The Professional Medical Journal
www.theprofesional.com

DOI: 10.29309/TPMJ/2019.26.09.720

ORIGINAL PROF-0-720

FREQUENCY OF MORTALITY IN NEONATAL MENINGITIS IN DEXAMETHASONE VS. PLACEBO GROUP.

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Article received on:
10/11/2018
Accepted for publication:
25/03/2019
Received after proof reading:
28/08/2019

ABSTRACT… Objectives: To determine the frequency of mortality in neonatal meningitis in dexamethasone vs. placebo group as an adjunct to the usual treatment. **Study Design:** Randomized control trial. **Setting:** Department of Paediatrics, Neonatal section, Mayo Hospital Lahore. **Period:** September 2014 to March 2015. **Material & Methods:** The consecutive non-probability sampling technique was used in this study. Total 100 patients were included, 50 in each group. Patients were assigned to either of following two treatment groups. One group received standard antibiotics plus Dexamethasone whereas the other group was given standard antibiotics plus Placebo. Trial and placebo groups received their respective treatments according to the protocol. Mortality between two study groups was compared by using Chi-square test. **Period:** From September 2014 to March 2015. **Results:** In our study the mean age of the patients was 14.92 days. The male to female ratio was 1:1. Total of Thirty four (34) patients expired – out of whom 12 were in the dexamethasone group and 22 patients belonged to the placebo group. The difference between two groups was statistically significant (p-value=0.035). **Conclusion:** Dexamethasone is efficacious drug and significantly reduces the mortality in infants neonatal meningitis.

Key words: Dexamethasone, Hospital Stay, Mortality, Neonatal Meningitis, Placebo.

Article Citation: Shahbaz U, Masood MK, Omer R, Ahmed T, Masood N, Shah A. Frequency of mortality in neonatal meningitis in dexamethasone vs. placebo group. Professional Med J 2019; 26(9):1404-1408.
DOI: 10.29309/TPMJ/2019.26.09.720

INTRODUCTION

Meningitis is an inflammation of the leptomeninges and subarachnoid cerebrospinal fluid (CSF).[1] It is more common in neonatal period than in any other age group; estimated mortality in neonatal meningitis is reported as 10% and the morbidity among survivors is 20-58% in developed countries but in developing countries it's mortality is 40-58% and morbidity is also considerably high.[2] Increased risk of meningitis in neonates is due to immature blood brain barrier and suboptimal cellular and humoral immunit immunity.[3]

The clinical features of the disease are usually non-specific and unreliable in neonates, so definite diagnosis is based on biochemistry and bacteriologic culture of CSF. Treatment includes antibiotics, fluid restriction and adjunctive therapy.[4]

In older children dexamethasone's role as an adjunct treatment in acute bacterial meningitis has been established especially in H. influenza and S. pneumonia meningitis. It's use is based on observation that dexamethasone reduces inflammatory reaction of host after administration of antibiotics, which if not reduced can have worse outcome.[5]

The beneficial function of this steroid in neonatal meningitis is not well established and the only two randomized clinical trials done so far show conflicting results. Although dexamethasone is not yet recommended for neonatal meningitis but its lack of effectiveness is not fully established too.[4] Daoud et al found that the use of dexamethasone in neonatal meningitis does not lower mortality.[6]

In their randomized controlled study 22% of children in dexamethasone group died as compared to 28% in the control group (P= 0.87).

Whereas Mathur et al showed in a randomized trial that dexamethasone significantly reduced mortality in neonatal meningitis from 40% in the control group to 12.5% in the dexamethasone group ($P < 0.01$).[5] There is no local study available on this subject.

This clinical study was done to assess the efficacy of dexamethasone in reducing mortality in neonatal meningitis. Since neonatal meningitis is associated with significant mortality, any intervention that reduces mortality in this disease would be highly beneficial. It is apparent that previous studies gave conflicting results regarding role of dexamethasone for mortality reduction. Our study aims to resolve this conflict so as to bring maximum benefit to neonates suffering from meningitis.

OBJECTIVE

To compare the efficacy of dexamethasone as an adjunct to usual treatment for reducing mortality in neonatal meningitis.

MATERIAL AND METHODS

This randomized controlled clinical trial was conducted at Department of Pediatrics, Neonatal Section, Mayo Hospital Lahore from September 2014 to March 2015. Newly diagnosed cases of neonatal meningitis were included; neonates with congenital malformation and those already receiving antibiotics were excluded from study. A total of 100 patients were included and divided into two groups by consecutive non-probability sampling.

Data collection was started after approval from hospital ethics committee (letter attached). After ensuring that neonate meets the inclusion criteria, an informed consent was taken from either parent to participate in the study. Study objectives and protocol explained to them. Neonates were randomly allocated to a treatment group by using table of random numbers generated by Open Epi software. Neonates were assigned a treatment group in a double blind manner so that neither the parents nor the medical staff knew actual components of that treatment group. Only one person who had no contact with the patients and was not concerned with collection of data was maintaining record of actual treatment categories of all the patients.

Patients were assigned to either of following two treatment groups:

1. Trial Group: standard antibiotics plus Dexamethasone.

Before giving first dose of antibiotics intravenous dexamethasone was given in the dose of 0.15 mg/kg and continued every 6 hours for 48 hours.

2. Placebo Group: standard antibiotics plus Placebo.

Before giving first dose of antibiotics normal saline was given intravenously in same quantity (ml), as dexamethasone was given in first group and this dose continued every 6 hours for 48 hours.

Basic demographic details like name, age, gender etc. were collected. All data entered in an especially designed Performa (attached). Trial and placebo groups received their respective treatments (Dexamethasone plus standard antibiotics and placebo plus standard antibiotics) according to the protocol.

Patients were followed up according to standard guidelines and mortality in both groups was noted for comparison.

Data was entered and analyzed by using SPSS version 20. Means ± SD was calculated for quantitative variables like age etc. Frequencies and percentages were calculated for qualitative variables like gender, mortality etc. Mortality in both groups was compared by using Chi-square test. Data was stratified for gestational age (term/preterm) and gender at time of admission to deal with effect modifiers. P-value$\leq$0.05 was considered as significant.

RESULTS

A total of 100 cases included in this study. The mean age of the patients was 14.92 days with minimum and maximum age values of 5 & 25 days respectively.(Table-I). The study results showed that the 50% cases were males and 50% cases were females.(Figure-1). 68(68%) patients

were preterm while 32(32%) cases were full term. (Table-II)

Mortality occurred in 34 neonates under study among which 12 cases were belonginged to dexamethasone group while on the other hand 22 patients expired in placebo group. This difference between the two groups is statistically significant. With p-value=0.035. Table-III

The results of present study indicates that mortality in male cases occurred in 16 patients among whom 6 belonged to Group 1 and 10 were in Group 2, while in female cases mortality occurred in 18 patients out of whom 6 belonged to Group 1 and 12 to Group 2. This difference between two study groups and mortality stratified by gender is not significant statistically, p-value=0.225 & 0.077 respectively. Table-IV

26 premature cases expired in this study, among these 10 were those who have received dexamethasone, (Group 1), and 16 were from group who have received just placebo,(Group 2) while in term age at birth patients mortality occurred in 8 cases and among these 2 were belonging to group A and 6 to group B. Statistically there is insignificant difference was found among dexamethasone and placebo groups and mortality stratifying by gestational age, p-value=0.091 & 0.152 respectively. Table-V

Age (Days)	N	100
	Mean	14.92
	SD	6.63
	Minimum	5
	Maximum	25

Table-I. Descriptive statistics of age (days)

		Frequency	Percent
Gestational Age at Birth	Preterm	68	68.0
	Term	32	32.0
	Total	100	100.0

Table-II. Frequency distribution of gestational age at birth

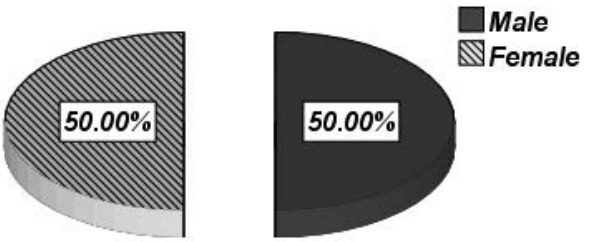

Figure-1. Frequency distribution of gender

		Study Group		Total
		Dexamethasone	Placebo	
Mortality	Yes	12	22	34
	No	38	28	66
Total		50	50	100

Table-III. Comparison of mortality in both study groups

Chi value=4.45
p-value=0.035 (Significant)

Gender			Study Group		Total	P-Value
			Dexame-thasone	Placebo		
Mortality	Male	Yes	6	10	16	0.225
		No	19	15	34	
	Female	Yes	6	12	18	0.077
		No	19	13	32	

Table-IV. Comparison of mortality in both study groups stratified by gender

Gestational Age at Birth			Study Group		Total	P-Value
			Dexame-thasone	Placebo		
Mortality	Preterm	Yes	10	16	26	0.091
		No	25	17	42	
	Term	Yes	2	6	8	0.152
		No	13	11	24	

Table-V. Comparison of mortality in both study groups stratified by gestational age at birth

DISCUSSION

This present randomized control trial was conducted at Department of Paediatrics, Neonatal section, Mayo Hospital Lahore to determine the frequency of mortality in neonatal meningitis in dexamethasone vs. placebo group as an adjunct to the usual treatment.

The first prospective, national neonatal

surveillance study in the UK was performed in England and Wales over the period 1985–1987.[7]

One of the earliest regional studies in the UK showed an incidence of neonatal bacterial meningitis of 0.5/1,000 live births over the years 1947–1960. Nearly 10 years later (1969–1973), a retrospective study of acute bacterial meningitis in the North West Metropolitan region reported a lower incidence of meningitis in neonates of 0.26/1,000 live births.[8]

In our study overall mortality occurred in 34 cases among which 12 belonged to dexamethasone group and 22 belonged to placebo group. Statistically significant difference was found in mortality between dexamethasone group and placebo group (P-value=0.035). In the use of dexamethasone there are many controversies regarding mortality in infants. There is conflicting data on use of dexamethasone in neonatal meningitis, some studies are advocating and others are not.

Dexamethasone treatment in childhood meningitis has become standard of care and is therefore an obvious consideration for the management of neonatal meningitis.[9]

One non-randomized study of newborns with bacterial meningitis in Nigeria between 1992 and 1995 revealed lower mortality and higher frequency of full recovery among babies treated with adjuvant dexamethasone.[10]

Carla et al concluded from their study that dexamethasone administration before the initiation of antibiotic therapy is beneficial and reduces morbidity and mortality in young children suffering from acute bacterial meningitis.[11]

McIntyre et al conducted a meta-analysis of different studies published between 1988-1996 and they concluded that adding dexamethasone with antibiotics has definite benefit in meningitis caused by H. influenza type b. They also found similar benefits in acute bacterial meningitis caused by pneuomococcous if dexamethasone is given before starting antibiotics.[12]

Daoud et al found that dexamethasone does not show add on benefit in neonatal meningitis in terms of mortality reduction.[6] In their randomized controlled study 22% of children in dexamethasone group died while in control group the mortality was 28% (p-value, 0.87). The function of dexamethasone in neonates and children with acute bacterial meningitis remains controversial.[13,14]

In two subsequent randomized controlled trials, one supported[15] and the other refuted[16] the benefit of dexamethasone.

Molyneux et al conducted a double blind randomized control trial in Malawi and found that mortality was equal in both groups (dexamethasone vs placebo). They concluded that dexamethasone has no role in reducing mortality in acute bacterial meningitis in children.[17]

Havens et al. demonstrated that dexamethasone did not reduce mortality or neurologic abnormalities at hospital discharge and late follow-up.[18]

Whereas Geiman and Smith found that dexamethasone did not reduce mortality, but decreased neurological sequelae and bilateral hearing loss up to six weeks after discharge.[19]

However Mathur et al showed in a randomized trial that dexamethasone significantly reduced mortality in neonatal meningitis from 40% in the control group to 12.5% in the dexamethasone group (P <0.01).[5]

CONCLUSION

According to our study the dexamethasone is efficacious drug and significantly reduces the mortality in infants as compared to the placebo group patients in the treatment of neonatal meningitis.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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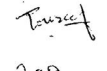
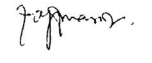
1	Umar Shahbaz	Main Theme, Lit. review	
2	M. Khalid Masood	Data collection, Discussion.	
3	Riffat Omer	Data collection, Discussion.	
4	Touseef Ahmed	Statistical analysis.	
5	Najaf Masood	Discussion.	
6	Azher Shah	Final drafting.