study. The investigation was conducted at the University of Agriculture, Faisalabad, within the Institute of Pharmacy, Physiology, and Pharmacology. The study was conducted over a day of one day in May 2020, during which a single dose of cefuroxime was administered to healthy male volunteers, and pharmacokinetics were assessed at predetermined time intervals. The study was performed in compliance with good clinical practices and was initially screened and accredited by the Ethical Committee of the University of Agriculture, Faisalabad. The experimental research was approved by the Graduate Studies and Research Board (GSRB) of The University of Agriculture Faisalabad.

(IRB:DGS No.2945– 60) Complete information regarding the experiment was provided to all participants and informed consent was obtained before the beginning of the investigation.

Volunteers were selected based on their previous medical history and laboratory investigations, including hematological parameter screening, blood chemistry, and urinalysis. Healthy individuals without the evidence of any acute or chronic hepatic & renal disease, and/or beta-lactam antibiotic allergy were included in the study. The volunteers were advised and monitored for not taking any medication two weeks before and during the investigation period. Obesity, cefuroxime sensitivity, known allergy to beta-lactam antibiotics, smoking, and exposure to any drug one week before study onset time, and missing informed consent were decided as exclusion criteria. All subjects were maintained on the same diet throughout the study period. The demographic characteristics of the male participants in the study were as follows: the average age was 26.87 years, with standard deviation (SD) of 0.29 years. The mean weight was 70.87 kg, with a SD of 0.63 kg. The average height of the subjects was 165.37 cm, with a SD of 1.1 cm.

A single dose study design was used as described by R. D. Foord (1976) to investigate the effects of genetic and environmental factors on the pharmacokinetics of cefuroxime in the Pakistani population.[18] After overnight fasting, a single dose of cefuroxime sodium 750 mg was administered intramuscularly to all the subjects. The same breakfast and lunch were given to the subjects according to their schedule. Beverages and foods containing caffeine were not allowed during the study period. A sterile cannula (24G) was used to withdraw 5ml blood samples in heparinized vacutainers at pre-selected or pre-determined time intervals of 0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, and 6h. Plasma was made from the blood samples. This was performed by centrifuging the vacutainers at 2500 rpm for 15 min. Once the plasma was separated, it was kept at -20°C till further analysis.

A reference standard powder of cefuroxime was provided by GlaxoSmithKline Laboratories Limited, Karachi, Pakistan. Zinacef® injection vials (cefuroxime sodium 750mg) of GlaxoSmithKline Laboratories Limited, Karachi. HPLC-grade acetic acid, methanol, and dimethylformamide (DMF) were purchased from Merck Chemical Laboratories (Germany).

Plasma samples for cefuroxime sodium were analyzed using high-performance liquid chromatography (HPLC), as described and validated by Olguin et al.[16] Separation of cefuroxime separation was carried out in a BDS thermohypersil (4.6×250 mm; 5µm) C18 column. The mobile phase, consisting of acetic acid/water/methanol at a ratio of 1:69:30 (v/v), was eluted at a flow rate of 1.5mL/min and the effluent was analyzed using a UV detector (Sycum S32012) at a wavelength of 281 nm, whereas the column temperature was fixed at 35 °C.

Control samples with known concentrations of cefuroxime were prepared by dissolving 1 mg of cefuroxime sodium in 1000µL distilled

water to obtain concentrations of 1µg/µL which were further used to prepare dilutions of the cefuroxime standard at concentrations of 1, 10, 20, 40, 50, 60, 100 and 500µg/mL.

Cefuroxime was extracted from the plasma samples by adding 1mL of dimethylformamide to 1mL of plasma. The mixture was vortexed for 5 min, followed by centrifugation at 400 g for 10 min. The supernatant (0.8mL) was diluted with an equal amount of water to allow it to pass through 0.45 µ filters.

The retention time for cefuroxime was 7.5 minutes without any significant interfering peaks. The calibration curve showed a linear relationship over the concentration range of 0.5-500µg/ml. The detection limit of cefuroxime was 0.5µg/mL and the limit of quantification was 1µg/mL. The regression equation was *y=24.2x+427.85* and the correlation coefficient was R_2= 0.9992.

A semi-logarithmic graph paper was used to plot a graph between plasma concentrations and time. Data was analyzed using two-compartmental open model. Drug concentration was calculated from plasma samples using individual plasma drug concentration-time curves. Cefuroxime Half-life (t1/2), peak plasma concentration (Cmax), time to peak plasma concentration (Tmax), and area under the curve (AUC) were the pharmacokinetic parameters that were calculated. The pharmacokinetic parameters of cefuroxime were calculated using MW/PHRAM software, version 3.02 (copyright 1987–1991) by F. Rombout. This MEDI WARE product was developed in collaboration with the University Centre for Pharmacy, Department of Pharmacology and Therapeutics at the University of Groningen, and Medi/Ware.

RESULTS:

Pharmacokinetic parameters of cefuroxime were analyzed by two-compartmental open model without lag time and are described in Table 2. The mean plasma concentration of cefuroxime in healthy subjects following a single intramuscular administration of cefuroxime at 10.7mg/kg is shown in Figure 1. Time to peak plasma concentration ($T_{max)}$ was calculated to be 0.75±0.02 hr at 10.7 mg/kg/IM. In the present study, absorption of cefuroxime was found to be rapid and the drug was detected in plasma after 0.25h. Maximum plasma concentration (C_{max}) was calculated to be 31.35±0.90µg/mL. The elimination half-life was calculated to be 1.4±0.1h.

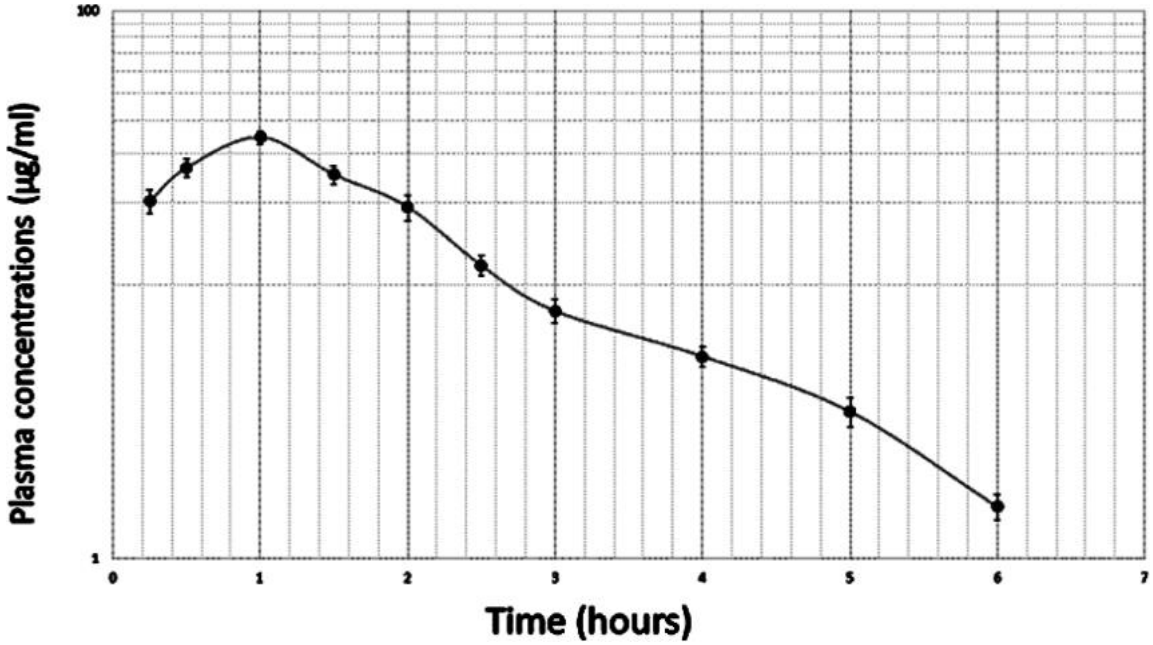

Figure 1: Mean ± SD plasma concentration time curve of cefuroxime

Parameter	C_{max} (µg/ml)	T_{max} (hr)	K_a (hr^{-1})	$t_{1/2\alpha}$ (hr)	A (µg/ml)	α (hr^{-1})	B (µg/ml)	β (hr^{-1})	$t_{1/2\beta}$ (hr)	V_c (l/kg)	V_d (l/kg)	K_{el} (hr^{-1})	K_{12} (hr^{-1})	K_{21} (hr^{-1})	Cl (l/hr/kg)
Mean	31.35	0.75	1.63	0.43	48.74	1.52	22.97	0.49	1.4	0.15	0.28	0.91	0.28	0.83	0.13
±SD	0.90	0.02	0.12	0.03	7.32	0.23	5.6	0.03	0.1	0.01	0.02	0.07	0.05	0.16	0.01

*maximum plasma concentration (**C_{max}**)*
*time to peak plasma concentration (**T_{max}**)*
*absorption rate constant (**Ka**)*
*distribution half-life (**$t_{1/2\alpha}$**)*
*zero-time drug concentration at distribution phase (**A**)*
*the distribution rate constant (**α**),*
*zero-time drug concentration at elimination phase (**B**)*
*the elimination rate constant (**β**)*
*elimination half-life (**$t_{1/2\beta}$**)*
*the volume of distribution of the central compartment (**V_c**)*
*volume of distribution (**V_d**)*
*the elimination rate constant (**K_{el}**)*
*first order transfer rate constant for distribution from central to peripheral compartment (**K_{12}**)*
*first order transfer rate constant for distribution from peripheral to central compartment (**K_{21}**)*
*clearance (**Cl**)*

DISCUSSION:

The values of maximum plasma concentration, time to peak plasma concentration, AUC, volume of distribution, t1/2, and clearance were compared to those reported in other studies conducted in various population subsets, as referenced in the literature. The differences in maximum plasma concentration and time to reach peak plasma concentration of the drug are influenced by physiological factors such as age, diet, sex, enzymatic polymorphism, and pharmaceutical factors that are related to drug such as particle size, crystal shape or salt form, and the nature of excipients, which ultimately affect the rate and extent of drug absorption from the site of administration.[7, 18] Both C_{max} and T_{max} are also influenced by the dose, dosage form, and route of administration.

The peak plasma concentration time (T_{max}) for the 10.7 mg/kg dose administered intramuscularly was 0.75 hours ± 0.02, which was consistent with a prior study conducted on the American population that used the same dosage.[17] In contrast, an Arab population study at a 7 mg/kg dose found a T_{max} of 1.92 hours ± 0.62.17 A study by Barbour et al. (2009) reported a T_{max} of 0.60 hours ± 0.22, which was similar to the current study's T_{max}.[20]

The maximum plasma concentration (C_{max}) for the present study, at 31.35 µg/mL ± 0.90, was lower than the C_{max} of 34.90 µg/mL observed at the same dosage in the prior study. The C_{max} in the current study was also lower than the C_{max} of 66.8 µg/mL ± 18.9 µg/mL observed in a study at a much higher dose of 20 mg/kg that was administered intravenously.[17, 19] The C_{max} of the suspension dosage form was 7µg/mL at a dose of 20mg/kg given orally, which was lower compared to the C_{max} in the present study.[19] In the Arab population, C_{max} was 4.28±1.47 and

4.48±1.18µg/mL at a dose of 7mg/kg of two different formulation.[17]

The elimination half-life ($t_{1/2\beta}$) of the drug depends on clearance and volume of distribution. It changes as a function of clearance and volume of distribution. An Iraqi study reported a half-life of 1.5 ± 0.62h for cefuroxime at a dose of 7mg/kg given orally while it was 1.4h in our study.[22] A study also found the same half-life of cefuroxime in children at a dose of 15mg/kg given orally.[21] However, it was 1.8h at a dose of 15mg/kg given intravenously (IV) in a study by Nascimento et al., which was longer than the present study.[23] The elimination half-life of cefuroxime was reported to be 3.07±0.37h in foreign neonates, which could be due to under-developed excretory organs that result in slow elimination of the drug from the body.[22] In the Arab population, the elimination half-life of two different brands of oral cefuroxime at a dose of 4mg/kg was 1.22±0.25h and 1.13±0.18h, which was shorter than the present study.[17] Similarly, a shorter half-life of cefuroxime in the Polish healthy population had been reported at a dose of 7mg/kg.[24,25] The half-life of cefuroxime was found 1.50±0.63h in dogs at a dose of 10mg/kg given intramuscularly (IM), while in rats was 37.5±8.5 min at a dose of 2.02mg/oral.[26,27] In goats, cefuroxime half-life was longer at a dose of 40mg/kg IM was 2.11h, which was considerably longer than the present study.[28] The difference in half-life might be due to differences in drug administration, elimination rate constants, and differences in species.

The average volume of distribution (Vd) in the Pakistani population was less than the reported Vd of cefuroxime at 25mg/kg/IV in neonates.[21,22] Nascimento et al. reported a reduced volume of distribution (Vd) for cefuroxime (0.19 L/kg) in patients undergoing cardiopulmonary bypass surgery.[23] The Vd in children with mild, moderate, and severe disease conditions was 1.5,1.9 and 3.1/kg, respectively, which was higher than the present study. This above-mentioned difference in Vd may be due to the drug-disease interaction.[17]

A study reported clearance of cefuroxime of 0.08 ± 0.016/kg/h in neonates while it was 0.14±0.01/kg/h in the present study.[24] The clearance of cefuroxime was calculated to be 6.01/h and 8.6/h in the Swedish and Dutch healthy population, respectively, which were comparable to the present study conducted in the Pakistani population.[29,30] The total plasma clearance of cefuroxime in goats and dogs was 29.08±2.61 at 20mg/kg/IM dose and 0.31±0.03/kg/h at 20mg/kg/IV dose, respectively, which was much higher than the present study.[26,31] The difference in total body clearance of cefuroxime in comparison to other population subsets and species may be due to differences in cefuroxime plasma protein binding and renal perfusion rate.[32,33]

Al-Said et al. reported a lower Kel of cefuroxime in the Arab population as compared to the findings of the present study.[19] No significant difference was found between the Kel in the current study and other studies conducted in varied subsets of the healthy population of different ethnicities.[20,22] Therefore, no effect of genetics and environment was found on the elimination rate constant of cefuroxime.

CONCLUSION:

Cefuroxime, a beta-lactam antibiotic, exhibits time-dependent killing. The dosing interval should be adjusted so that the plasma drug concentration remains above the minimum inhibitory concentration for the duration of the dosing interval. Based on results obtained and subsequent analysis from the present investigation, the recommended dosage regimen for cefuroxime in the Pakistani population is recommended to be 7.31 mg/kg and 7.16 mg/kg as priming and maintenance dose, respectively, to be administered every 8 hours.

CONFLICT OF INTEREST

None

SOURCE OF FUNDING

None

AUTHOR'S CONTRIBUTION:
SS: Conceptualization
MHUR: Statistical Data Analysis, Manuscript writing
MR: Manuscript Writing and Editing
SY: Manuscript Editing
QAI: Supervision, Critical Review
SR: Data Collection

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Original Article

PLACENTA ACCRETA: IS PRIMARY ELECTIVE CAESAREAN SECTION A PREDISPOSING RISK FACTOR?

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Abstract:

Background: Placenta accrete spectrum is a fatal obstetrical condition associated with serious feto-maternal morbidity and mortality. It is associated with a variety of risk factors including primary elective caesarean section. The objective of this study is to determine the association of placenta accreta spectrum with primary elective caesarean section.

Materials & Methods: This case-control study was conducted over two years (June 2022 to May 2024) at Sir Ganga Ram Hospital, Lahore, including 100 pregnant women with placenta previa. Demographic and obstetric details were noted in all patients and their caesarean section and postoperative management were done as per hospital policy. Intraoperatively type of placenta previa and type of placenta accreta spectrum was noted. Based on intraoperative findings 50 women with placenta previa, adherent placenta, and one or more previous caesarean sections were enrolled in Group A (cases), while 50 women with placenta previa and previous caesarean sections were enrolled in Group B (controls). Maternal outcomes along with demographic and obstetric details were noted in preformed proforma and analyzed using SPSS. Results were considered statistically significant with a p-value less than 0.05.

Results: The number of elective primary lower segment caesarean section (LSCS) were higher in Group A (cases) 37 (74%) than 27 (54%) in Group B (controls) (P value= 0.037). Amongst women with placenta accreta spectrum in Group A (cases), the present study found placenta accreta in 64%, placenta increta in 22%, and placenta percreta in 14% of women.

Conclusion: Elective primary caesarean section is associated with a higher risk of placenta accreta spectrum.

Keywords: Placenta Accreta, Primary, Elective, Caesarean Section, Risk Factor.

doi: https://doi.org/10.51127/JAMDCV06I03OA04

How to site this:
Chaudhry S, Humayun S, Ahsan S, Ashraf N. Placenta Accreta: Is Primary Elective Caesarean Section a Predisposing Risk Factor? JAMDC, 2024: 6(3): 107-113
doi: https://doi.org/10.51127/JAMDCV06I03OA04

INTRODUCTION

Placenta accreta spectrum (PAS), a serious and potentially fatal complication of pregnancy, is marked by the abnormal attachment of the placenta to the uterine wall, resulting from the absence or insufficiency of Nitabuch's layer in the decidua.[1,2] Placenta accreta spectrum is categorized into three types: placenta accreta, where the placental tissue attaches to the decidual layer of the myometrium; placenta increta, where the placental villi infiltrate deeper into the myometrium; and placenta percreta, where the chorionic villi extend through the uterine serosa and may invade nearby structures, such as the bladder or broad ligament.[3] This can cause considerable maternal morbidity including severe

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Date of Submission: 23-07-2024
Date of 1st Review: 07-08-2024
Date of 2nd Review 15-08-2024
Date of Acceptance: 30-08-2024

peripartum haemorrhage, renal failure, disseminated intravascular coagulation (DIC), adult respiratory distress syndrome (ARDS), massive blood transfusion, hysterectomy, intensive care unit (ICU) care, bladder damage and even maternal death.[4, 5, 6, 7]

In the last 50 years, the incidence of PAS has increased 10-fold. Recently the frequency of PAS has been reported to be between 1:2500 and 1:540. It is currently the most commonly reported indication of peripartum hysterectomy. The incidence is mainly rising due to the increasing rate of caesarean delivery.[3,7] The other important predisposing factors for this serious complication include advanced maternal age, increasing parity, smoking, vigorous curettage leading to Asherman syndrome, submucous fibroid, and myomectomy.[3,8] M. Kamara et al. revealed that elective primary cesarean section influences the risk of placenta accreta. Their findings indicated that women who had a primary elective cesarean section were three times more likely to experience placenta accreta in the next pregnancy complicated by placenta previa, compared to those who had primary emergency caesarean section.[7]

Risk factors like advanced maternal age, increasing parity, and several caesarean sections, etc. have been proven to have an association with the placenta accreta spectrum in the literature but limited evidence is present to examine the association of the nature of caesarean section with placenta accreta. The objective of the present study was to determine the association of PAS with primary elective caesarean section. This study may identify yet another preventable risk factor for placenta accreta. The current study was based on the hypothesis that primary elective caesarean section increases the risk of placenta accreta spectrum in patients with placenta previa.

MATERIALS AND METHODS

It was a case-control study, conducted and completed in 2 years period (June 2022 to May 2024) in Labor room of Gynae Unit 1, Sir Ganga Ram Hospital Lahore, after obtaining permission from the institutional ethical review board (IRB # 67/CIERB). Hundred women with placenta previa, 20-35-year-old, para 1 or more, in their 2nd or 3rd trimester, and history of 1 or more caesarean sections presenting in the emergency labor room for caesarean section, were enrolled in the study after informed consent using a purposive convenient sampling technique. They were interviewed to gather demographic details on a proforma. Their caesarean section and postoperative management were done as per hospital protocol. Intraoperatively type of placenta previa and type of placenta accreta spectrum was noted. Based on intraoperative findings, 50 pregnant women with placenta previa, a history of 1 or more caesarean sections and adherent placenta were enrolled in Group A (cases). Similarly, 50 pregnant women with placenta previa and a history of 1 or more caesarean section were enrolled in Group B (controls). Morbidity including caesarean hysterectomy, B Lynch suture application, and mortality were also noted. All data was recorded in a preformed proforma.

Women with placenta previa without any caesarean section, primigravida, placenta accreta without placenta previa and women unaware of the nature of their primary caesarean sections were not included in the study.

A number of previous caesarean sections was kept equal in both groups to address this confounding factor. Confidentiality and anonymity were ensured.

The data analysis was done by using SPSS (Statistical Package for Social Sciences) version 26. Mean ± SD and range were given for quantitative variables i.e. age and gestational age, while, frequency and percentages were given for qualitative variables like parity, number of abortions, number of previous caesarean sections, vaginal deliveries before primary caesarean section,

nature of primary caesarean section, etc. Chi square test at 5% level of significance was used to assess the association for qualitative data. A p-value <0.05 was considered as statistically significant.

RESULTS

The study included an overall hundred patients with placenta previa, 50 in each group (Group A and Group B). The age of Group A (cases) ranged from 23- 40 (mean± SD: 30.29 ±1.13 years), while that of Group B (controls) ranged from 22-37 (mean± SD: 28.18 ±1.28 years). The mean± SD gestational age was 33.97 ±0.23 weeks in Group A (cases) compared to 35.84 ±0.25 weeks in Group B (controls). In Group A (cases) 37 patients were para 2–4, while 13 were para 5 or more, which was similar to Group B (controls) (p value 0.475). Both groups had similar parity, number of abortions, and number of lower segment Caesarean section (LSCS). The two groups differed in the number of abortions and previous cesarean sections. (Table 1).

Our main outcome parameter was the number of elective primary LSCS in women with placenta accreta spectrum (Group A) compared to women with placenta previa (group B). It was observed that the majority (74%) of patients with placenta accreta spectrum (Group A) had pre-labor elective primary caesarean section, while in women with placenta previa (group B) number of elective primary LSCS was 54%, which was significantly lesser than group A (p value= 0.037) (Table 1).

Number of vaginal deliveries before primary caesarean section was not significantly different between groups (p value=0.65).

Table 1: Comparison of Demographic and Pregnancy Characteristics Between Placenta Accreta group A and B

Maternal age (Years)			
	Group A (Cases) (n=50)	**Group B (Controls) (n=50)**	**P value**
Mean age (Years)	30.29 ±1.13	28.18 ±1.28	0.001
Minimum age	23	22	
Maximum Age	40	37	
Gestational age (Weeks)			
	Group A (Cases)	**Control (n=50)**	**p-value**
Mean age (weeks)	33.97 ±0.23	35.84 ±0.25	0.001
Minimum age	24	24	
Maximum Age	40	39	
Parity			
	Group A (Cases) (n=50)	**Group B (Controls) (n=50)**	**p-value**
P (2 - 4)	37 (74%)	40 (80%)	0.475
P >5	13 (26%)	10 (20%)	
No. of Abortions			
	Group A (Cases)	**Group B (Controls)**	**p-value**
0	37 (74%)	34 (68%)	0.4825
1	8 (16%)	13 (26%)	
2	4 (8%)	3(6%)	
6	1 (2%)	0	
Number of Previous LSCS			
	Group A (Cases)	**Group B (Controls)**	**p-value**
1	12 (24%)	10 (20%)	0.934
2	26 (52%)	29 (58%)	
3	10 (20%)	10 (20%)	
4	2(4%)	1(2%)	

Nature of primary LSCS			
	Group A (Cases)	**Group B (Controls)**	**p-value**
Elective	37 (74%)	27 (54%)	0.037
Emergency	13 (26%)	23 (46%)	
Normal Delivery before primary LSCS			
	Group A (Cases)	**Group B (Controls)**	**p-value**
Yes	15(30%)	13(26%)	0.65
No	35 (70%)	37 (74%)	

It was observed that majority of patients had major degree placenta previa in both groups. Significantly higher number of patients with placenta accreta spectrum in group A ended up in hysterectomy as compared to patients with placenta previa group B (p-value = 0.000) (Table 2). Only one mortality was observed in study population, which was a woman with placenta accreta spectrum in group A.

Table 2: Maternal outcome

Type of Placenta			
	Group A (Cases) (n=50)	**Group B (Controls) (n=50)**	**p-value**
Minorant	3 (6%)	3 (6%)	0.0068
Minor Post	0 (0%)	9 (18%)	
Major	47 (94%)	38 (76%)	
Hysterectomy			
	Group A (Cases) (n=50)	**Group B (Controls) (n=50)**	**p-value**
Yes	35 (70%)	5 (10%)	0.00
No	15 (30%)	45 (90%)	
B lynch			
	Group A (Cases) (n=50)	**Group B (Controls) (n=50)**	**p-value**
Yes	6 (12%)	7 (14%)	0.766
No	44 (88%)	43 (86%)	
Maternal Mortality			
	Group A (Cases) (n=50)	**Group B (Controls) (n=50)**	**p-value**
Yes	1 (2%)	0 (0%)	0.31
No	60 (98%)	50 (100%)	

Intraoperatively, it was noted that 64% of women with placenta accreta spectrum had placenta accreta, while placenta increta and placenta percreta were noted in 22% and 7% respectively. (Table 3)

Table 3: Types of Placenta accreta spectrum among Group A (women with placenta accreta spectrum)

		(n=50)	**Percentage**
Abnormal Placentation	Accreta	32	64%
	Increta	11	22%
	Percreta	7	14%

DISCUSSION

The rising rate of caesarean section is paralleled by an increase in placenta accrete.[9] This study highlights the role of primary elective caesarean section in contributing to placenta accreta spectrum. The uterine myometrium heals through the deposition of collagen and fibrin, instead of regenerating muscle cells. Scar tissue often shows edema, inflammation, and myofiber disarray, with apoptosis reducing myometrial volume and density. Scarring leads to permanent changes in vascularization and myometrium. In patients with repeated lower-segment caesarean sections (LSCS), there is a lower uterine segment composed mainly of fibrotic scar tissue and fewer myofibers, making it more prone to disruption of myometrium at the surgical site.[10] The literature suggests that the mechanism behind placenta accreta in elective primary caesarean sections may be due to differences in incision level, size, and healing compared to emergency caesareans. In an elective caesarean, the quiescent uterus has a thicker myometrium, resulting in a higher and thicker lower uterine segment. This makes the incision, suturing, and hemostasis more difficult and traumatic.

Additionally, uterine contractions during labor may help shorten the wound, reduce endometrial damage, and facilitate healing. Another hypothesis suggests that the immunologically active environment in the laboring uterus promotes healing, and the absence of this activation in an elective caesarean might lead to abnormal placentation in future pregnancies.[11]

In the present study women in Group A were older than Group B. Kamara et al and Qureshi et al reported no difference in maternal age between the two groups while, Shi XM et al reported women with placenta accreta spectrum to be younger.[7,11,12] In current study, mean gestational age was lesser in Group A than Group B, which is comparable to other studies.[11,12,13,14] Parity and number of abortions were comparable in both groups in current study. In current study, the number of previous caesarean sections are kept equal in both groups to remove the bias in the result as number of previous LSCS is itself a strong risk factor for placenta accreta spectrum. The current study observed a higher rate of elective primary caesarean sections in the women with placenta accrete spectrum (Group A) compared to women with placenta previa (Group B) (p-value = 0.037), consistent with findings from Shi XM et al, who also reported a greater frequency of elective primary caesarean section in women with PAS in comparison to women with placenta previa (Group B) (90.1% vs. 69.9%, $p < 0.001$).[11] This finding has also been reported by other researchers, who demonstrated a positive association between elective primary caesarean section and placenta accreta spectrum. Normal vaginal delivery before primary LSCS was not associated with placenta accreta in present study, which is consistent with the results of others.[12] Hu et al found patients having a primary elective section to be 2.11 times, more likely to have placenta previa (95% CI: 1.52–2.94), 2.11 times more likely to have placenta accreta (95% CI: 1.47–3.04), similar to our findings.[14] Downes et al. reported 2 folds increased risk of placenta previa in patients with pre-labour cesarean section.[15] This underscores the importance of labor about caesarean section and its role in the potential development of future placenta previa and subsequently placenta accreta. It also emphasizes that clinical decisions regarding primary caesarean section should be done very cautiously and strictly on medical grounds.[16]

The present study found placenta accreta (64%) to be the most common form of PAS in patients with placenta accrete spectrum followed by increta (22%) and percreta (14%). Kamara et al demonstrated a similar trend of placenta accreta spectrum in his study but Shi XM reported placenta increta to be most common type of placenta accreta spectrum followed by accreta and percreta.[7,11] Another researcher has documented placenta accrete in 70.9%, placenta increta in 15.2% and placenta percreta in 10.8%, which are almost similar to our findings.[5,6]

CONCLUSION

Elective primary caesarean section is associated with a higher risk of placenta accreta spectrum in later pregnancies with placenta previa.

Thus, obstetricians should decide on elective primary caesarean section very thoughtfully, only in women at unacceptable risk of complications due to vaginal delivery or an emergency caesarean. Additionally, one should anticipate the risk of placenta accreta spectrum when managing women with placenta previa with primary elective caesarean section.

CONFLICT OF INTEREST

None

SOURCE OF FUNDING

None

DISCLOSURE

All authors declare there was no financial facilitation by any pharmaceutical company or any other commercial institution.

AUTHOR'S CONTRIBUTION

SC: Conceptualization, study design, proforma design, Manuscript draft writing, review & editing

SH: Manuscript draft review & editing

SA: Data collection & confirmation

NA: data analysis& interpretation

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Original Article

ELUCIDATING THE EFFECT OF MULTIMODAL THERAPY (MMT) ALONE AND MMT ALONG WITH COGNITIVE BEHAVIORAL THERAPY (CBT) ON DISABILITY IN PATIENTS OF CHRONIC LOW BACK PAIN (CLBP).

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Abstract:

Background: Low back pain (LBP) is considered one of the leading global public health issues. It contributes to significant disability and limits participation in regular work activities and the social life of people. The World Health Organization (WHO), stated an estimate that people around 619 million all around the globe have been or are going through low back pain. Most individuals hold the capability to recover within 12 weeks while a significant number of people progress towards chronic low back pain which is further marked by persistent pain and disability. The objective of this research is to study the effect of multimodal therapy (MMT) alone and MMT along with cognitive behavioral therapy (CBT) on disability in patients of chronic low back pain (CLBP).

Material & Methods: A randomized controlled trial involved two intervention arms which was performed at the Akhtar Saeed Physiotherapy Clinic in Lahore, Pakistan. The people who participated in the study were split into two groups: Group A received only Multimodal Therapy (MMT), whereas Group B was treated with a combination of MMT and Cognitive Behavioral Therapy (CBT). Each group included equal participants.

Results: The mean difference in MODI scores was 8.66 (95% CI = 6.20-11.12, P < 0.001) for Group A and 17.24 (95% CI = 15.15-19.32, P < 0.001) for Group B which highlighted the effectiveness of the combination treatment of CBT & MMT in reducing disability than MMT alone.

Conclusions: The results indicated a significant mean difference in group B. The mean difference suggests that the combination of CBT & MMT is more effective in reducing disability as measured by MODI than MMT alone.

doi: https://doi.org/10.51127/JAMDCV06I03OA05

How to site this:
Alam M. M., Chandran S. P., Alam S., Elucidating the Effect of Multimodal Therapy (MMT) Alone and MMT Along with Cognitive Behavioral Therapy (CBT) On Disability in Patients of Chronic Low Back Pain (CLBP). JAMDC, 2024: 6(3): 114-119
doi: https://doi.org/10.51127/JAMDCV06I03OA05

INTRODUCTION:

Low back pain (LBP) is one of the most significant public health concerns globally, affecting millions of individuals. It limits participation in regular work and social activities, contributing to disability and significant economic burden. The World Health Organization (WHO) estimates that 619 million people worldwide suffer from LBP, a condition that greatly impacts work productivity and causes considerable social and economic challenges.[1] While many individuals recover from acute LBP within 12 weeks, a substantial proportion progresses to chronic low back pain

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Date of Submission: 18-07-2024
Date of 1st Review: 01-08-2024
Date of 2nd Review: 06-08-2024
Date of Acceptance: 15-08-2024

(CLBP), which is marked by persistent pain and disability that lasts beyond this period.[2]

The transition from acute to chronic pain is often influenced by psychosocial factors, including depression, fear-avoidance beliefs, and maladaptive coping strategies. These factors are central to the fear-avoidance model of chronic pain, which highlights how psychological responses can exacerbate the perception of pain and delay recovery.[3] Thus, understanding and addressing these psychosocial components is crucial for managing LBP effectively. A bio-psychosocial model that integrates both physical and psychological factors is essential in treating this complex condition.[4]

Traditional treatment approaches for LBP, such as spinal manipulation, massage therapy, and acupuncture, often focus solely on the physical aspects of pain. While these treatments may provide short-term relief, they do not address the full spectrum of factors contributing to chronic pain. Therefore, physiotherapists are increasingly encouraged to integrate psychological interventions like cognitive behavioral therapy (CBT) into their practice to enhance long-term outcomes for patients with CLBP.[5] CBT helps patients identify and modify negative thoughts and behaviors related to pain, thus improving both pain perception and overall emotional well-being. [6]

Research has shown that combining CBT with multimodal therapy (MMT), which includes exercises and other physical interventions, is more effective than MMT alone in managing chronic LBP. A multidisciplinary approach, addressing both the psychological and physical components of pain, leads to better clinical outcomes, including reductions in pain and disability.[7] However, one of the challenges in implementing CBT is the limited access to trained professionals, particularly in rural or underserved areas. The development of digital health solutions, such as online CBT programs, has shown promise in bridging this gap and providing accessible treatment options for individuals with CLBP.[8,9]

The benefits of CBT extend beyond pain relief. Studies have shown that CBT can help improve self-efficacy, reduce fear, and enhance patients' overall quality of life. For example, patients who undergo CBT are more likely to engage in physical activity, which is essential for managing CLBP in the long term. Integrating CBT with MMT provides a more comprehensive treatment approach, especially for those whose pain is significantly influenced by psychological factors.[10] In addition to traditional CBT, other approaches like cognitive functional therapy (CFT) have emerged, offering a more holistic treatment that combines physical exercises with psychological strategies.[11,12]

Despite the growing evidence supporting the use of CBT and MMT for chronic LBP, there remains a significant gap in integrating these therapies into routine clinical practice. Further training for physiotherapists and other healthcare professionals is needed to ensure that these evidence-based practices are effectively delivered to patients. Additionally, more research is needed to evaluate the long-term effectiveness of these combined approaches and their potential for reducing the global burden of CLBP.

MATERIAL & METHODS

A randomized controlled trial with two treatment groups was carried out at the Akhtar Saeed Clinic of Physical Therapy in Lahore, Pakistan after approval of study from Research and Ethic Committee of Akhtar Saeed College of Rehabilitation Sciences Lahore; reference no. REC-18-2023. Participants were randomly divided into two groups: Group A, receiving only Multimodal Therapy (MMT), and Group B, undergoing a combination of MMT and Cognitive Behavioral Therapy (CBT). Both groups had the same number of people added to the study. The study involved 108 people suffering from chronic low back pain (LBP), identified as being at moderate risk for disability in longer terms. Recruitment was done through advertisements placed in local

medical and allied health facilities, inviting individuals with LBP to join the study.

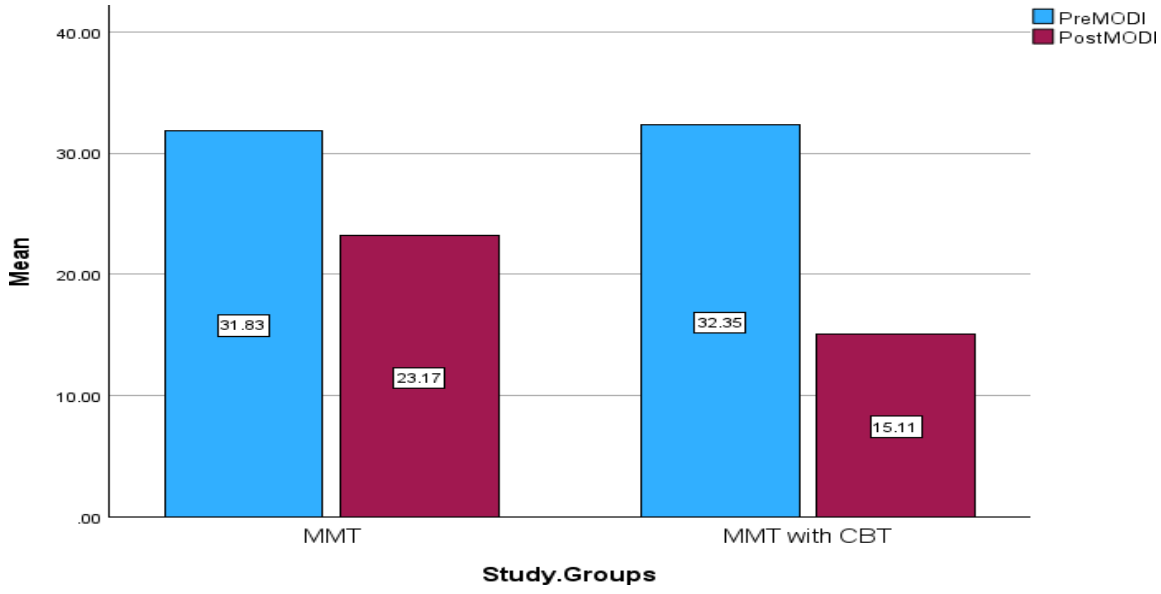
The physiotherapist used the Keele STarT Back Screening Tool along with an evaluation form to assess the eligibility of the people willing to take part in the study. This tool categorized the people into the medium-risk group, indicating a moderate probability of chronic low back pain (LBP) development. All qualifying participants signed informed consent forms after receiving detailed explanations of the study procedures. Eligibility required participants to be at least 18 years of age and should have non-specific low back pain, which should be persisting for over three months, as determined by the Keele STarT Back Screening Tool. Individuals with serious spinal issues (such as fractures, cancer, or infections), inflammatory conditions, canal stenosis, or cauda equina syndrome were excluded from the study.

RESULTS

The demographic characteristics of the participants in the two groups were similar in terms of age. The average age of participants in Group A (MMT) was 47.01 years, with a standard deviation of 15.25 years, while Group B (CBT & MMT) had an average age of 47.16 years, with a standard deviation of 15.03 years.Regarding gender distribution, Group A (MMT) consisted of 46.3% males and 53.7% females. In contrast, Group B (CBT & MMT) had 51.9% males and 48.1% females.

Table 1; Between and within the group comparison for MODI

Variable	Group A (MMT) (Mean ± SD)	Group B (CBT & MMT) (Mean ± SD)	Mean Diff 95% CI	P value
Pre-Treatment MODI	31.83 ± 6.81	32.35 ± 6.15	-0.51 (-2.99,1.95)	0.679
Post-Treatment MODI	23.16 ± 5.52	15.11 ± 5.31	8.05 (1.04,5.98)	<0.001
Mean Diff	8.66 (6.20,11.12)	17.24 (15.15,19.32)		
P value	<0.001	<0.001		



The results of this study revealed that demographic analysis showed consistency with both groups having a similar mean age and gender distribution. The results of Pre-treatment MODI (Modified Oswestry Disability Index) scores were nearly identical between both the group with Group A having a mean ± SD of 31.83 ± 6.81 and Group B at 32.35 ± 6.15 with no significant difference (P = 0.679). The results of post-treatment of both the groups experienced a significant reduction in their MODI scores which indicated an improvement in their disability levels. However, the results of Group B (CBT and MMT) revealed a substantial decrease with a mean ± SD of 15.11 ± 5.31 as compared to Group one with a mean 23.16 ± 5.52. The mean difference in MODI scores was 8.66 (95% CI = 6.20-11.12, P < 0.001) for Group A and 17.24 (95% CI = 15.15-19.32, P < 0.001) for Group B which highlighted the combination of CBT & MMT is more effective in reducing disability than MMT alone.

DISCUSSION

The study results indicate that the combination of Cognitive Behavioral Therapy (CBT) and Multimodal Therapy (MMT) (Group B) is significantly more effective at reducing disability in patients with chronic low back pain (CLBP) than MMT alone (Group A). This is demonstrated by the Modified Oswestry Disability Index (MODI) scores, which showed a greater reduction in Group B compared to Group A. These findings align with existing research, which supports the effectiveness of combining CBT with physical therapies in managing chronic pain. A demographic analysis highlighted that both groups were well-balanced in age and gender distribution, consistent with the importance of demographic matching in randomized controlled trials to minimize bias.[13]

The pre-treatment MODI scores were almost identical between Group A (31.83 ± 6.81) and Group B (32.35 ± 6.15), with no statistically significant difference (P = 0.679). This similarity in baseline scores ensures that the post-treatment effects observed are attributable to the interventions rather than any pre-existing differences between the groups. Post-treatment, both groups experienced a significant reduction in their MODI scores, indicating an improvement in disability levels. However, the reduction was more pronounced in Group B (CBT & MMT) with a mean score of 15.11 ± 5.31 compared to Group A (MMT alone) with a mean score of 23.16 ± 5.52. The mean difference in MODI scores was 8.66 for Group A and 17.24 for Group B, both of which were statistically significant (P < 0.001).[14,15]

These findings align with the growing body of evidence suggesting that integrating psychological approaches with physical therapy provides superior outcomes for individuals suffering from CLBP. For instance, CBT, when integrated with physical therapy, leads to better functional outcomes and reduced disability.[16,17] Similarly, Cognitive Functional Therapy (CFT), which combines CBT principles with physical exercises, has proven more effective than traditional muscle training programs in improving function and reducing disability.[18]

One of the primary reasons for the superior outcomes in Group B could be attributed to the psychological benefits of CBT. By addressing maladaptive thought patterns, CBT helps patients develop more adaptive coping strategies. It also reduces fear-avoidance behaviors, breaking the cycle of pain and disability perpetuation.[19] Furthermore, CBT as part of a multidisciplinary approach helps patients manage the psychological distress often associated with CLBP, such as depression and anxiety, which exacerbate pain perception.[20,21]

CONCLUSION

Based on the findings of this study, it is observed that the participants of group B, showed better results when they were given a combination treatment of MMT combined with psychological sessions (CBT). The results showed a significant mean difference in Group B, indicating that when combined, Cognitive

Behavioral Therapy (CBT) and Multimodal Therapy (MMT) come out to be more effective at reducing disability, as measured by (MODI), as compared to MMT alone.

CONFLICT OF INTEREST

None

SOURCE OF FUNDING

None

AUTHOR'S CONTRIBUTION

MMA: Conceptualization, Data Collection, Manuscript Writing
SPC: Review of Manuscript
SA: Data Analysis

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Case Report

AN INFANT WITH A RARE ACQUIRED CNS DISORDER

Ahtisham Ali[1], Salwa Naeem[2], Maira Mahmood[3], Muhammad Usman Ajmal[4], Agha Shabbir Ali[5]

ABSTRACT

Acute disseminated encephalomyelitis (ADEM) or post-infectious encephalomyelitis is a rare neurological condition particularly affecting young children.

We report a case of 1-year 1-year-old boy with high grade fever, altered mental status, lower limb weakness and seizures. One week before these symptoms the child had complaints of loose stools and vomiting. His initial reports showed leukopenia, raised acute phase reactants and CSF showed elevated proteins. Clinical evaluation and MRI imaging confirmed the diagnosis of ADEM. Prompt treatment with high dose corticosteroids led to gradual improvement in neurological symptoms. The child was discharged with a tapering course of oral corticosteroids and followed up after 1 week, then after 2 weeks with improved neurological deficit and advised for further close follow-up.

This case emphasizes the importance of early recognition, aggressive treatment, and long-term monitoring in managing ADEM in children.

Keywords: Acute Disseminated Encephalomyelitis, ADEM, Pediatrics, IVIG

doi: https://doi.org/10.51127/JAMDCV06I03CR01

How to cite this:

Ali A., Naeem S., Mahmood M., Ajmal M. U., Ali A. S. An Infant with A Rare Acquired CNS Disorder. JAMDC, 2024; 6(3): 120-123

doi: https://doi.org/10.51127/JAMDCV06I02CR01

INTRODUCTION

ADEM is an acute, immune-mediated inflammatory disorder of the central nervous system, principally involving the demyelination of white matter in the brain and spinal cord.[1.] This condition is precipitated by an acute viral infection like chicken pox, smallpox, Epstein-Barr virus, or herpes simplex virus. ADEM is considered a rare illness with an estimated incidence of 0.8 per 100,000 population per year.[2.] The mean age of clinical presentation in pediatric cohort's ranges from 5 to 8 years[3] with slight male predominance.[4.]

ADEM is a monophasic disease but can present with relapsing cases. Literature reported that treatment with oral corticosteroids is associated with a reduced relapse rate. In recent collaborative studies, treatment other than steroids, like B cell targeted treatment and intravenous immunoglobulins were also associated with a reduction in relapse frequency.[5.]

In Pakistan, for three years, almost 25 children with polysymptomatic monophasic ADEM were reported from 2006-2008.[6.]

Here we present a case of ADEM in 1-year-old boy to highlight the significance of prompt diagnosis and treatment for a better outcome of the disease course.

CASE DESCRIPTION

A 1-year-old boy presented with a complaint of high-grade fever for 2 weeks and seizures for 3 days followed by altered mental status and weakness in lower limbs. The patient also had a history of loose stools and vomiting 1 week

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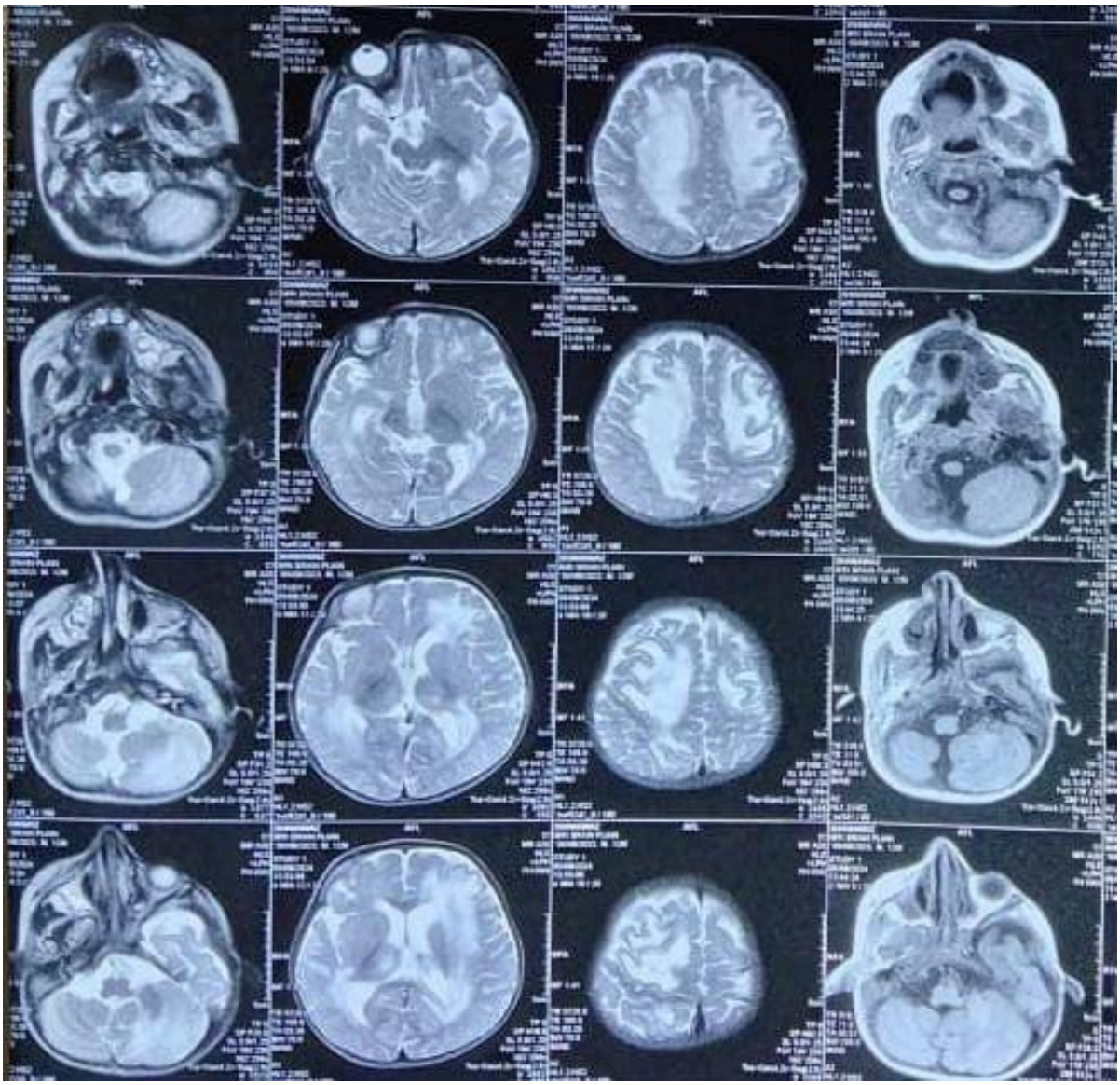
Date of Submission: 02-08-2024
Date of 1st Review: 15-08-2024
Date of 2nd Review: 20-08-2024
Date of Acceptance: 30-08-2024

back. On admission, the child was febrile (102 F) and drowsy with vitals; Pulse Rate 142/min, Respiratory Rate 46/min, Oxygen saturation 96% at room air, and Basal Sugar Rate 100mg/dl. Neurological examination revealed signs of encephalopathy with GCS 5/15 (E2V1M2), brisk tendon reflexes, hypertonia, and bilateral extensor planter responses with Power 3/5 in both lower limbs. The patient was admitted to the Pediatric Department of Public Sector Tertiary Care Hospital. Laboratory work-up showed relative leukopenia 4.4×10^9/l(4-11×10^9/l) and raised acute phase reactants CRP 25.1mg/L (Normal Range less than 0.700mg/L). Cerebrospinal fluid (CSF) was clear and analysis showed Glucose 82 mg/dl, Protein 149mg/dl (20-40mg/dL), LDH 45U/l, WBC 4/mm3 and RBCs 10/mm3. On Cranial Ultrasound, there was bilateral symmetrically increased echogenicity of deep cerebral white matter with periventricular cystic changes. A provisional diagnosis of viral encephalitis was made. The patient was started on the anti-viral drug acyclovir along with anti-epileptics i.e. Phenytoin and Lerace. As there was no improvement in neurological status after initial management, it led to extended workup i.e. MRI Brain which showed diffuse periventricular white matter hyperintensities in T2 and FLAIR extending to subcortical region, diffuse symmetrical intensities in thalamus and abnormal signal intensities in left cerebellar hemisphere including margins of fourth ventricle, suggestive of ADEM.



Based on clinical presentation and MRI findings, the diagnosis of ADEM was confirmed. Definitive management started with high-dose intravenous methylprednisolone for 5 days along with neuroprotective care, nasogastric feeding, and bladder, bowel, skin, and mouth care. Throughout treatment, the child showed gradual improvement in neurological status with GCS 11/15(E4V3M4) and was discharged after 14 days of hospital stay on a tapering course of oral corticosteroids (Prednisolone) over 4-6 weeks and scheduled for close outpatient follow-up with MRI report. On follow-up after 2 weeks, the patient developed eye contact and has started to respond to commands as well with GCS 13/15 (E4V4M5).

DISCUSSION

ADEM is an immune-mediated central nervous system (CNS) disorder, characterized by multifocal symptoms, encephalopathy, and typical MRI findings. While the etiology is not fully understood, ADEM is commonly preceded by viral infection suggesting an autoimmune response to myelin basic protein. In some children, ADEM can occur in a recurrent pattern or can lead to chronic diseases, such as multiple sclerosis[7].

ADEM can occur at any age but usually affects children and young adults. Initial symptoms and signs of ADEM usually begin within 2 days to 4 weeks after a viral infection (influenza, EBV, CMV, measles, mumps, rubella) and include systemic symptoms such as fever, malaise, headache, nausea, and vomiting followed by rapid onset encephalopathy (behavioral change or altered consciousness) associated with a combination of multifocal neurological deficits. CSF examination shows lymphocytic pleocytosis and elevated proteins. Typical lesions on MRI are multiple, bilateral but asymmetric, and widespread within the CNS, predominantly involving the white cerebral matter. MRI brain identifies lesions of subcortical white matter in 93% of patients while the percentage of lesions identified in other parts of the brain are as follows: cerebral cortex 80%, periventricular white matter 60%, deep gray matter and brainstem 47%[8].

ADEM is treated with high-dose intravenous corticosteroids as first-line therapy. One common protocol is 10-30 mg/kg/d of methylprednisolone (maximum dose of 1g/d) for 3–5 days[9]. Improvement may be observed within hours but usually requires several weeks for full recovery. An oral steroid tapering for 4-6 weeks is recommended, however, if it is 3 weeks or less it may increase the risk of relapse[10]. Other treatment options include IVIG 2g/kg given over 2-5 days[11] or plasmapheresis (5-7 exchanges done every other day). Even in those children who acquire good neurological recovery; behavioral, visual, and motor impairments may be seen. In this case, neurocognitive testing may prove useful in recognizing these impairments.

CONCLUSION

ADEM is a rare but serious condition that affects young children. Early recognition and prompt treatment with corticosteroids are crucial for a favorable outcome. Long-term follow-up is essential to monitor for potential relapses and to assess the child's neurological recovery. In this case, our patient responded well to treatment, highlighting the importance of a multidisciplinary approach in managing ADEM in pediatric patients.

CONFLICT OF INTEREST

None

SOURCE OF FUNDING

None

AUTHOR CONTRIBUTION

ASA: Supervision, Editing
MUA: Supervision, Editing, Discussion
AA: Discussion, References, Conclusion
SN: Abstract, Case Description
MM: Introduction, References

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