ORIGINAL ARTICLE

Comparison of Dexamethasone Versus Placebo for Management of Bacterial Meningitis

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ABSTRACT

Aim: To compare the efficacy of dexamethasone vs. Placebo in decreasing in hospital mortality in addition to usual antibiotics for the management of patients presenting with bacterial meningitis.
Methods: This present randomized control trial was done in the Department of Medicine, Mayo Hospital, Lahore. The non-probability purposive sampling technique was used in this study. Informed consent was obtained from all patients. All patients were given a combination of Cefotaxime in a dose of 2gramIV 8 hourly and Vancomycin 1g IV 12 hourly. Then patients were randomly divided in two groups by using lottery method. In group D, patients were given 10mg IV dexamethasone every six hoursfor four days and patients in group P not given dexamethasone with standard regimens.Patients were followed during hospital stayfor mortality. Data was stratified for age gender, duration of disease, TLC count at admission to deal with effect modifier. Post stratification chi-square test was applied. P-value of <0.05 was considered significant.
Results: In this present study total 480 cases were enrolled. The mean age of the patients was 40.98±14.28 years. The male to female ratio of the patients was 2:1. In our study the mortality occurred in 55(11.5%) patients. Statistically significant difference in mortality was observed between study group and placebo group.
Conclusion: Our study results concluded that the dexamethasone is more effective in reducing the hospital mortality of bacterial meningitis patients as compared to placebo group.
Keywords: Antibiotic Treatment, Bacterial Meningitis, Dexamethasone, Placebo, Mortality

INTRODUCTION

Bacterial meningitis (BM) consists of pyogenic inflammation of the meninges and the underlying subarachnoid CSF. If not treated, it may lead to lifelong disability or death.It is a clinical syndrome characterized by inflammation of the meninges, the 3 layers of membranes that enclose the brain and spinal cord[1].

Patients with meningitis who present with an impaired level of consciousness are at increased risk for neurologic sequele or death. A seizure during an episode of meningitis also is a risk factor for mortality or neurologic sequele, particularly if the seizure is prolonged or difficult to control[2].

Early antibiotic treatment improves outcomes, but the effectiveness of widely available antibiotics is threatened by global emergence of multidrug-resistant bacteria. Additionally, whether or not adjunctive anti-inflammatory therapies (e.g., dexamethasone) improve outcomes in patients with bacterial meningitis remains controversial; inIn a nationwide observational cohort study from The Netherlands, adjunctive use of dexamethasone decreased pneumococcal meningitis mortality from 30% to 20%[4].

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On the other hand, a meta-analysis of individual patient data by van deBeek et al was unable to identify which patients were most likely to benefit from dexamethasone treatment; indeed, no significant reduction in death or neurologic disability

Rationale of this study is to compare the rate of mortality with dexamethasone versus placebo for management of patients presenting with bacterial meningitis. Literature is evident that dexamethasone is effecting in preventing high rate of mortality but due to controversy, physicians do not recommend dexamethasone in routine for management of BM. Through this study we want to confirm that whether dexamethasone can help in preventing mortality. Moreover, no local study has been conducted yet. Through this study we will also get local magnitude and results of this study will also help us to recommend the use of dexamethasone with standard therapy for BM.

MATERIAL & METHODS

This present randomized control trial was done at South Medical Ward, Department of Medicine, Mayo Hospital, Lahore. The study was conducted after six months of approval of synopsis. The non-probability purposive sampling technique was used in this study. Informed consent was obtained from all patients. Their demographic information (name, age, gender,

address and contact) was also noted. All patients were given a combination of Cefotaxime in a dose of 2gramIV 8 hourly and Vancomycin 1g IV 12 hourly. Then patients were randomly divided in two groups by using lottery method. In group D, patients were given 10mg IV dexamethasone every six hoursfor four days and patients in group P not given dexamethasone with standard regimens.Patients were followed during hospital stayfor mortality. Data was stratified for age gender, duration of disease, TLC count at admission to deal with effect modifier. Post stratification chi-square test was applied. P-value of $\leq$0.05 was considered significant.

RESULTS

In this present study total 480 cases were enrolled. The mean age of the patients was 40.98±14.28 years with minimum and maximum ages of 20 & 69 years respectively (Table 1).

In our study 66.67% patients were male and 33.33% patients were females. The male to female ratio of the patients was 2:1 (Fig.1)

The study results showed that the mortality occurred in 55 cases in which 13 were from dexamethasone group and 42 were from placebo group. Statistically significant difference in mortality was found between the study group and the placebo group and mortality of the patients. i.e p-value=0.000 (Table 3).

In our study the mortality in patient under 35 years occurred in 25 cases in which 5 were from dexamethasone group and 20 were from placebo group. Similarly in above 35 years patients the mortality occurred in 30 cases of which 8 were from dexamethasone study group and 22 were from placebo group. Statistically there is significant difference in mortality between the mortality and study groups and placebo groups in both below and above 35 years patients. P-value=0.002 & 0.005 respectively (Table 4).

In this study the mortality in male patents occurred in 45 cases of which 12 were from dexamethasone group and 33 were from placebo group.Similarly mortality in female patients occurred in 10 cases of which 1 was from dexamethasone study group and 9 were from placebo group. Statistically significant occurred in mortality between male study and female study group P-value 0.002 & 0.1 respectively (Table 5).

Table 1: Descriptive statistics of age (years)

n	480
Mean	40.98
SD	14.28
Minimum	20.00
Maximum	69.00

Fig.1: Frequency distribution of gender

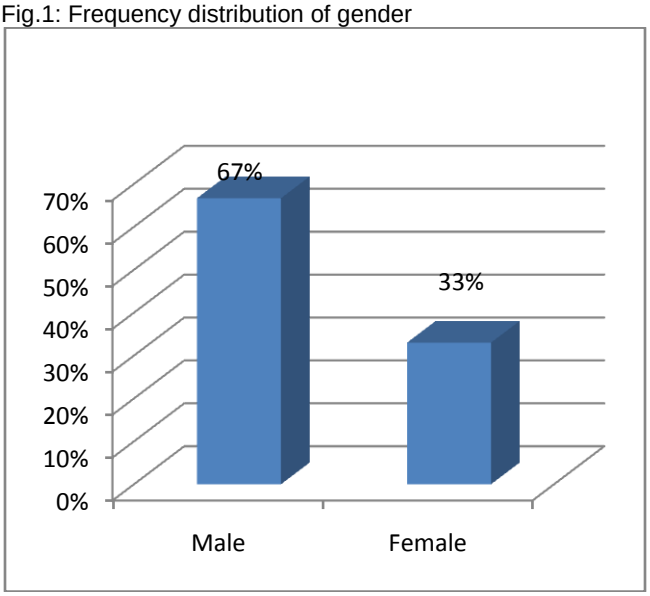

Table 2: Frequency distribution of Mortality

Mortality	Frequency	%age
Yes	55	11.5
No	425	88.5
Total	480	100.0

Table 3: Comparison of mortality in both study groups

Mortality	Study group		Total
	Dexamethasone	Placebo	
Yes	13	42	55
No	227	198	425
Total	240	240	480

Chi value= 17.27
p-value=0.000 (Significant)

Table 4: Comparison of mortality in both study groups stratified by age

Age group	Study group		Total
	Dexamethasone	Placebo	
≤35 years (P value 0.002)			
Yes	5	20	25
No	100	89	189
>35 years (p value 0.005)			
Yes	8	22	30
No	127	109	236

Table 5: Comparison of mortality in both study groups stratified by gender

Gender	Study group		Total
	Dexamethasone	Placebo	
Male (P value 0.002)			
Yes	12	33	45
No	144	131	275
Female (p value 0.010)			
Yes	1	9	10
No	83	67	150

DISCUSSION

This present randomized control trial was conducted at South Medical Ward, Department of Medicine, Mayo Hospital, Lahore to determine the efficacy of dexamethasone vs Placebo in decreasing in hospital mortality in addition to usual antibiotics for the management of patients presenting with bacterial meningitis.

In 1977, the Centers for Disease Control and Prevention (CDC) established a nationwide surveillance system to gather prospective epidemiological data that would supplant the retrospective and community-based studies of cases of bacterial meningitis in previous reports. In the first published study, 13,974 cases of bacterial meningitis reported to the CDC from 27 states in the United States from 1978 through 1981 were analyzed[8].

Since 2002, three large trials have been performed to evaluate the role of adjunctive dexamethasone therapy for adults with community-acquired bacterial meningitis[9,10].

In our study the overall mortality occurred in 55(11.5%) patients, of which 13 were from dexamethasone group and 42 were from placebo group, Mortality did not occur in 425 cases of which 227 were from dexamethasone group and 198 were from placebo group. Significant difference in mortality was observed between the study groups and the placebo groupi.e. p-value=0.000. Some of the studies are discussed here supporting the findings of our study.

In a nationwide observational cohort study from The Netherlands, adjunctive use of dexamethasone decreased pneumococcal meningitis mortality from 30% to 20%[4].

A RCT involving 301 adults with bacterial meningitis in European countries showed a beneficial effect of the corticosteroid dexamethasone on unfavorable outcome and mortality[9]. In this European study, dexamethasone or placebo was administered before or with the first dose of antibiotic. The beneficial effect of dexamethasone on mortality was most apparent in patients with pneumococcal meningitis[9].

This evidence was also supported by one study which reported that with dexamethasone the rate of mortality insignificantly differ i.e. 5.8% while with placebo it was 11.7% (p-value>0.05). Although the rate of mortality was lower with dexamethasone but the difference was insignificant so authors did not reach to some reliable decision[6].

But one study reported that with dexamethasone the rate of mortality was significantly lower i.e. 7% while with placebo it was 15% (p-value=0.04). Authors concluded that Early treatment with dexamethasone improves the outcome in adults with acute BM[7].

One study included 228 of 246 evaluable participants surviving the initial trial period. After a median follow-up of 13 years, mortality in the dexamethasone group was 22% compared to 33% in the placebo group (P = 0.029)[10].

A meta-analysis included four recent trials in adults[9,11,12] and concluded that dexamethasone reduced mortality in high-income countries.

A study conducted in Pakistan by Qazi et al. They showed the mortality for the dexamethasone group was 25% as compared with 12% in the group receiving placebo. Presentation to the hospital after four days of symptoms and with impaired conscious state was independent predictors of death[16].

One study conducted by Girgis et al showed that the Dexamethasone therapy was associated with reduced overall mortality compared with placebo (9.5% versus 19.2%, P < 0.01)[17].

A European trial showed a clear reduction in mortality for all suspected bacterial meningitis patients, while trials in Malawi and Vietnam did not. The Vietnam trial, however, did show a decreased rate of mortality for patients with confirmed bacterial meningitis[10].

Currently, adjunctive dexamethasone is advised for patients with suspected bacterial meningitis in high-income countries.

One study showed that in 87 out of 99 eligible patients, 46(53%) of whom were treated with dexamethasone and 41(47%) of whom received placebo, no significant differences in outcome were found between patients in the dexamethasone and placebo group.

REFERENCES

1. Swartz MN. Meningitis: bacterial, viral, and other. In: Goldman L, Schafer AI, editors. Cecil Medicine. 24th ed. Philadelphia, Pa: Saunders Elsevier; 2011: chap 360.
2. Schut ES, Brouwer MC, Scarborough M, Mai NTH, Thwaites GE, Farrar JJ, et al. Validation of a Dutch risk score predicting poor outcome in adults with bacterial meningitis in Vietnam and Malawi. PloS one. 2012;7(3).
3. van de Beek D, Brouwer MC, Thwaites GE, Tunkel AR. Advances in treatment of bacterial meningitis. Lancet. 2012;380(9854):1693-702.
4. Brouwer M, Heckenberg S, De Gans J, Spanjaard L, Reitsma J, Van De Beek D. Nationwide implementation of adjunctive dexamethasone therapy for pneumococcal meningitis. Neurology. 2010;75(17):1533-9.
5. van de Beek D, Farrar JJ, de Gans J, Mai NTH, Molyneux EM, Peltola H, et al. Adjunctive dexamethasone in bacterial meningitis: a meta-

analysis of individual patient data. Lancet Neurol. 2010;9(3):254-63.
6. Ahsan T, Shahid M, Mahmood T, Jabeen R, Jehangir U, Saleem M, et al. Role of dexamethasone in acute bacterial meningitis in adults. J Pak Med Assoc. 2002;52(6):233-9.
7. De Gans J, Van de Beek D. Dexamethasone in adults with bacterial meningitis. New Engl J Med. 2002;347(20):1549-56.
8. Schlech WF, Ward JI, Band JD, Hightower A, Fraser DW, Broome CV. Bacterial meningitis in the United States, 1978 through 1981: the national bacterial meningitis surveillance study. J Am Med Assoc. 1985;253(12):1749-54.
9. De Gans J, Van de Beek D. Dexamethasone in adults with bacterial meningitis. New England Journal of Medicine. 2002;347(20):1549-56.
10. Nguyen MH, Husain S, Clancy CJ, Peacock JE, Hung C-C, Kontoyiannis DP, et al. Outcomes of central nervous system cryptococcosis vary with host immune function: results from a multi-center, prospective study. J Infect. 2010;61(5):419-26.
11. Fritz D, Brouwer MC, van de Beek D. Dexamethasone and long-term survival in bacterial meningitis. Neurology. 2012;79(22):2177-9.
12. Nguyen TH, Tran TH, Thwaites G, Ly VC, Dinh XS, Ho Dang TN. Dexamethasone in Vietnamese adolescents and adults with bacterial meningitis. N Engl J Med. 2007;357:2431-40.
13. Scarborough M, Gordon SB, Whitty CJ, French N, Njalale Y, Chitani A, et al. Corticosteroids for bacterial meningitis in adults in sub-Saharan Africa. N Engl J Med. 2007;357(24):2441-50.
14. Thomas R, Le Tulzo Y, Bouget J, Camus C, Michelet C, Le Corre P, et al. Trial of dexamethasone treatment for severe bacterial meningitis in adults. Intens Care Med. 1999;25(5):475-80.
15. Assiri AM, Alasmari FA, Zimmerman VA, Baddour LM, Erwin PJ, Tleyjeh IM, editors. Corticosteroid administration and outcome of adolescents and adults with acute bacterial meningitis: a meta-analysis. Mayo Clinic Proceedings; 2009: Elsevier.
16. Qazi SA, Khan MA, Mughal N, Ahmad M, Joomro B, Sakata Y, et al. Dexamethasone and bacterial meningitis in Pakistan. Arch Dis Child. 1996;75(6):482-8.
17. Girgis NI, Farid Z, Mikhail IA, Farrag I, Sultan Y, Kilpatrick ME. Dexamethasone treatment for bacterial meningitis in children and adults. Pediatr Infect Dis J. 1989;8(12):848-51