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Original article

A RETROSPECTIVE ANALYSIS OF THE USAGE OF DEXAMETHASONE TO TREAT BACTERIAL MENINGITIS IN ADULTS AND CHILDREN.

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Abstract

Objectives:

The study aims to evaluate the use of dexamethasone as additional therapy in bacterial meningitis (BM), particularly when any one of the adverse prognostic cerebrospinal fluid parameters (WBC lesser than 1000 per mm^3, lactate greater than 10 mg per dL, or glucose lesser than 20 mg per dL) is present, with a focus on outcomes and complications.

Methods:

This retrospective cohort study was conducted at A. N. M. Medical College in India over 6 months from January 2023 to June 2023, involved 276 confirmed cases of bacterial meningitis. Patient data from the hospital registry were reviewed, applying inclusion criteria such as positive gram stain or CSF culture, CSF white cell count exceeding 1000/mm^3, or cloudy CSF, while excluding cases of nosocomial BM, neurotrauma or neurosurgery history, and neonatal meningitis.

Results:

In this investigation of 276 BM patients, *S. pneumoniae* and *N. meningitidis* were the main causes of death, with rates of 19% and 2%, respectively, slightly lower than previously reported. As previously reported, *S. pneumoniae* cases had more negative outcomes, and the triad of symptoms was found in only 25% of patients but linked with nerve-related or auditory sequelae. Dexamethasone appears to be more beneficial in instances with low cerebrospinal fluid leukocyte counts (< 1000/mm^3), although further research is needed to confirm this.

Conclusion:

This retrospective analysis suggests that dexamethasone may enhance outcomes in bacterial meningitis with specific cerebrospinal fluid characteristics. To confirm these findings, dexamethasone should be tested in clinical trials, especially in children, given the decline in infections in this population due to vaccination deployment.

Recommendation:

Considering the limitations of this retrospective analysis, prospective large-scale clinical trials are recommended to establish the efficiency of dexamethasone in diverse bacterial meningitis subgroups and to guide its routine use in clinical practice.

Keywords: Bacterial meningitis, *Streptococcus pneumoniae*, *Neisseria meningitides*, Cerebrospinal fluid

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Introduction.

Bacterial meningitis remains a significant global infectious threat, with an estimated number of 1.2 million new patients and 135,000 deaths every year [1,2]. The landscape of ambulatory meningitis has undergone remarkable changes in the last two decades. The advent of Haemophilus influenza type b (Hib) vaccines in advanced nations led to a remarkable 90 % reduction in invasive Hib infections [3]. Consequently, *Streptococcus pneumoniae* has now emerged as the predominant causative agent, accounting for 47 % of cases, followed by *Neisseria meningitidis* at 25 % and 8 % of the cases by *Listeria monocytogenes* in ambulatory meningitis within advanced countries [4].

In the pre-vaccine era, during the early 19th century, fatality rates were 100 % for *S. pneumoniae* and Hib-induced meningitis, while for *N. meningitidis*, it posed a 75 to 80 % fatality risk. The 1980s marked a significant turning point by reducing death rates for pneumococcal meningitis (20 to 30 %), Hib meningitis (5 %), and meningococcal meningitis (10 %) with the use of 3rd generation cephalosporins. Despite advancements in

diagnostic tools, new antibiotics, additional therapies, and critical care developments, there has been no significant improvement in these rates [4].

Meningococcal meningitis carries a 10 to 20 % risk of aftermath, such as irreparable hearing impairment and intellectual disability [5-7]. Distinct patterns are noticed with pneumococcal meningitis, which is linked with substantial illness (30 %) and death in adults. Surprisingly, nerve-related complications are the primary cause of death in young people, while in the geriatric population, systemic complications result in fatality [8]. Although children experience lower mortality rates (7.7 to 15.3%), they still face a significant pervasiveness of nerve-related complications (25 %) and impairment of hearing (32 %) [9,10].

The secondary inflammatory reaction of the host concerning microbial infiltration of the arachnoid chamber during bacterial meningitis (BM) can result in harm to neurons. Although antibiotics efficiently remove bacteria from the cerebrospinal fluid (CSF), they expedite the release of inflammation-causing and harmful substances, initiating a cytokine-driven inflammation and formation of brain fluid accumulation (in interstitial, vasogenic, and cytotoxic forms) [11-13]. Elevated intracranial pressure in BM patients can cause irreversible brain injury and mortality [1]. Therefore, beyond antibiotic treatment, addressing the immune response's adverse effects is crucial. Dexamethasone has shown success in minimizing the inflammatory response in clinical trials, animal models, and systematic overviews [14-16]. It interferes with the production of mediators of inflammation, reduces CSF abnormalities, and mitigates brain edema, ultimately lowering intracranial pressure [14,17].

The study aims to discern prognostic factors impacting the progression of bacterial meningitis (BM) and to evaluate the effect of dexamethasone as additional therapy on associated complications and overall outcomes in such scenarios.

Materials and Methods.

Study design.

The retrospective analysis employed a population analysis conducted retrospectively in a hospital, utilizing medical record reviews of patients identified and treated as cases of bacterial meningitis.

Study setting:

The study was conducted at the Department of Pediatrics, A. N. M. Medical College in Bihar, India. The retrospective analysis was carried out for a period of 6 months from January 2023 to June 2023.

Inclusion and exclusion criteria.

A thorough study was conducted on all admitted patients with bacterial meningitis (BM) in A. N. M. Medical College, India. The hospital registry was used to get the patient data, and individuals exhibiting a positive gram stain or demonstrating a positive culture in their cerebrospinal fluid, CSF white cell count surpassing 1000/mm³ or cloudy cerebrospinal fluid. Postmortem diagnoses from autopsies (when lumbar puncture was not performed) were considered. Exclusion criteria were nosocomial BM, a history of neurotrauma or neurosurgery, and neonatal meningitis. Patients receiving antibiotics within 2 days before admission were not excluded if they met the inclusion criteria.

Study size.

The study included 276 patients confirmed positive for bacterial meningitis and admitted to the hospital for treatment. Among 276 patients diagnosed with bacterial meningitis (BM), 40 were excluded due to nosocomial BM or neurosurgery, and an additional 12 were disregarded due to neonatal bacterial meningitis. Another 26 patients failed to meet the criteria for study inclusion, but, 2 patients without lumbar puncture yet diagnosed postmortem was included, resulting in a total of 196 individuals (adults and children) analyzed.

Study data analysis

The investigation centered on discerning factors predicting a negative outcome within the studied population. Adverse outcomes encompassed mortality, less positive conditions eight weeks post-discharge (as per the Glasgow Outcome Scale), hearing impairment, along specific nerve-related complications such as palsy of the cranial nerve, gait disturbance, and hemiplegia. The Glasgow Outcome Scale (GOS) scores, were extracted from medical records eight weeks post-discharge, starting from one (referring mortality) to five (minimal or lack of impairment). Attaining a GOS score of 5 was considered a positive result, while an adverse outcome involved scoring within the range of 1 to 4. Data on auditory loss and nerve-related adverse effects were recorded at discharge and, were accessible in medical reports, 8-weeks post-hospitalization.

Bias.

There was a chance that bias would arise when the study first started, but we avoided it by giving all participants identical information and hiding the group allocation from the nurses who collected the data.

Statistical Analysis.

Statistical analysis involved SPSS 12.0, employing the t-test, unpaired type, to compare outcomes between *S.*

pneumoniae and *N. meningitidis* meningitis. Odds ratios with 95 % confidence intervals measured associations for prognostic factors linked to detrimental outcomes after eight weeks and for aftermath at hospital discharge. Additionally, Fisher's PLSD and ANOVA tests evaluated the impact of dexamethasone on brain-related and auditory outcomes in highly vulnerable populations. A significance level of 5 % was applied, with $P < 0.05$ considered significant.

Ethical considerations .

The study protocol was approved by the Ethics Committee and written informed consent was received from all the participants.

Results/Outcomes .

Upon BM diagnosis, appropriate antibiotics were administered based on laboratory signs or clinical manifestations. Empirical therapy featured ceftriaxone, with ampicillin added for those under 3 months or over 60 years or with immunocompromised conditions. Ceftriaxone plus vancomycin was prescribed for resistant pneumococcal strains. For septic shock, inotropics were employed, and in cases of respiratory failure, intubation, and mechanical ventilation were implemented. H2-antihistamines were given to all patients for gastric protection.

Out of the 196 patients, 18 succumbed to their illness. Among them, 10 received dexamethasone, while the remaining 8 did not. Etiological pathogen identification was successful for 14 patients, with 12 having *S. pneumoniae* and 2 with *N. meningitidis*. The fatality rates for *N. meningitidis* and *S. pneumoniae* stood at 2 % and 19 %, respectively.

In our study population, both these pathogens emerged as the predominant causes of acute BM, accounting for 39 % and 32 %, respectively. Only 2 patients were affected by *H. influenzae*. *L. monocytogenes* failed to cause BM in any of the patients included in this study. While individuals affected with *N. meningitidis* were generally younger than those with the other major pathogen, the difference was not prominent.

Out of the entire population, 98 individuals achieved a favorable outcome, 34 experienced a detrimental outcome after 8 weeks, and 66 were lost to follow-up. Nerve-related or auditory aftereffects at discharge were observed in 42 patients, while 132 showed no aftermath. Convulsions at admission were associated with a fivefold increase in unfavorable outcomes, and focal nerve-related abnormalities at this juncture resulted in a tenfold increase. The triad of symptoms comprising high body temperature or fever, change in mental status, and stiffness of the neck, was linked to audiological and neurological sequelae. Positive *S. pneumoniae* in the cerebrospinal fluid, abnormal parameters of the CSF, high blood protein, particularly the C-reactive protein, at admission, low levels of sodium in the first 3 days, and referral from another hospital were linked with negative outcomes and aftermaths (Table 1).

Table 1: Predictors of Detrimental versus Beneficial Outcomes After eight Weeks

Unfavorable (n = 27)		Favorable (n = 97)	Odds ratio (95 % CI) *
Age (years)	21	0	NA
Men (%)		51	NA
Period of symptoms prior to admission (average hours)	45	34	NA
Period of symptoms prior to admission < 24 hours — number/total number (percentage)	15/27 (59)	57/97	0.48 (0.14 to 1.53)
Treated with dexamethasone - number/total number (percentage)	17/27 (65)	64/97 (67)	0.89 (0.19 to 2.34)
Received AB in last 2 days - number/total number (percentage)	6/27 (24)	18/97 (19)	1.33 (0.39 to 5.05)
Comordities - number/total number (percentage)			
Sinusitis/otitis	3/27 (12)	30/97 (31)	0.30 (0.065 to 1.59)
Pneumoniae	4/27 (18)	7/97 (8)	2.41 (0.44 to 11.09)
Immunocompromise	6/27 (24)	5/97 (6)	4.72 (0.95 to 23.4)
Convulsions on admission - number/total number (percentage)	11/27 (41)	11/97 (12)	**5,0 (1.5** to **18.1)**
Findings on admission - number/total number (percentage)			
Normal consciousness	3/27 (12)	61/97 (63)	**0.07 (0.02** to **0.28)**
Triad (neck stiffness, fever, and altered mental status)	9/22 (36)	27/97 (28)	1.43 (0.31 to 4.97)
Petechiae	1/27 (6)	41/97 (43)	**0.08 (0.01** to **0.64)**
CSF culture - number/total number (percentage)			

S. pneumonia	18/27 (70)	30/97 (31)	**5.44 (1.52** to **17.2)**
N. meningitidis	4/27 (18)	33/97 (35)	0.4 (0.112 to 1.64)
Other bacteria	1/27 (6)	15/97(16)	0.32 (0.037–2.77)
CSF parameters			
Positive bacterial culture - number/total number (percentage)	27/27 (100)	75/97 (78)	NA
WBC < 1000/mm^3 - number/total number (percentage)	20/26 (77)	30/97 (31)	**7,6 (1.82** to **31,4)**
Proteins > 500 mg/dL - number/total number (percentage)	11/26 (46)	23/97 (24)	2,64 (0,74 to 9,39)
Glucose < 20 mg/dL - number/total number (percentage)	22/26 (85)	39/97 (41)	**7,98 (1.59** to **39.9)**
Glucose CSF/serum ratio average	16	28	NA
Lactate > 10 mmol/L - number/total number (percentage)	14/18 (78)	29/88 (34)	**6,77 (1.25** to **36.7)**
Positive blood culture, number/total number (percentage)	14/26 (56)	53/96 (56)	1.52 (0.49–4.75)
Blood parameters			
Hb** (g per dL) – avg	10.8	12.0	NA
Platelets (×10^3 per mm^3) – avg	269	280	NA
CRP*** (mg per L) – avg	258	176	NA
CRP > 200 mg/L - number/total number (percentage)	67/27 (70)	37/97 (39)	**3,78 (1,15–12,5)**
Hyponatremia** in first 3 days - number/total number (percentage)	23/27 (24)	3/97 (4)	**7,23 (1,19–43,9)**
Referred from other hospital - number/total number (percentage)	57/27 (59)	17/97 (18)	**6,35 (1,9–21,2)**

*CI =confidence interval, **Hb =hemoglobin, ***CRP =C-reactive protein.

Discussion.

**Results: **

The present study encompassed a diverse population, including both children and adults, and observed that the classic triad of symptoms associated with bacterial meningitis was less frequently observed in the pediatric group, particularly in those under 12 months of age. This observation is consistent with prior research [8, 18, 19]. Notably, the presence of convulsions, nerve-related complications, and altered consciousness during hospitalization emerged as strong predictors of negative outcomes and subsequent sequelae [8, 18, 19]. Although the classic triad of symptoms was present in only 25 percent of patients, its presence correlated with the development of nerve-related or auditory sequelae, which aligns with findings in existing literature [18-20].

Furthermore, a low cerebrospinal fluid (CSF) leukocyte count, particularly in cases of fulminant meningitis and meningococcal sepsis, was associated with detrimental effects, consistent with previous reports [8, 18, 21]. CSF parameters, including low glucose levels and high lactate levels, were linked with worse outcomes and sequelae, corroborating findings in both adult and pediatric populations [18, 22, 23].

In this study, detrimental outcomes were significantly associated with the presence of C-reactive protein levels exceeding 200 mg per liter in blood upon hospitalization and low sodium levels within the first 3 days post-hospitalization. Notably, dexamethasone exhibited heightened effectiveness when the CSF leukocyte count was low (<1000/mm³), potentially due to its role in modulating inflammatory reactions [8, 18, 21]. These findings align with previous research indicating reduced complications in cases with CSF white blood cell counts below 1000 per mm³, low glucose levels (< 20 mg per dL), and high lactate levels (> 10 mmol per liter). While the results suggest promising outcomes, further studies are warranted to validate these findings. A recent trial focusing on adult bacterial meningitis patients also supported the positive impact of dexamethasone, particularly in patients with a Glasgow Coma Scale (GCS) between 8 and 11 upon admission.

Prognostic factors, in conjunction with the established benefits of dexamethasone in pneumococcal meningitis, may aid in identifying patients who would benefit most from this therapy. Dexamethasone is increasingly incorporated into routine care for both pediatric and adult bacterial meningitis (BM). Although its efficacy is not universally demonstrated across all causative subgroups, especially *Neisseria meningitidis*, this lack of evidence may be attributed to limited statistical power stemming from low incidence rates and small study sizes. Physiological mechanisms involving the central nervous system, stimulating the production of TNF-α and IL-1, suggest that dexamethasone should have a similar positive

impact in meningococcal meningitis as observed in BM caused by *Streptococcus pneumoniae* and Haemophilus influenzae type b (Hib). The beneficial effects of dexamethasone have already been established in cases where *Streptococcus pneumoniae* is the causative agent, especially when the Glasgow Coma Scale (GCS) on admission ranges from 8 to 11 [24].

In this retrospective study, it was found that dexamethasone had the most benefit when at least one of three cerebrospinal fluid parameters was present. However, in clinical practice, dexamethasone and antibiotics are often administered when bacterial meningitis is suspected, prior to identifying the responsible pathogen.

Given the limitations inherent to retrospective analyses, further studies are indispensable to validate these results and explore the potential benefits of dexamethasone in patients affected by bacterial meningitis. The possibility of conducting clinical trials in the pediatric population, already constrained by a limited patient count, is further hindered by the decline in invasive meningococcal and pneumococcal (serogroup C) infections in this population due to vaccine implementation.

Conclusion

The current study on the use of dexamethasone in bacterial meningitis in children and adults offers promising insights in this aspect. Three prognostic indicators, specifically low white blood cell count (< 1000/mm³), reduced glucose levels (< 20 mg per dL), and elevated lactate levels (> 10 mg per dL), appear to correlate with detrimental outcomes in bacterial meningitis (BM). Employing supplementary dexamethasone therapy under these circumstances could yield the most promising impact on the overall outcome.

Limitations.

The limitations of this retrospective analysis emphasize the need for more studies to confirm and explore the benefits of dexamethasone in meningococcal meningitis. Challenges in conducting trials in children arise from small patient numbers and the declining infections due to vaccines.

Recommendations.

The study recommends that in cases of bacterial meningitis where prognostic indicators such as low leukocyte count, reduced glucose levels, and elevated lactate levels are present, the administration of adjunctive dexamethasone therapy may have the most beneficial impact on the overall outcome.

List of Abbreviations.

Hib – Haemophilus influenzae type b
BM – Bacterial Meningitis
CSF – Cerebrospinal Fluid
GOS - Glasgow Outcome Scale
NVBDCP - National Vector Borne Disease Control Programme

Source of funding.

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Conflict of interest.

No conflict of interest was declared by the author.

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