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A Clinical Outcome of Dexamethasone therapy of Patients with Pyogenic Meningitis

Authors

Atul Kumar[1], Md Izhar Alam[2], Taskeen Ahmad Reza[3], Shruti Sonal[4], Kaushal Kumar Sinha[5], Karan Bhargav[6], Wasim Alam[7]

[1]Associate professor, Dept of Medicine, Katihar Medical College, Katihar, Bihar, India
[2]Assistant professor, Dept of Pathology, Katihar Medical College, Katihar, Bihar, India
[3]Assistant Professor, Dept of Medicine, Katihar Medical College, Katihar, Bihar, India
[4,5,6,7]PGT, Department of Medicine, Katihar Medical College, Katihar, Bihar, India

Corresponding Author

Dr Atul Kumar

Associate Professor, Dept of Medicine, Katihar, Medical College, Katihar, Bihar, India.
Email: *dratulkumarkmc@gmail.com Ph: +91 8227040025*

ABSTRACT

Objective: *Observation of hastening effect of dexamethasone on recovery time and reductions of case fatality and neurological complications of pyogenic meningitis.*

Methodology: *A total of 39 patients with pyogenic meningitis were considered on the basis of short clinical history and laboratory findings like, fever, headache, projectile vomiting, confusion/delirium, unconsciousness and neck rigidity and kerning's sign, raised CSF pressure, presence of turbidity or purulent CSF with identification of bacteria on gram staining or culture of CSF, High CSF cell count (> 10 to < 10000 /Cumm) with neutrophilic predominance, Reduced CSF glucose level (<40mg%), Low CSF to blood glucose concentration ratio (<40 %), High CSF protein level (>50mg/dl).*

Results: *Data was analyzed by using MS-Office software.*

Conclusions*: Adjunctive dexamethasone therapy may improve the outcome of pyogenic meningitis in adolescent and adult patients. And the intensity of headache, vomiting and fever were also relieved by using dexamethasone therapy.*

Key words: *pyogenic meningitis, dexamethasone therapy, clinical outcome.*

Introduction

Acute Pyogenic (Bacterial) meningitis is a potentially life threatening disease that is an inflammation of the meninges and underlying subarachnoid cerebro-spinal fluid (CSF). Acute pyogenic meningitis and with its associated high morbidity and mortality remains a major health problem worldwide. At least 30 countries worldwide including the United States, have reported serious outbreaks of meningococcal meningitis in recent years.[1]

Organism's most commonly responsible community acquired Pyogenic Meningitis are: Streptococcus Pneumonia (-50 %), N. Meningitis (- 25 %), Group B Streptococci (- 15%), Listeria Monocytogens (-10%), H. Influenza (< 10%). Most of the organism gains entry into central nervous system via the blood stream secondary to respiratory tract infection giving rise to cerebral edema and raised intra cranial tension which impairs blood flow subsequently leading to complication of meningitis. Various investigators found that subarachnoid space inflammation and various inflammatory cytokines have a major role in pathophysiology of pyogenic meningitis that contributes to morbidity and mortality. [2]

Lumbar puncture remains the gold standard in the diagnosis of meningitis there are people who argue strongly against it because of fear of brain herniation. Despite significant advances in the understanding of the pathogenesis and antibiotic treatment of acute Pyogenic meningitis, the mortality and morbidity from the disease remains unacceptably high. The large number of those who survive may have neurological disabilities and squeal.[3]

The discovery penicillin by Alexander Fleming and its first uses in 1941 was the first major break in the treatment of Pyogenic infection including meningitis. It is uniformly accepted that empirical antibiotic treatment based on the age of the patient and health status should be instituted as soon as possible. If there is delay in detection of organisms and its antibiotic susceptibility, once the organisms isolated, drug treatment should be modified according to sensitivity pattern.[4]

Much controversy exists in the use of Dexamethasone as an adjunctive therapy to antibiotics in the treatment of acute pyogenic meningitis especially in adults. Different clinical trial have revealed that suppression of inflammation by dexamethasone has brought significant reduction in CSF pressure, brain edema and lactate concentration in CSF in experimental models of S. Pneumoniae and H. influenza meningitis it decreases the leakage of low molecular weight proteins from serum into the CSF in the experimental models of Pneumococcal meningitis.[5] Dexamethsone given in children with meningitis at the initiation of antibiotics therapy significantly reduces the concentration of interleukin-1 B and prostaglandin E2 and the degree of inflammation in samples of CSF obtained 24 hours apart after the first dose as compared with the result in children who received placebo. It has now been shown in in-vitro experiment that interleukin 1b and tumor necrosis factor gene transcription is induced by lipopolysaccharides and that dexamethasone inhibits this gene.[6] Objective of our study was to observation the hastening effect of dexamethasone on recovery time and reductions of case fatality and neurological complications of pyogenic meningitis.

Material and methods

Study was done in emergency ward and indoor wards of Katihar Medical College, Katihar, Bihar, India, patients who were suffering of pyogenic meningitis, included in this study.

A total of 39 cases (24 males and 15 females) of patients with age group 10 to 65 years were included. The attendant of entire subject signed an informed consent approved by institutional ethical committee of Katihar Medical College, Katihar, Bihar, India was sought. Data were collected in emergency ward and indoor ward of Katihar Medical College, Katihar, Bihar, India, during period of November 2013 to May 2015.

Procedures

It was divided into clinical criteria and laboratory criteria. Clinical criteria were short history of fever, headache, projectile vomiting, confusion/delirium, unconsciousness and neck rigidity and kernig's sign. Laboratory criteria were raised CSF pressure, presence of turbidity or purulent CSF with identification of bacteria on gram staining or culture of CSF, High CSF cell

count (> 10 to < 10000 /Cumm) with neutrophilic predominance, Reduced CSF glucose level (<40mg%), Low CSF to blood glucose concentration ratio (<40 %), High CSF protein level (>50mg/dl).

Treatment

Randomization

There were two groups, group A and Group B. Group A were 22 patients, treated with dexamethasone and group B were 17 patients treated without dexamethasone.

Group A: Dexamethasone therapy:

Patients were randomly assigned to receive either dexamethasone (group A) or placebo (Group B) in case and control manner.

2 ml vials were prepared which contained a clear colorless solution and were identical in appearance. Group A patients received dexamethasone sodium phosphate in a dose of 0.6 mg/kg body weight per day in a 4 divided doses for four days. The first dose of dexamethasone was given 20 minutes prior to first dose of antimicrobial agents. The group receiving dexamethasone were further subdivided into two groups, (i) which received dexamethasone, 20 minutes prior to first dose of antibiotic and (ii) which received dexamethasone simultaneously with first dose of antibiotic.

Antibiotic therapy

The patients were assigned to receive either conventional antibiotic of third generation cephalosporins.

Antibiotics used in this study are: ceftriaxone 2 gm twice daily (maximum 4 gm/day) and G penicillin 20-24 million units, every four hours + chloramphenicol 1 gm 8 hourly + gentamycin 80 mg, 8 hourly.

Antibiotic therapy was given for 10 to 14 days as a rule, and extended only in those patients whose condition failed to improve within this duration. Other supportive therapy was instituted, as required.

Follow up assessment

Course of illness during hospitalization

Each patient was examined daily for fever, meningeal signs, level of consciousness, presence or absence of neurologic deficit and occurrence of seizures and mild treatment reviewed on the 5th day and comparison was made. A cranial CT scan was done to find out the evidence of persistently raised intracranial pressure suggesting the possibility of hydrocephalus, subdural effusion or empyema or brain abscess, the presence of any focal neurologic deficit and the persistence of pyrexia beyond 7 days in the hospital. And at the time of discharge complete neurological examination was done.

Statistical Analysis

Data was analyzed by using Ms-Office software and standard statistical methods.

Observations

This present study was carried out on 39 patients of purulent meningitis admitted in Katihar Medical College, Katihar, during November 2013 to May 2015.

Out of 39 patients 24 (61.15%) were male and 15 (38.5 %) were female. At the time of admission, 100 % patients were complaining headache, nausea, vomiting and fever. 76.9 % patients were symptom like sweating, 41.02 % cases were myalgia, 58.9 % cases were photophobia, 23.07 % cases were convulsion, 87.17 % patients were confusion and 79.48 % were in coma. Tachycardia were present in 89.74 % cases, bradycardia in 10.26 % cases, hypertension were present in 12.82 % cases, hypotension in 30.76 % cases, respiratory depression in 20.51 % cases and tachypnea in 61.53 % cases. Temperature was found in 100 % cases, altered sensoriums in 100 %, unconscious were found in 89.74 % patients. Papillary abnormality was seen in 33.33 % cases, cranial nerve palsies in 15.38 % cases, neck rigidity and Kerning's sign were present in 66.6 % cases, and focal neurological deficit was found in

15.38 % cases. 51.2 % patients were presented with Glass Gow Coma scale (GCS) of 3-5 with males 70 % and female 30 % of the cases presented with the GCS between 6-10 with males being 60 % and females 40 %. Only 4 patients (10.3 %) were presented with a GCS between 11-15.

20.5 % cases were the positive history of predisposing factors of which 75 % of females and 25 % were males. 50 % were otitis media where as 25 % cases were pneumonia. And 12.5 % patients were head injury with CSF leak and with sinusitis.

66.6 % patients were received a combination of ceftriaoxone, and 33.3 % received a combination of C. penicillin, chloramphenicol and gentamycin.

66.65 % patients were received ceftriaoxone of which 57.7 % were received steroids and 42.3 % patients were not received steroids.

Out of 15 patients of ceftriaoxone group, 53.3% patients with steroid therapy were GCS between 3-5, 33.3 % steroid therapy were GCS 6-10, and 13.3 % patients with steroid therapy were GCS 11-15.

Out of 11 patients of the ceftriaoxone group, 54.5 % patients of ceftriaoxone group was not received steroids had GCS 3-5, 27.3 % had GCS 6-10, 18.7 % had GCS 11-15.

In the penicillin group, 53.8 % out of 13 patients received steroids and 46.2 % were not received steroids.

Out of 7 patients receiving steroids in penicillin group (57.1 % had a GCS 3-5, 28.6 % had a GCS 6-10 and 14.3 % had a GCS 11-15.

Penicillin group patients who were not received steroids (33.35 %) had a GCS 3-5, 3(50 %) had a GCS 6-10 and 1 (16.7% had a GCS) 11-15.

Symptomatically comparison of two groups, group I with steroid therapy and other group II without steroid therapy, on 5^{th} days of treatment was found that, In group I patients, out of 14 patients, 4 (28.57 %) patients were persisted with headache. In group II, Out of 12 patients, 6(50 %) patients were persisted with headache. In group I, 4 (22.2 %) patients were persisted with nausea and vomiting and in group II 4 (40 %) patients were persisted with nausea and vomiting on 4^{th} days of treatment. Fever was seen in 4 (28.5 %) patients in group I, and 6 (50 %) patients in group II.

Confusion/delirium was present in 6 (46.15 %) out of 13 patients of group I, and 5 (50 %) patients of group II.

2 (15.3 %) patients were remained in coma of group I, and 3 (25 %) of group II after 4^{th} days of treatment.

Comparison of signs of the two group, in group I, 14.2 % patients were persisted with tachycardia, and in group II, 16.6 % cases were persisted on 5^{th} days of treatment. Hypotension was seen in 33.3 % cases of each group and tachypnea was persisted in 25 % patients of group I, 20 % patients of group II.

28.5 % patients of group I, were remained febrile and 50 % patients of group II were febrile.

Altered sensorium was seen in 46.1 % cases of group I, and 50 % patients of group II. Unconscious were persisted in 15.4 % patients of group I, and 25 % patients of group II.

Neck rigidity was seen in 37.5 % cases of group I, and 30 % patients of group II .

In group I, 68.6 % patients were reduced total leukocyte count of peripheral blood, and in group II, 79.5 % patients were reduced.

In group I, 14.3 % patients were turbidity in CSF, and in group II, 67 % patients were turbidity in CSF.

The total number of cells in the CSF was reduced to 39.5 % of the initial value, which receiving the dexamethasone as an adjunctive therapy, and 87.5 % patients were increase sugar who were not receiving dexamethason therapy.

The decrease in CSF protein was to about 58.15 % of the initial value and reduced to 71.42 % of the initial value after 4^{th} days of treatment.

When 9 (40.9 %) patients received dexamethasone 20 minutes prior to, in which 3 patients died. And patients 13 (59.1 %) who received simultaneously with the first dose of antibiotic, 5 patients died.

Comparison of clinical features in prime steroid group (1a) and concomitant steroid group (1b), headache in group 1a persisted in 1 (16.6 %) out of 6 patients on 5th days as compared to 3 (33.5 %) out of 9 patients in group Ib. Nausea / vomiting disappeared in all 3 patients in group 1a and in group 1b it persisted in 2 (33.3%) out of 6 patients. Fever in group 1a was seen in 1 (16.6 %) out of 6 patients where as in group 1b it persisted in 3 (33.5 %) out of 9 patients on 5^{th} days of treatment. Confusion / delirium persisted in 2 (33.3 %) patients in group 1a and 4 (50 %) in group Ib. neck rigidity and Kerning's sign was seen in 1 (33.3 %) in group 1a and 2 (40 %) in group 1b patients on 5th days of treatment. Unconsciousness disappeared in all 6 patients in group 1 a, 2 (25 %) out of 8 patients on 5^{th} days of treatment.

Comparison of CSF finding in primed steroid group 1a and concomitant steroid group 1 b patients, it was shown that turbidity persisted in 1(16.6 %) patients of group 1a and 1(11.1%) of group 1b patients on 5^{th} days of treatment. Total cell count in group 1a was reduced to 28.7 % of the initial in group 1 a and 43.3 % in group 1b. polymorphs in CSF were reduced to 13.3 % of the initial value in group 1 a patient and 20 % in group 1 b patients. Sugar was showed an increase to about 150 % of the initial value in group 1a and 113 % in group 1 b patients. Protein was reduced to 50 % in group 1a and 46.25 % in group 1b patients. 14.2 % patients who received dexamethasone were developed to manifestation of upper gastrointestinal bleeding.

Risk of secondary fever of total of 39 patients, 42.8 % patients developed fever after receiving dexamethasone therapy. Only one patient developed acute psychosis on 4^{th} days of treatment.

7 (26.9 %) patients were death in ceftriaxone therapy group and 6 (46.2 %) patients were death in penicillin therapy group. Out of the 15 patients in the ceftriaoxone group, who received dexamethasone, 4 (26.7 %) were died. Out of the 11 patients in the ceftriaoxone group, who did not receive dexamethasone, 3 (27.3 %) were died. Out of the 7 patients in the penicillin group receiving dexamethasone, 3 (42.8 %) was died. Out of the 6 patients in the penicillin group not receiving dexamethasone 3 (50 %) were died.

Mortality of patients with CSF glucose level < 20 mg/dl was 100 % and CSF glucose level > 40 mg/dl at the time of admission had no mortality.

Table.1. Mortality of using various antibiotics with steroids and without steroids therapy.

			Ceftriaoxone				C. penicillin + chloramphenicol + gentamycin		
Sr. No	GCS score	Grade of coma	Total No.	With steroids (n=15)	No steroids (n=11)	N (%)	With steroid (n=7)	No steroid (n=6)	N (%)
1	3-5	III	20	3 (75%)	2 (66.7%)	5	2 (66.7%)	2 (66.7%)	4 (66.7%)
2	6-10	II	15	1 (25%)	1 (33.3%)	2	1 (33.3%)	1 (33.3%)	2 (33.3%)
3	11-15	I	4	0	0	0	0	0	0
			39	4 (26.7%)	3 (27.3%)	7	3 (42.8%)	3 (50%)	6 (46.2%)

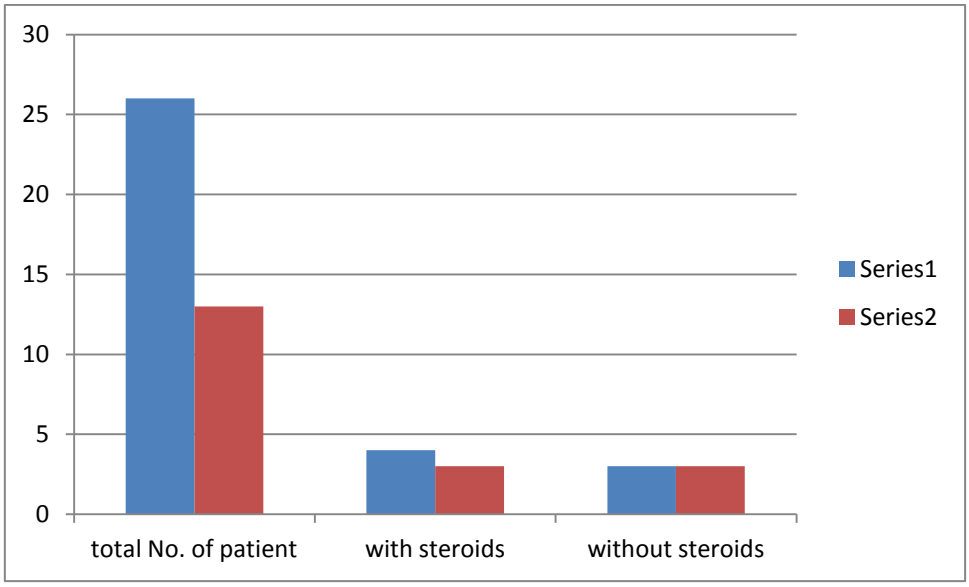

Figure.1. Mortality of using antibiotics with steroids and without steroids therapy.

Discussion

This study was carried out on 39 patients of purulent meningitis admitted in ward of Katihar Medical College, Bihar, India. Patients were randomly devided into two groups, Group 1 (n=22) which received dexamethasone as an adjunctive therapy along with antibiotics and group II (n=17) which did not received dexamethasone.

Group I further subdivided into two groups, group 1a which received dexamethasone 20 minutes prior to first dose of antibiotics and group 1b, which received dexamethasone simultaneously with the first dose of antibiotics.

Antibiotics used were either a combination of ceftriaoxone (n=26), or a combination of G. penicillin + chloramphenicol + gentamycin (n+13).

Dexamethasone was used in a dose of 0.6 mg/kg body weight 6 hourly for 4 days.

Tunkel AR and Scheld WM (1995) observed that headache, nausea, vomiting, meningismus, often with signs of cerebral dysfunction were in 85 % patients. Seizures were present in 40 % of the patients. Kerning's sign and/or Brudzinski's sign were elicited in only about 50 % cases. Papilloedema was present in <1% patients. When they examined the CSF, found that opening pressure was virtually elevated in all patients. The gross appearance was cloudy of turbid if the white cell count was elevated. Approximately 10 % of the cases presented initially with the predominance of lymphocyte in the CSF. Very low white cell counts in the CSF were also observed in few cases.[7]

Our study was found that, headache, nausea, vomiting, and fever were in 100 % patients. Signs of cerebral dysfunction such confusion/delirium was seen in 87.17 % patients and coma in 79.48 % patients. Neck rigidity and Kerning's sign was seen in 66.6 % patients. Cranial nerve palsies and focal neurological deficit was seen in 15.38 % patients. Seizure was present in 23 % patients. And cloudy or turbid CSF was found in almost all cases (>95%). 95 % patients presented with neutrophilic predominance. Only 5 % of the case had initial lumphocyte predominance but gram stain positive. CSF sugar concentration was <40 mg/dl in 95 % of the patients and CSF to blood glucose ratio was approximately 0.27 on an average. In our study mortality reached 100 % in patient having CSF glucose less than 20 mg/dl of CSF/serum glucose ratio of less than 0.20.

Tunkel et al also concluded that predisposing factors as otitis media, sinusitis, pneumonia were present in 30 % of the patients.[6]

Our study was found that 20.5 % patients was a positive history of predisposing factors, out of

which 50 % had otitis media and 25 % had pneumonia.

Aswasthi S, Moin S. et al (1997) was used of Glass Gow Coma scale and concluded that 42.2 % was pyogenic meningitis, 36.9 % was tubercular meningitis and 20.9 % was meningo-encephalitis . And within first three days of hospitalization 18.7 % patients were death.[7]

In our study, 51.2 % patient were GCS between 3-5, 38.5 % patients were GCS between 6-10 and 10.3 % between 11-15. Mortality was 33.3 %, 45 % of patients with GCS 3-5, 26 % of patients with GCS, 6-10. 60 % of the total mortality was within first 3 days of hospitalization. It was predicted that patients with pyogenic meningitis with GCS 3-5 only 55 % of the patients were discharged, and with GCS 6-10, 73.3 % of the patients were discharge and patients with GCS 11-15, 100 % were discharged.

Dr. Lebels (1988) concluded that children treated by dexamethasone along with antibiotics, were less incidence of sensori neural deafness, more rapid increase in glucose concentration, and a rapid decrease in protein concentration in the CSF, and dexamethasone was not affected the sterilization of CSF.[8]

Kanra, Ozan et al (1995) was also studied on children with pneumococcal meningitis and concluded that over all neurological sequel, including hearing loss, at one year were higher in the placebo group at 23 % vs 7.4 % and 26.9 % vs 7.4 % respectively.[9]

In our study, we were observed that there was reduction in symptoms like headache, vomiting and fever in the group treated with dexamethasone. And the persistence of confusion/delirium and come were less in group , receiving the dexamethasone (46.15 % vs 50 % and 15.3 % vs 25.5 %). Similarly there was a significant increase in CSF glucose and decrease in CSF protein in the dexamethasone group, and total number of cells in the CSF was also decreased. Thus, our study was found that dexamethasone was played a beneficial role in bacterial meningitis patients in terms of clinical features and CSF findings.

And this present study was also found that patients with dexamethasone and cetriaoxone were mortality 26.7 % and patients treated with alone ceftriaoxone mortality were 27.3 %. Patients treated with older combination of G. penicillin, chloramphenicol and gentamycin, mortality rate was higher than patients treated with ceftriaoxone. And found that appropriate antibiotics with dexamethasone combination was more effective.

Dr. Odeo et al. was used the dexamethasone before administration of first dose of cefotaxim, and observed that mean opening CSF pressure was lesser in dexamethasone group patients, and after 12 hours of treatment cerebral perfusion increased by 21 %, tumour necrosis factor was also decreased, CSF glucose level was increased, and reduction of CSF protein and leukocytes.[10]

Our study was observed that, patients who received dexamethasone prior to first dose of antibiotic were minimally persisted the symptoms such as headache, vomiting and fever, confusion/delirium and coma. Thus we were observed that the use of dexamethasone at least 20 minutes prior to first dose of antibiotics was more effective.

Pichard E, Gillis D et al observed that 81.8 % patients treated with dexamethasone were secondary fever. Our study observed that 42.8 % patients treated with dexamethasone were secondary fever, and those patients who were not receiving dexamethasone, they were no fever.[11]

Van Wees J, Tegtmeyer KF observed that neurological squeal and fatality rate were significantly decreases the patients who were receiving dexamethasone therapy.[12]

Our study observed that, fatality rate was 28 % in S pneumonia, 40 % in Staphylococcus aureuos, 30 % in gram negative bacilli. Mortality rate of patients treated with ceftriaoxone was 26.9 %, and patients treated with G penicillin, chloramphenicol, gentamycin was 46.28 %. Patients who receiving dexamethasone with

ceftriaoxne, mortality rate was 26.7 %, and patients treated dexamethasone with combination of penicillin, chloramphenical and gentamycin, mortality rate was 42.8 %. Patients treated with dexamethasone, mortality rate was 33.3 % and patients who treated without dexamethasone mortality rate was 35.3%.

Our study was shown that mortality rate was higher with respect to other studies, because of, in our study 51.2 % patients were low GCS, we were used the penicillin + chloramphenicol + gentamycin in 33.3 % patients, and duration of our study was 5 days. And also observed that the poor prognostic factors were advanced age, longer duration of prehospitalisation period, low GCS at the time and admission, presence of cranial nerve palsies or focal neurological deficit at the time of admission, CSF leukocytes count > 1000 mm^3 and glucose < 20 mg/dl.

Conclusion

Adjunctive dexamethasone therapy may improve the outcome of pyogenic meningitis in adolescent and adults. And the intensity of headache, vomiting and fever were relieved, and reduction in neurological complications and mortality were seen in dexamethasone group patients.

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