

ORIGINAL ARTICLES**COMPARISON OF THREE ANTIBIOTICS REGIMENS IN THE TREATMENT OF ACUTE PYOGENIC MENINGITIS**

Akhtar Waheed, Syed Anees Ahmed Gardezi

Armed Forces Institute Rehab Medicine Rawalpindi, Combined Military Hospital Kohat

ABSTRACT

Object: Aim of this study is to compare various antibiotics in setting of acute pyogenic meningitis.

Design: A quasi-experimental study.

Place and Duration of Study: CMH Kohat from Dec 1999 to March 2002.

Patients and Methods: Study was conducted in department of medicine Combined Military Hospital Kohat from Dec 1999 to March 2002. A total of sixty patients with provisional diagnosis of acute pyogenic meningitis between 13 - 50 years age belonging to heterogenous group of population mainly recruits from various military training centers were included in the study. Ten patients were excluded from study because of negative cerebro spinal fluid findings. These patients were started on group A antibiotics (Ceftriaxone, Ampicillin plus Chloramphenicol), group B (Ampicillin plus Chloramphenicol) and group C (Ceftriaxone) at random.

Result: The analysis of results of treatment with three different treatment regimens was done by noting complete recovery, complications and death. Twenty patients who were given group A regimen showed 90% complete recovery, one patient developed fulminant meningococemia recovered fully and another patient developed deafness with gradual recovery (10% complications). Amongst fifteen patients in group B regimen 87% patients showed complete recovery, one patient developed seizure finally controlled, another patient developed hydrocephalus and was referred for shunt procedures (13% complications). Fifteen patients who were started group C regimen 93.33% patients fully recovered and one patient developed fulminant meningococemia completely recovered but developed gangrene of toes for which amputation was done at a later stage (7% complications). The results of three treatment regimens were compared by using chi square test and were almost comparable (p-value > 0.05).

Conclusion: In the empirical treatment of acute pyogenic meningitis, ceftriaxone alone cheap, safe and is as effective as combination of ceftriaxone plus ampicillin plus chloramphenicol or combination ampicillin plus chloramphenicol.

Keywords: Pyogenic meningitis, antibiotics, ceftriaxone, ampicillin, chloramphenicol

INTRODUCTION

Bacterial meningitis continues to be an important source of morbidity and mortality inspite of the availability of effective

bactericidal antibiotics [1]. The annual incidence of bacterial meningitis is about 2-3/100,000 with peak incidence in infants and adolescents. More than 2000 deaths are reported annually in the United States. The disease is even more common in developing countries. Meningitis is a major health problem, as is evident by recent experience in

Correspondence: Brig Akhtar Waheed, Comdt, Armed Forces Institute Rehab Medicine, Rawalpindi.

Africa and South America. The disease is common in younger age group and populations where overcrowding occurs. In armed forces, over crowding in barracks and training centers is commonly seen [2], therefore outbreaks of acute pyogenic meningitis may occur. The disease is mostly common in winters and early spring, while lowest attack rate is in mid summer. Few diseases have been affected more by advent of antimicrobial therapy than bacterial meningitis [3]. From its recognition in 1805 to early 20th century, bacterial meningitis was fatal. The causative organisms responsible for bacterial meningitis differ according to different age groups.

In adults the common pathogens responsible for bacterial meningitis are *Neisseria meningitidis* and *Streptococcus pneumoniae* and less common organisms are *Hemophilus influenzae*, *Listeria monocytogenes*, *Staphylococcus aureus* (in skull fracture), *Cryptococcus neoformans* (in immunosuppressed) and *Mycobacterium tuberculosis*. Although introduction of antibiotics made it curable, morbidity and mortality from the disease remains unacceptably high. In any patient presenting with fever, abnormal behaviour, altered level of consciousness headache, vomiting and skin rash, signs of meningeal irritation should be elicited [4]. When positive or doubtful, lumbar puncture should be performed for CSF examination, if no contraindications exist. The turbid or greenish appearance of CSF is almost diagnostic of acute pyogenic meningitis. Appropriate antibiotics should be immediately started with out even waiting for CSF report, which has proven to minimize the ensuing complications [5]. Initially Penicillin and Chloramphenicol were the drugs of choice in this fatal disease in adults but the advent of third generation Cephalosporin has revolutionized the treatment of acute pyogenic meningitis. Third generation Cephalosporins almost cover all the bacteria responsible for acute pyogenic meningitis in adults except tuberculous and fungal

meningitis, however at the extremes of age Ampicillin is usually added with third generation Cephalosporins to cover the *Listeria monocytogenes* infection. The integration of a vaccine for H influenza type b (Hib) into the UK vaccination programme has led to marked decline in H influenza meningitis [6].

The purpose of this study was to see the effects of three different regimens of treatment of acute pyogenic meningitis by evaluating the improvement in clinical condition, rate of complications of disease and incidence of death due to this fatal disease.

PATIENTS AND METHODS

A quasi-experimental study was conducted in the department of medicine CMH Kohat. The period of study extended from Dec 1999 to March 2002. A total number of sixty patients between 13-50 years of age group were included in the study. These patients belonged to personals of armed forces, their families, civilian employees of defense forces and non-entitled civilian patients. Majority of patients were recruits of armed forces from various military training centers. Therefore patients included in the study belonged to a heterogeneous group of population regarding age, sex, occupation and residence. Ten patients were excluded from study because of negative CSF findings. On the basis of investigations fifty patients were found to be suffering from acute pyogenic meningitis. Gram staining of CSF, CSF culture, complete blood count (CBC), blood culture and antigen detection test was done on CSF of all patients. Three different regimens of treatment were started in these patients at random.

Drug regimens used included; group A : Ceftriaxone 2 gram iv x 12 hourly plus Chloramphenicol 1 gram iv x 6 hourly plus Ampicillin 2 gram iv x 4 hourly, group B : Ampicillin 2 gram iv 4 hourly plus Chloramphenicol 1 gram iv x 6 hourly, and group C : Ceftriaxone 2 gram iv x 12 hourly.

Twenty patients were given group A regimen, fifteen patients were started on group B regimen and fifteen patients were put on group C therapy. Response to different drug regimens was noted by observing fever, headache, vomiting, neck stiffness and level of consciousness. Complications during or after treatment was noted by observing Herpes labialis, disseminated intravascular coagulation (DIC), seizures, Water House Friderichsen syndrome, raised intracranial pressure, cranial nerves palsies, fits and hydrocephalus. The incidence of death was also noted in all three regimens of treatment. Drug toxicity was noted in the form of rash, anaphylaxis, gastrointestinal symptoms and bone marrow depression.

STATISTICAL ANALYSIS

Data was analyzed using SPSS version 10.0. Descriptive statistics had been used to describe the data. Chi-square test was used to compare the final outcome in three groups.

RESULTS

Fifty patients (n= 50) with diagnosis of acute pyogenic meningitis were started on three different regimens of treatment. Mean age of patients in group A was 26 years, in group B was 27 years and in group C was 25 years. The detail of age, gender, clinical features and investigations is tabulated in (table 1-3).

The analysis of results of treatment with three different regimens was done by noting complete recovery, complications and death if any.

Twenty patients who were given group A regimen (Ceftriaxone + Ampicillin + Chloramphenicol) in which 2 (10%) patients developed complications. One patient developed fulminant meningococemia who recovered with optimal treatment and one patient developed deafness which gradually recovered.

Fifteen patients who were started on group B regimen (Ampicillin + Chloramphenicol) 2 (13%) patients developed

complications. One patient had seizures which were controlled and one patient developed hydrocephalus confirmed by CT scan brain and was referred for shunt procedures.

Fifteen patients who were started on group C regimen (Ceftriaxone alone) only one (7%) developed fulminant meningococemia who recovered but developed gangrene of toes for which amputation was done at a later stage.

Insignificant difference was observed between the results of three different

Table-1: Age, gender and occupation distribution of group samples (n=50).

Patient Characteristics	Group A (n= 20)	Group B (n= 15)	Group C (n=15)
Gender:			
Male	18 (90%)	13 (87%)	15 (100%)
Female	2 (10%)	2 (13%)	-
Occupation:			
Military Recruits	17	13 (87%)	14 (93%)
Retd army personnel's	01	1 (6.7%)	-
Civil patients	02	1 (6.7%)	1 (7%)

Table-2: Clinical data of Group samples (n=50).

	Group A (n= 20)	Group B (n= 15)	Group C (n= 15)
(a) Symptoms			
Fever	20 (100%)	15(100%)	14 (93%)
Headache	17 (85%)	12 (80%)	14 (93%)
Vomiting	15 (75%)	14 (93%)	14 (93%)
Altered consciousness	08 (40%)	06 (4%)	07 (47%)
Abnormal behaviour	03 (15%)	02 (13%)	02 (13%)
(b) Signs			
Neck stiffness	19 (95%)	15(100%)	14 (93%)

treatment regimens (p-value > 0.05) (table-4).

DISCUSSION

Acute pyogenic meningitis is potentially fatal but a treatable disease. It may kill a young fit individual within hours, if prompt treatment is not instituted well in time [7]. The most common presentations of disease were fever, headache, vomiting and deteriorating level of consciousness. Signs of meningeal irritation were elicitable in most of patients. CSF was turbid in all cases with

Table-3: Laboratory data of group samples (n=50).

	Results	Group A (n= 20)	Group B (n= 15)	Group C (n= 15)
(a) CSF				
Nacked eye appearance	Turbid	20 (100%)	15 (100%)	15 (100%)
Gram staining	Gram negative diplococci	15 (75%)	07 (47%)	06 (4%)
CSF Culture	Meningococcal growth	14 (70%)	08 (53%)	06 (4%)
Antigen detection test	Meningococci	16 (80%)	13 (87%)	13 (87%)
Antigen detection test	Pneumococci	04 (20%)	02 (13%)	02 (13%)
(b) Blood				
Blood CP	TLC > 10,000/cmm	16 (80%)	14 (93%)	13 (87%)
Blood Culture	Growth of Meningococci	02 (10%)	01 (7%)	01 (7%)
C-Reactive protein	Raised	20 (100%)	15 (100%)	15 (100%)

Table-4: Outcome of three regimens of treatment (n=50).

Comparison	*Group A		**Group B		***Group C	
	No. of patients (n=20)	Percentage	No. of patients (n=15)	Percentage	No. of patients (n=15)	Percentage
Complete recovery	18	90%	13	87%	14	93%
Complications	2	10%	2	13%	1	7%
Death	0	0	0	0	0	0

P-value > 0.05

*Ceftriaxone + Ampicillin + Chloramphenicol, **Ampicillin + Chloramphenicol, ***Ceftriaxone

variable intensity. Gram staining of CSF revealed diplococci in 28 (56%) patients and Meningococci were subsequently grown in cultures. Antigen detection test was done on CSF of all patients which revealed forty two of these patients (84%) to be suffering from Meningococcal meningitis and eight patients 16% to be suffering from Pneumococcal meningitis [8]. C - reactive protein levels were raised in all patients [9]. Blood culture was positive in two patients (4%); a growth of Meningococi was obtained. Patients in our study were treated with three regimens of treatment. The results of treatment of three regimens were compared by noting complete recovery, complications and death. The results of treatment with three regimens of drugs were compared by applying chi square test and were almost comparable. The patients included in this study depict only tip of iceberg because majority of patients included in our study belong to defence forces where regular medical checkup and treatment is free as well as easily available to them. The results obtained in our study are comparable to those mentioned in international literature.

Aronin, Peduzzi and Quagliarcllo conducted a retrospective cohort study on 269 patients between 1970 to 1995, who suffered community acquired meningitis. The results of treatment were almost comparable to our study [2].

In another study conducted in Poland between 1992 to 1996 by Tyski and Grazybowska W, by analyzing filled questionnaires recovered from 38 different hospitals of 27 provinces. In this study Penicillin, Cefotaxime, Ceftriaxone and Chloramphenicol were used in the treatment of bacterial meningitis. The results of treatment with these different regimens were almost comparable to those mentioned in our study [10].

A delay in diagnosis and initiation of treatment was associated with increased morbidity and mortality. A high index of suspicion is required in a case with fever, headache, vomiting, altered level of consciousness and abnormal behaviour. CSF examination is mandatory if no absolute contraindication exists and appropriate anti microbial therapy should be started without even waiting for laboratory results. High

mortality is seen in patients developing disseminated intravascular coagulation (DIC) [11]. The treatment of bacterial meningitis was revolutionized by antimicrobial drugs, but therapeutic problems continue to affect management decision regarding the timing and choice of antimicrobial therapy [12]. The successful implementation of H. Influenzae vaccination and wide use of antibiotics have led to changes in epidemiology of meningitis and emergence of antibiotic resistant strains [13]. In the next millennium our success will depend on worldwide scrutiny of patterns of antibiotic resistance, continued development of new antimicrobial drugs and judicious use of drugs we have.

CONCLUSION

Acute pyogenic meningitis, a dreadful condition of the past, is being managed more confidently with antibiotics especially Cephalosporins. Expanding bacterial flora causing meningitis may lead to emergence of various antibiotic combinations but third generation Cephalosporins still have wide coverage alone. However treatment should be initiated promptly without waiting for CSF culture in a patient with fever, headache, vomiting and altered level of consciousness.

Comparison of three different regimens of drugs ie group A (Ceftriaxone + ampicillin + Chloramphenicol), group B (ampicillin + Chloramphenicol) and group C (ceftriaxone alone) showed comparable results. So Ceftriaxone alone in a dose of 2 gram iv Bid is recommended for treatment of acute pyogenic meningitis in adults for good recovery, less disease complications and death rate. Moreover Ceftriaxone is convenient and economical with less side effects as compared to combination of drugs. The Ampicillin should be added to Ceftriaxone / Cefotaxime at two extremes of ages to cover listeria monocytogenes infection of meninges.

REFERENCES

1. Bell WE, McCormick WF. *Neurological infection in children, major problems in clinical pediatrics*. Philadelphia: W. B Saunders; 1981. p. 77-80.
2. Aronin SI, Peduzzi P, Quagliarcllo VJ. Community acquired bacterial meningitis: risk stratification for adverse clinical outcome and effect of antibiotic timing. *Ann Intern Med* 1998 Dec; 29 (11): 826-9
3. Telan DA, Zibulewsky J. Relationship of clinical presentation to time to antibiotics for the emergency treatment and management of suspected bacterial meningitis. *Ann Emerg Med* 1993;22:1733-8
4. Richard P. Lumbar Puncture and normal values of CSF. *Med int* 1992; 5: 4106-8.
5. Feign RD, Kaplan SL. Commentary. *Pediatr infect Dis J* 1992; 11: 98-700.
6. Tang LM, Chen SI, Wu YR. Haemophilus influenza meningitis in adults. *Diagn Microbial Infect Dis* 1998 Sep; 32 (1): 27 - 32
7. Quagliarello V, Scheld WM. Bacterial meningitis: pathogenesis, pathophysiology and progress. *N Eng J Med* 1992;327:864-72
8. Marcos MA, Martinez E, Almela M, Mensa J, Jimenez de-Anta MT. New rapid antigen test for diagnosis of pneumococcal meningitis. *Lancet* 2001 May 12, 357; (2967): 1499 - 500
9. Sheikh A. The diagnostic value of C-reactive protein estimation in differentiating bacterial from viral meningitis. *J Coll physicians Surg Pak* 2001; 10: 622 - 24.
10. Tyski S, Grzybowska. W. Andysis of bacterial meningitis during 1992 - 1996 in Poland. *Cent. Euray public health* 1998; 6(3): 225-30.
11. Herf C, Nichols J, Fruh S, Holloway B, Anderson CU. Meningococcal disease: recognition treatment and prevention. *Nurse Pract* 1998 Aug (8); 30: 33 -6, 39 - 40
12. Lin TY, Chrane DI, Nelson JD, McCracken H Jr. Seven days of ceftriaxone therapy as effective as ten days treatment for bacterial meningitis. *JAMA* 1985; 253: 3359 - 63.

Comparison of three Antibiotics Regimens

Pak Armed Forces Med J 2008; 58(2): 120-124

13. Adams WG, Deaver KA, Cochi SL, Plikaytis BD, Zell ER, Broome CV, et al. Decline of childhood haemophilus

influenza type b (Hib) disease in the Hib vaccine era. *JAMA* 1993 Jan 13; 269: 264-6.