

Dexamethasone efficacy on bacterial meningitis – a retrospective analysis of Albanian adult patients

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Abstract

Background: Research on the effects of corticosteroids in bacterial meningitis (BM) yielded conflicting results. While some studies reveal that corticosteroids improve the outcomes in BM treatments, others provide strong evidence that patients do not profit from this treatment. We investigated the factors that may impact the dexamethasone efficacy in patients with BM.

Methodology: In this retrospective study, we analyzed the medical records of patients with probable acute bacterial meningitis hospitalized between 2002 and 2008 at the Infectious Diseases Department, University Hospital Centre “Mother Theresa” of Tirana, Albania. They were all treated with dexamethasone.

For study purposes, patients were divided into two subgroups: 1) Severely ill patients (Glasgow Coma Scale [GCS] ≤ 7 and 2) Less severely ill patients (GCS 8-12). Patients were considered recovered when they reached a GCS ≥ 13 .

Results: Sixty-seven patients analyzed had a mean age of 43.8 ± 17.0 years old, forty-five (67.2%) of whom were males. The mean recovery time (RT) was 3.5 ± 1.3 days, and four (6%) died. In the severely ill subgroup (GCS ≤ 7 points), the Pearson correlation between the dexamethasone daily dose and the RT was -0.579 , $p < 0.01$ level (2-tailed). There was no correlation found in the less severely ill group of patients (GCS 8-12 points).

Conclusions: This study suggests that the patients with lower GCS scores were significantly more likely to benefit from dexamethasone therapy. In this subgroup, high doses of corticosteroids can significantly reduce BM recovery time; however, patients with a high GCS do not benefit from dexamethasone therapy.

Key words: bacterial meningitis, corticosteroid, recovery time

J Infect Dev Ctries 2009; 3(11):849-855.

(Received 11 May 2009 - Accepted 13 October 2009)

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Introduction

Bacterial meningitis (BM) was first described in the early years of the twentieth century with a virtual mortality of 100%. Its present incidence varies from four to six cases per 100,000 adults [1]. Despite essential advances in antibiotic therapy, BM still has a worldwide mortality rate varying from 20% to 30% [2–6]. Nearly 50% of survivors have neurological sequelae, such as hearing impairment, seizure disorders, and various problems in learning and behaviour [7–9].

Quagliarello *et al.* demonstrated the sterilization of cerebrospinal fluid cultures 24 to 48 hours after the first dose of antibiotic [10]. Furthermore,

experimental studies in animals have demonstrated that the different components derived from the bacterial lyses are the promoters of the inflammation in the subarachnoid space. These bacterial breakdown components are also consequences of antibiotic treatment [11,12]. These studies also show that adjuvant treatment with anti-inflammatory agents, such as dexamethasone, reduces both cerebrospinal fluid inflammation and neurological sequelae [11-13]. Other studies revealed that corticosteroid therapy is most beneficial if it is started before the first dose of antibiotics [5,6,14,15], with results indicating that early treatment with dexamethasone improved the outcome and reduced the death risk in adults with

Table 1. Demographic data, baseline symptoms and antibiotic therapy of the patients hospitalized during the period October 2002 - March 2008 at the ICU of infectious diseases with PBM.

Sex (M/F)	
M	45 (67.2%)
Residency (Rural/Urban)	
Rural	38 (56.7%)
Employment status	
Worker	20 (29.8%)
Retired	16 (23.9%)
Student	12 (17.9%)
Unemployed	12 (17.9%)
Employer	6 (8.9%)
Invalid	1 (1.5%)
Symptoms	
Confusion	27 (40.3%)
Stupor	21 (31.3%)
Coma	17 (25.4%)
Neck stiffness	
<i>Strong</i>	23 (34.3%)
<i>Moderate</i>	14 (20.9%)
<i>Light</i>	12 (17.9%)
<i>No</i>	18 (26.9%)
Bruzinski	38 (56.7%)
Kerning	37 (55.2%)
Vomits	46 (68.7%)
Headache	53 (79.1%)
Convulsions	12 (17.9%)
Direct Hospitalization (without recommendation)	40 (59.7%)
Antibiotic Therapy	
Ampicillini	15 (22.4%)
Chloramphenicol	1 (1.5%)
Ceftriaxone	19 (28.4%)
Cefotaxime	7 (19.4%)
Ampicilini and Amikacini	13 (19.4%)
Ceftriaxone and Vankomicini	1 (1.5%)
Ceftriaxone and Amikacini	8 (11.9%)
Chloramphenicol and Ampicillini	3 (4.5%)
Deaths	3 (4.5%)

BM [6,15,16]. A meta-analysis of all the controlled, randomized trial studies reported between 1966 and 2001 showed that corticosteroids reduced both the rate of death, neurological sequelae, and hearing loss in children, but these beneficial effects could not be confirmed in adults due to the minimal data available [17].

While many studies support the efficacy of early dexamethasone therapy on BM, others suggest a neutral or potentially harmful effect. In 2002, one study that involved 598 Malawian children showed that dexamethasone had no effect on the death rates and the neurological sequelae [18]. In 2007, a study

on Vietnamese adolescents and adults with BM revealed that dexamethasone does not improve the outcome in all adolescents and adults with suspected bacterial meningitis. Only patients who have a microbiologically proven disease (including those who have received prior treatment with antibiotics) appear to benefit from this therapy [6].

These apparently contradictory data were the impetus for this study. Our intention was to investigate the factors that may have impact on the efficacy of dexamethasone therapy in patients with BM.

Methods

This is a retrospective clinical study.

Data Source

In the intensive care unit (ICU) of the Infectious Diseases Department in Tirana's Mother Theresa University Hospital Center, there is approximately a seven year history of dexamethasone use in adults with probable acute bacterial meningitis (PABM). The doses were different and adapted empirically to the patients and the scale of disease severity.

The data used in this study were extracted from the medical records of all the patients diagnosed and hospitalized for PABM in the ICU of the Infectious Diseases Department between October 2002 and March 2008.

Study Definitions

In this study, we included all patients with PABM who were meningitis-symptomatic with a Glasgow Coma Scale (GCS) \leq 13 whose cerebrospinal fluid (CSF) was macroscopically altered, with the total number of cells more than 400 cells/mm³ where the polymorphonuclears (PMN) represented at least 60% of them and a CSF to serum glucose concentration ratio of \leq 50%.

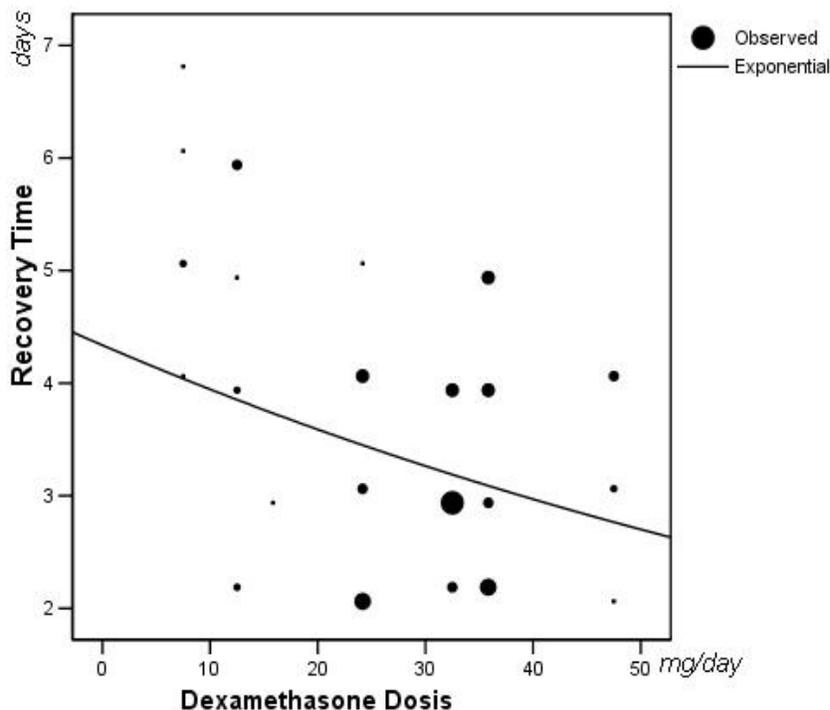
For the purposes of this study, we divided the patients in two subgroups: 1. Severely ill patients (GCS \leq 7) and 2. Less-severely ill patients (GCS 8-12).

We considered the patient recovered when he or she had a GCS \geq 13, and a normal CSF.

Outcome Measures

Our main outcome evaluation measure was recovery time (RT), which means the time (in days) from the beginning of the dexamethasone therapy until patients met the criteria to be considered recovered as stated in the study definitions.

Figure 1. Exponential regression curve shows inverse dependence of Recovery Time from Dexamethasone Doses on the first day in all patients in study. ($p < 0.05$).



Statistical Analysis

Statistical analyses were performed using the SPSS 12.0 for Windows. The continuous variables were presented in mean value and standard deviation. The discrete variables were presented in absolute and percent value. To compare the differences between different subgroups, we used T-test, Chi-square test, and Mann-Whitney Test, matching testing mechanism to data analysis needs. To identify the relationship between the dexamethasone doses and RT, we used the Pearson two-tailed correlation test. The significance threshold was settled by $p \leq 0.05$ (5%).

Results

Demographic Characteristics

Sixty-seven patients analyzed had a mean age of 43.8 ± 17.0 years (range: 14-73 years). The majority of the patients ($n = 45$; 67.2%) were males and there were no gender differences with regard to recovery time, dexamethasone dose (Mann-Whitney Test), or severity of disease (Chi-square test). Other detailed data is listed in Table 1.

Clinical Characteristics

Patients usually presented the clinical features characteristic of meningitis with high temperature,

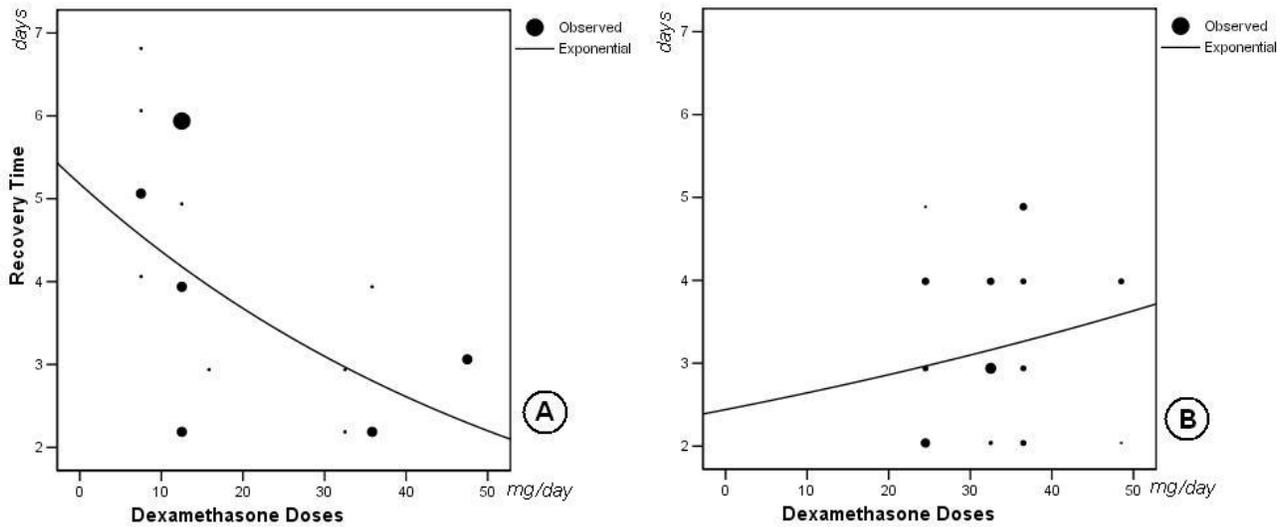
headaches, and neck stiffness being the predominant symptoms (Table 1). The initial GCS evaluation at hospitalization ranged from 9 to 12. Seventeen (25.4%) patients had a GCS ≤ 7 , while the remainder (50 patients) had a GCS ranging from 8 to 12.

At the beginning of therapy, patients had a blood O_2 saturation mean of $85.3 \pm 6.8\%$ (range 63.7-98.1%). CSF cell concentration was 3232 ± 1979 cell/ m^3 with maximum value of 8,569 cell/ mm^3 and minimum value of 409 cell/ mm^3 with a majority $\geq 60\%$ ($80 \pm 12\%$) of these being polymorphonuclear cells. There were no significant differences in CSF cell count between the two subgroups (severely ill and less severely ill patients).

Treatment and Outcome

All the patients were treated with dexamethasone for four consecutive days, and treatments always began after the first dose of the antibiotic. The mean daily dose was 27.6 ± 11.6 mg dexamethasone. The maximum dexamethasone dose given per day of treatment was 48 mg, and the minimum was 8 mg. Sixty-six (99%) patients received diuretic treatment with mannitol. All patients were under maximal doses of antibiotic therapy. Some of the antibiotics were initiated prior to our hospital admission. There were

Figure 2. A. Exponential regression curve shows inverse dependence of Recovery Time from Dexamethasone daily dexamethasone doses in severely-ill patients ($p < 0.01$). **B.** Exponential regression curve shows direct non-significant ($p > 0.05$) dependence of Recovery Time from Dexamethasone and daily dexamethasone dose in less severely-ill patients.



no significant differences between the two subgroups with regard to the antibiotic treatment. The mean recovery time ranged from two to seven days (3.5 ± 1.3 days), and four patients (6%) died. Two of the patients who died had diabetes mellitus, one had a history of past head trauma (Basis Cranial Fracture), and the other had no accompanying health problems. All the patients who died came from rural areas.

The Pearson Correlation between the first-day dexamethasone doses and the recovery time was -0.365 , $p < 0.01$ level (2-tailed), which reveals an inverse dependence between the first day dexamethasone dose and the recovery time (Figure 1).

In the severely ill subgroup ($GCS \leq 7$ points), the Pearson correlation between the first-day dexamethasone dose and the RT was -0.579 , significant at the 0.01 level (two-tailed). This is a stronger correlation than that observed when the test was performed for all patients together. Furthermore, there was no correlation found with the less severely ill group of patients (GCS 8-12 points). The exponential regression curve shows a direct dependence between RT and first-day dexamethasone dose, but this was statistically non-significant ($p > 0.05$) (Figure 2).

Discussion

The main result emerging from this survey shows that benefits from dexamethasone therapy in PABM are evident, but they are more prominent in the

severely ill patients (in our study, those with a $GCS \leq 7$). Furthermore, in this subgroup there is a significant negative correlation between daily dexamethasone doses and the recovery time ($p < 0.01$). Thus, the use of dexamethasone up to 0.17 mg/kg weight separated in three or four doses during the first 24 hours proved to shorten the recovery time significantly from five days to three days, in comparison to treatment with lower dexamethasone doses (up to 0.05 mg/kg weight). Surprisingly, the less severely ill subgroup ($GCS > 7$) showed no benefit from dexamethasone therapy. Furthermore, this finding suggests that dexamethasone could have delayed the recovery time of these patients (no statistical significance) (Figure 2). The death rate in the severely ill subgroup was higher compared to the less severely ill subgroup, respectively three (17.6%) and one (2%), but all the patients who died in the first subgroup had important health problems that impacted the outcomes (one patient with past head trauma and two with diabetes mellitus). The only patient who died in the less severely ill subgroup had no other accompanying health problems and had received a relatively low dose of dexamethasone on the first day (8 mg).

There were no differences with respect to the age and sex between the two subgroups. While there were more patients from rural areas in the severely ill subgroup than in the less severely ill subgroup, investigation showed no correlation between urban/rural residency and recovery time.

Table 2. Laboratory data at the moment of hospitalization, treatment and the recovery time.

Parameters	Mean	Standard Deviation	Maximum	Minimum
At the moment of hospitalization				
Temperature ($^{\circ}$ C)	38.5	0.89	40.1	37.0
Sat O ₂ (%)	85.3	6.80	98.1	63.7
PCO ₂ (mmHg)	38.0	6.70	57.3	22.3
PO ₂ (mmHg)	55.9	17.00	89.3	10.9
CSF cell concentration (cell/mm ³)	3232.0	1979.00	8569.0	409.0
CSF PMN (%)	80.0	12.00	100.0	60.0
Therapy and outcome				
Dexamethasone doses (mg per day)	27.6	11.60	48.0	8.0
Dexamethasone therapy duration (days)	4.0	1.00	7.0	2.0
Manitol treatment (days)	4.9	1.90	8.0	2.0
Recovery time (days)	3.5	1.30	7.0	2.0

Additionally, neither the CSF total cell count nor polymorphonuclear percentage seemed to impact the recovery time.

Other demographic factors of relevance include more male patients with PBM than females, more physical laborers, and more workers retired and unemployed than employed or with other professions. These subgroups usually have higher prevalence of exposure to trauma and compromised health with respect to age-dependent diseases that are risk factors for this pathology [14].

The most prevalent symptoms were alteration of mental status, fever, headache, neck stiffness, and vomiting, but the association of all symptoms occurred only in a minority of subjects, while three to four of them were present in every case. Similar data are reported from different authors [5,6,14-16].

Despite limitations such as the lack of bacterial findings, our results reveal new information that early dexamethasone use in severely ill patients with PABM could lead to the shortening of recovery time. Furthermore, the more severely ill patients are more responsive to high doses of dexamethasone. As previously mentioned, according to van de Beek *et al.*, in meningitis patients who show elevated leucocytes ($> 1000/\text{mm}^3$) in the cerebrospinal fluid, the reduction of risk of unfavorable outcome was attributed to the fact that the initial dose of adjunctive treatment with dexamethasone was administered

before or with the first dose of antimicrobial therapy [1]. In this case, the indicator of illness severity was the number of leucocytes, while in our case it was the presence of lower GCS.

Bacterial Meningitis is, functionally, a “battle” between the bacteria and different components of the immune system, so unfavorable outcomes may result from both the parts. Though it is difficult to assess the contribution of each element (bacteria and immunity) in the pathogenesis, we can hypothesize about the role each plays in the progression of the disease and treatment outcomes. As CSF cultures sterilized 24 to 48 hours after the first dose of antibiotic [10], we can speculate that the subsequent problem must be “the non-stopping inflammatory machine”. It has been demonstrated that the bacterial breakdown components are the promoters of different inflammatory processes and that these components are mainly a consequence of antibiotic effects on bacteria [11,12]. It therefore seems reasonable, and research strongly suggests, that anti-inflammatory therapy is beneficiary in BM [5,6,11-15]. With regard to dexamethasone, the anti-inflammatory and antitoxic effects are associated with a general immunosuppressive effect, as well. We must therefore consider anti-inflammatory and immunosuppressive effects in our evaluation of the overall impact of corticosteroids in BM therapy. Generally, corticosteroids are used before the first dose or soon after the antibiotic therapy has begun.

Theoretically, if we have a hyper-reaction of the immunity, the corticosteroid therapy may be beneficial, and if we have a hypo-reaction, it might be non-beneficial or even harmful. Interestingly, the signs and symptoms on which the Glasgow Coma Score is based are largely consequences of the CNS inflammation, so a low GCS reflects a high CNS inflammation. This may be the reason the dexamethasone treatment is effective in the severely ill group of patients (those with a low GCS) in contrast with the results in the less severely-ill patients (those with a high GCS). In addition, the bacteriolytic effect of antibiotics leads to the organism intoxication and therefore to cerebral intoxication, which can also be suppressed by dexamethasone; therefore, we speculate that the hypothesis alluded to above may explain the “different” results of dexamethasone therapy on BM in different studies. Studies that reveal no effect of dexamethasone in children and adults with BM are from countries such as Malawi, South America, Pakistan, *etc.* [18–21]. In contrast, studies that support the efficacy of dexamethasone in bacterial meningitis (especially caused *Haemophilus influenzae* type b) in children and in adults are from industrialized countries [15,22,23]. Another study performed by Mai *et al.* in Vietnam reveals improved outcomes only in “microbiologically proven disease”. Patients with probable bacterial meningitis treated with dexamethasone had a higher mortality rate compared with the placebo group. No reliable reason was found to explain this result [6].

In developing countries, there might be high rates of immunologic alteration among the general population as a consequence of HIV infections or malnutrition [24–26]. In this population, the adjunctive therapy with dexamethasone might decrease the level of bacteriolysis-dependent intoxication and inflammation and suppress the limited immune abilities. Nutrition, stress, chronic illness, and environmental pollution can influence the immune response, not simply by depressing or empowering it, but also by changing the way this response is rendered [25–30]. In respect to these factors, reports from developing countries have shown differences compared with findings in industrialized ones; for example, the high prevalence of allergic diseases confirms the “over-reacting” immune systems in industrialized countries [27,29]. It should be taken in consideration that factors such as the access to and efficacy of the health services may contribute directly in the contingent of the

patients under studies by which the other part has impact on the dexamethasone therapy efficacy. Dexamethasone is more useful as an inhibitor of inflammation during hyperergic immune response; consequently, meningitis symptomatic patients showing furious immune response (high number of leucocytes in CSF) as well as showing consistent inflammation (cerebral edema/low GCS score) should be treated with dexamethasone as soon as possible. These findings indicate the need to conduct further prospective clinical trials to evaluate and explore the bacteriologic criteria in BM patients who need immediate glucocorticoid therapy, especially when associated with a severely altered consciousness.

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Conflict of Interest: No conflict of interest is declared