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Study of Role of Dexamethasone in Pyogenic Meningitis

KEYWORDS: Dexamethasone, pyogenic meningitis, antibiotic

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ABSTRACT *INTRODUCTION - Acute Bacterial meningitis is still a cause of morbidity and mortality despite the use of antibiotics. Role of steroids in reducing the morbidity and other unfavourable outcomes in patients suffering from meningitis has always been debated in medical science. We conducted a study to assess the role of dexamethasone in patients with pyogenic meningitis.*

AIM – To evaluate the role of dexamethasone in patients with acute bacterial meningitis.

METHOD AND MATERIALS - Dexamethasone was administered 20 minutes before or with the first dose of antibiotic and the outcome studied. A total of 55 patients were studied who were divided into two groups. Group I received dexamethasone and antibiotic while group II received only antibiotic. Group I was further divided into two subgroups – Group Ia consisted of patients receiving dexamethasone 20 minutes prior to administration of antibiotic and Group Ib comprised of those who received dexamethasone simultaneously with antibiotics. Patients in Group I showed early resolution of confusion, fever and nausea while no significant change was seen in any symptom in Group Ia and Group Ib.

RESULT - Patients on dexamethasone showed significant improvement in their sensorium and neck rigidity also resolved earlier in this group. Among the CSF parameters sugar and WBC count were better in Group I patients than in Group II patients. Comparison between Group Ia and Group Ib patients revealed statistically significant improvement in WBC count only while other parameters were similar. Administration of Dexamethasone showed improvement in clinical features as well as CSF parameters although the timing of administration did not show any significant change.

CONCLUSION - Patients with acute pyogenic meningitis should be administered dexamethasone along with antibiotics to improve their clinical outcome and reduce complications.

INTRODUCTION – Bacterial meningitis is an acute inflammation of meninges characterised clinically by presence of inflammatory cells in cerebrospinal fluid (CSF). It is caused by a plethora of microorganisms. The first report of bacterial infection underlying meningitis was by the Austrian bacteriologist, Anton Weichselbaum, who in 1887 described the meningococcus. The bacteriological profile of acute bacterial meningitis has gone significant alteration in recent years. In the earlier years Haemophilus influenza type b (Hib) was the most common bacterial agent causing meningitis but since the incorporation of Hib vaccine in National Immunization Programme of various countries, the incidence of Haemophilus influenza type b has dropped considerably.[1] At present, Streptococcus pneumoniae is the most common etiological agent causing bacterial meningitis with Neisseria meningitidis, Haemophilus influenza type b, Listeria monocytogenes, Streptococcus agalactiae, Escherichia coli and Klebsiella spp. also contributing.[2]

Despite advances in medical research, acute bacterial meningitis continues to be a major cause of mortality and morbidity. Approximately 1.2 million cases and 135,000 deaths due to acute bacterial meningitis occur worldwide.[3,4] Regardless of the use of antibiotics the frequency of neurological sequelae to meningitis remains high. The cerebrospinal fluid becomes sterile 24 to 48 hours after administration of antibiotics indicating some other mechanism, rather than the presence of microorganisms themselves, responsible for long term complications. Inflammation of subarachnoid space is responsible for pathology of meningitis which is induced by bacterial components like peptidoglycan and teichoic acid of gram positive bacteria and lipopolysaccharide endotoxin of gram negative bacteria generated as e result of bacterial lysis. These components stimulate the production of cytokines and chemokines by various inflammatory cells in the nervous system. Cytokines like tumour necrosis factor (TNF) and interleukin-1 (IL 1) increase the amount of protein and leukocytes in CSF leading to increased viscosity. This causes obstruction in the flow of CSF and also reduces its reabsorption. Inflammatory mediators further increases vascular permeability and causes cerebral edema and increased intracranial pressure. So antibiotics alone are not sufficient to control the pathological changes induced by bacterial components rather paradoxically they may enhance these effects by causing bacterial lysis. Therefore the role of glucocorticoids in relieving the clinical features and lowering the complication rate is worth analysing. Dexamethasone has been used in treatment of tubercular meningitis since long time but much controversy exists in its use in treatment of acute bacterial meningitis. Dexamethasone brings significant reduction in CSF pressure, brain edema and lactate concentration while also decreasing the leakage of low molecular weight proteins from serum into CSF. When given along with antibiotics, it significantly reduces the concentrations of interleukin-1 and prostaglandin E2. Those who oppose the steroid treatment advocate that due to its strong anti-inflammatory affect it may reduce the penetration of antibiotics in CSF, more over steroid may flare those organism that are partially sensitive to antibiotics.

AIM: To evaluate the role of dexamethasone in patients with acute bacterial meningitis

METHODS

ELIGIBLE PATIENTS

This study was conducted in Department of Medicine,

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Katihar Medical College over a period of two years between September 2009 to August 2011. Patients with clinical evidence of meningitis along with cerebrospinal fluid abnormalities were included in the studies. Patients were excluded from the study if they had received antibiotics before the first dose of dexamethasone, if any congenital or acquired abnormality of central nervous system was present, if they had recurrent or post traumatic meningitis, if there was history of allergy to antibiotic or dexamethasone or if patient was not willing to give consent.

Fifty five patients were analysed who were assigned into two groups. Group I comprised of 30 patients and included those who received dexamethasone. This group was further divided into two subgroups, Ia- consisted of 14 patients and included those who received the first dose of dexamethasone 20 minutes prior to first dose of antibiotic and Ib – consisted of 16 patients and included those who received dexamethasone simultaneously with first dose of antibiotic. Group II was formed by patients who were not given dexamethasone and consisted of 25 patients.

The study was commenced after obtaining approval from the institutional ethical committee. Written informed consent was obtained from all patients orfrom their relatives in case the patient could not provideconsent. Left thumb impression was obtained from those patients who were illiterate.

TREATMENT PROTOCOL

Patients were randomly assigned to receive either dexamethasone (Group I) or placebo (Group II). Patients received dexamethasone sodium phosphate in a dose of 0.6mg/kg body weight per day in a divided dose for four days. Group Ia received it 20 minutes prior to first dose of antibiotic while Group Ib received it simultaneously with the first dose of antibiotic. Ceftriaxone 100mg/kg twice daily (maximum 4g/day) was the antibiotic administered to all patients. Antibiotic therapy was given for 10 to 14 days and extended only in those patients whose condition failed to improve .other supportive therapy was instituted as required.

FOLLOW UP ASSESSMENT

Each patient was examined daily for fever, meningeal signs, level of consciousness, presence or absence of neurological deficit and occurrence of seizures and mid treatment review on the 5th day and comparison cranial CT scan was done when required. At the time of discharge from hospital a complete neurological examination was carried out in all patients. Hearing was assessed by otologists by pure tone audiometry.

STATISTICAL ANALYSIS

Statistical analysis was conducted using Stata version 10 (Stata Corp, Texas, USA). T-test was applied for testing the mean difference between two continuous variables, and difference of proportion for binomial variables. P-value less than 0.05 was taken as significant.

RESULTS

A total of 55 patients were analysed in this study, 30 were assigned to group I who received steroid therapy and 25 were assigned to group II who received only antibiotics and no steroid therapy. Group I was further divided into two subgroups – Ia (14 patients) who received steroid 20 minutes prior to antibiotic treatment and group Ib (16 patients) who received steroid along with antibiotics.

32 (58.18%) of patients were male and 23 (41.82%) were females. 19 of the 32 males were assigned to group I where as 11 of the 23 females were assigned to group II. Maximum patients were in age group of 12-24 and 55-65, both groups contained 16 patients each. Gram's staining was positive in 33 cases (60%) whereas CSF culture was positive in 42 cases (76.36%). The most common pathogen isolated was Streptococcus pneumoniae, followed by Haemophilus influenza and Neisseria meningitidis.

After 5 days of treatment it was observed that the percentage of patientswith an unfavourable outcome was significantlysmaller in the dexamethasone group than in the placebo group. Disease parameters associated with meningitis and their changing pattern after institution of dexamethasone therapy was noted.

TABLE 1

SYMPTOMS	DAY	GROUP I (N=30)	GROUP II (N=25)	P-Value
Headache	0	30 (100%)	25 (100%)	1.00
	5	06 (20%)	04 (16%)	0.70
Nausea/ Vomiting	0	30 (100%)	25 (100%)	1.00
	5	05 (16.67%)	10 (40%)	0.05
Fever	0	30 (100%)	25 (100%)	1.00
	5	05 (16.67%)	13 (52%)	0.01
Sweating	0	16 (57%)	12 (48%)	0.69
	5	09 (30%)	08 (32%)	0.87
Myalgias	0	18 (60%)	14 (56%)	0.76
	5	08 (26.66%)	07 (28%)	0.91
Confusion	0	28 (73.33%)	23 (92%)	0.85
	5	04 (13.33%)	10 (40%)	0.02

TABLE -2

CLINICAL FEATURES	GROUP- 1A (N=14)		GROUP- 1B (N=16)		P-VALUE	
	DAY 0	DAY 5	DAY 0	DAY 5	DAY 0	DAY 5
Headache	14	2	16	4	1	0.46
Nausea/Vomiting	14	2	16	3	1	0.74
Fever	14	2	16	3	1	0.74
Confusion Delirium	13	1	15	3	0.922	0.35
Neck Rigidity & Kerning's Sign	14	1	16	2	1	0.625
Unconsciousness	1	1				

Table 1 and 2 show changes in various signs and symptom in group I and II and group Ia and group Ib on day 0 and 5 days after administration of dexamethasone. Headache persisted in 6 (20%) out of 30 patients in group I and 4 (16%) out of 25 patients in group II, although the difference was not statistically significant. Nausea and vomiting was seen in 5 (16.6%) cases in group I as compared to 10 (40%) patients in group II after 5 days of treatment which was statistically significant (P value = 0.05). 5 (16.66%) of patients in group I and 13 (52%) of patients in group II were still suffering from fever on day 5 despite treatment, exhibiting a statistical difference (P value = 0.01). The persistence of confusion also showed statistical difference on day 5 with 4 (14.28%) of patients in group I and 10 (40%)

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patients in group II still showing this symptom.Despite the fact that there was improvement in symptoms in group Ia and group Ib it was not statistically significant.

TABLE 3

SIGNS	GROUP - I (N=30)		GROUP - II (N=25)		P-Value	
	DAY 0	DAY 5	DAY 0	DAY 5	DAY 0	DAY 5
Bradycardia	6 (20%)	0	4 (16%)	0	0.70	1.00
Tachycardia	22 (73.33%)	5 (16.66%)	23 (92%)	10 (40%)	0.07	0.05
Hypotension	3 (10%)	1 (3.33%)	4 (16%)	1 (04%)	0.51	0.85
Hypertension	6 (20%)	1 (3.33%)	4 (16%)	1 (04%)	0.70	0.90
Tachypnea	14 (46.66%)	2 (6.66%)	15 (60%)	3 (12%)	0.32	0.49
Temperature	30 (100%)	5 (16.66%)	25 (100%)	10 (40%)	1.00	0.05
Altered Sensorium	30 (100%)	5 (16.66%)	25 (100%)	10 (40%)	1.00	0.05
Unconsciousness	2 (6.66%)	0	3 (12%)	0		
Cranial Nerve Palsies	1 (3.33%)	1 (3.33%)	0	0		
Neck Rigidity &Kernig's Sign	30 (100%)	3 (10%)	25 (100%)	10 (40%)	1.00	0.01
Focal Neurological Deficit	2 (6.66%)	0	1 (04%)	0		

The patients in group I showed appreciable decrease in neck rigidity and Kernig's sign (P=0.01) which are important diagnostic sign in case of meningitis. There was decrease in heart rate, temperature and altered sensorium in both groups, the decrease being more significant in group I patients than in group II patients (P=0.05).Although there was decrease in other signs also but they were statistically not significant.

Table- 4

S. No	Lab Investigation	Day	Group A (N=30)	Group B (N=25)	P-Value
1	Turbidity	0	28	24	0.66
		5	4	8	0.095
2	Cells	0	172 ± 40	164 ± 45	0.4884
		5	68 ± 15	110 ± 25	0.001
3	Lymphocytes	0	25	25	
		5	80	80	
4	Polymorphs	0	75	75	
		5	14	20	
5	Sugar	0	27 ± 10	24 ± 12	0.3379
		5	62 ± 12	95 ± 18	0.0001
6	Protein	0	156 ± 87	140±96	0.5198
		5	100 ± 26	100±30	1.00

Table 4 shows changes in CSF on day 0 and day 5. On day 5 WBC count showed significant improvement in patients receiving dexamethasone when compared with those who did not receive dexamethasone (P=0.001). Mean of sugar was increased from 27 mg% to 62 mg% in group I after 5 days of treatment compared to 24 mg% to 45 mg% in group II. Thus Glucose level increased considerably on day 5 in Group I patients than in Group II patients (P=0.0001). Even though other parameters like protein level and turbidity of CSF showed better control in group I patients they were not significant statistically.

TABLE 5

CSF FINDINGS	GROUP- 1A (MEAN VALUES)		GROUP- 1B (MEAN VALUES)		P-VALUE	
	DAY 0	DAY 5	DAY 0	DAY 5	DAY 0	DAY 5
TURBIDITY	6	1	9	1	0.46	0.92
CELLS	188±45/ cumm	54±12/ cumm	166±42/ cumm	72±20/ cumm	0.18	0.01
POLYMORPHS	75%	10%	75%	15%		
SUGAR	28±10 mg%	70±15 mg%	30±12 mg%	64±18 mg%	0.63	0.33
PROTEINS	156±87 mg%	78±28 mg%	160±90 mg%	86±30 mg%	0.90	0.46

Table 5 depicts the changes in CSF parameters in group Ia and group Ib. The patients who received dexamethasone 20 minutes prior to antibiotic administration showed considerable decrease in their WBC count (P=0.01). Even though other parameters like sugar and protein showed improvement in this group of patients, it was statistically insignificant.

DISCUSSION

In spite of the use of antibiotics the mortality rate in cases of acute bacterial meningitis remains high. This can be explained from the fact that the meningeal inflammation in case of bacterial meningitis is not only due to presence of bacteria but also due to presence of bacterial cell wall components which are liberated as a result of antibiotic treatment. These components lead to inflammatory response subsequently increasing the blood brain barrier permeability and resulting in exudation of serum protein in CSF. Tumor necrosis factor (TNF) and interleukin 1 are responsible for these changes.[5,6,7] Combined therapy with antibiotic and steroids may improve the clinical condition as well as CSF parameters of the patient. The production of IL-1 and TNF by bacterial toxin stimulated macrophages is inhibited by steroids. Steroid therapy has reduced brain edema, intracranial pressure and CSF lactate levels in animals suffering from Streptococcus pneumoniae and Haemophilus influenzae meningitis.[8,9,10]

Studies on dexamethasone therapy in meningitis patient have shown variable results and there is no consensus on its use along with antibiotics. Therefore it was necessary to analyse the effect of dexamethasone on meningitis patients. The results of our study showed that patients receiving dexamethasone were benefitted. There was appreciable improvement in their clinical profile as well as CSF parameters. Clinical features like fever, confusion and neck rigidity were reduced after 5 days of treatment with dexamethasone. CSF sugar and wbc level exhibited appreciable improvement. In a similar study conducted by T. Ahsan et al there was significant improvement in clinical features of patient suffering from meningitis who received dexamethasone therapy.[11] Their study showed that duration of pyrexia and headache was halved in patients receiving steroids. Cranial nerve involvement was also less and no patient in steroid group suffered from seizures. These findings were not significant statistically and they attributed this to small sample size. Their study also revealed that CSF glucose level increased in the steroid group

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which is concurrent with our study. Other studies, where dexamethasone has been administered before and simultaneously with antibiotics, have shown improvement in the patients.[12,13,14,15] In a study conducted by Qazi et al steroid therapy did not provide any additional benefit to patients. They attributed this to delay from the patients in seeking medical attention.[16]

Adverse effects due to use of any drug is a matter of concern for physicians. In our study no adverse effect due to use of dexamethasone was observed but since our sample size was small this aspect needs further evaluation. Those who oppose use of dexamethasone suggest that it decreases the passage of antibiotics through Blood Brain Barrier (BBB). Dexamethasone does not affect the entry of antibiotics across the BBB. Animal studies have also shown that except vancomycin steroid therapy does not restrict the passage of antibiotics through the BBB.[17,18,18,20,21] Vancomycin requires inflammation of meninges to cross this barrier. In a study in children dexamethasone administration did not reduce vancomycin levels in cerebrospinal fluid.[22] Therefore in patients receiving vancomycin close monitoring of the clinical condition is required to detect any detoriation. Taking into consideration the long term benefit and no serious side effects, dexamethasone along with antibiotics should be given. Steroids should not be given in patient with septic shock because it can lead to detoriation in clinical condition.[23,24]

The duration and timing of dexamethasone administration is important. Both two and four day regimen have been followed with most study recommending the four day regimen.[25,26] In our study we followed the four day regimen which was also followed by Jan de Gans et al. [11] We divided the patients into two groups, one which received dexamethasone 20 minutes prior to antibiotic administration and the other simultaneously with it. Although improvement was seen in clinical profile and CSF findings but except for wbc value none were statistically significant. This suggests that steroids can be given before or along with the first dose of antibiotics. Similar suggestion were given by McIntyre et al who recommended a four day regimen given either before or along with antibiotics resulted in a better outcome. [27]

CONCLUSION

The results of our study suggest that concomitant administration of dexamethasone with antibiotics improved the clinical condition as well as the CSF parameters of patients with acute bacterial meningitis without causing any adverse effect. Hence a four day course of dexamethasone should be administered to all patients with meningitis.

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