

Effectiveness of the association of dexamethasone with antibiotic therapy in pediatric patients with bacterial meningitis

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SUMMARY

Objective: To evaluate the efficacy of the association of corticosteroids with the standard treatment of bacterial meningitis in pediatric patients. **Methods:** A systematic review of the literature was conducted through the MEDLINE database. Only randomized controlled trials comparing dexamethasone with placebo in the treatment of pediatric patients with bacterial meningitis were included. **Results:** Eight articles met the inclusion criteria and were selected for analysis. There were no differences in mortality ($p = 0.86$), and incidence of neurological ($p = 0.41$), and auditory ($p = 0.48$) sequelae between the groups. **Conclusion:** There are no benefits in associating corticosteroids with the standard treatment of bacterial meningitis in pediatric patients.

Keywords: Bacterial meningitis; dexamethasone; mortality.

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Study conducted at Academic Center of Studies and Research in Evidence-Based Medicine, Faculdade de Medicina de Santos, Centro Universitário Lusíada (UNILUS), Santos, SP, Brazil

Submitted on: 10/10/2011
Approved on: 01/20/2012

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Conflict of interest: None.

INTRODUCTION

Bacterial meningitis is an important cause of death and permanent neurological disability despite advances in antimicrobial therapy and diagnostic techniques, and the improvement in general care. The physiopathology of neurological lesions in meningitis correlates with the severity of inflammation in the cerebrospinal fluid (CSF), which can be alleviated with the use of systemic corticosteroids.

The adjunct therapy with dexamethasone is based on the observation that the host's inflammatory response, especially after the start of antibiotic therapy, can prevent adverse results. Its use is controversial in patients older than two months, and it is banned in patients younger than this age.

The objective of this study is to evaluate the effectiveness of the association of corticosteroids with the standard treatment for bacterial meningitis in pediatric patients.

METHODS

A systematic review of the literature was conducted through MEDLINE, EMBASE and LILACS databases. The following combination of keywords was used through the Clinical Queries interface (Therapy/Narrow): meningitis AND (adrenal cortex hormones OR dexamethasone). The survey was finished on October 8, 2011. Articles were selected based on their respective titles and abstracts.

Only randomized controlled trials comparing dexamethasone with placebo in the treatment of pediatric patients with bacterial meningitis were included. The analyzed outcomes were mortality and incidence of neurological and auditory complications.

The assessment of the methodological quality of the included studies was carried out using the criteria proposed by Jadad et al.¹. These criteria assess the description of randomization, adequacy of randomization, description of blinding, adequacy of blinding, and description of follow-up losses in a scale ranging from zero to five points. Only studies with a score ≥ 3 were included in this review.

Univariate analysis of the dichotomous data was performed using a 2×2 table and compared by the chi-square test (Mantel-Haenzel) and the level of the null hypothesis rejection was set at 0.05. All data were analyzed by intention to treat. Moreover, the power of each study was calculated, adopting a minimum value of 80% as significant. A meta-analysis of the obtained data was performed for all outcomes.

RESULTS

A total of 73 articles were retrieved through the search strategy. Ten articles met the inclusion criteria and were selected for the analysis²⁻¹¹. Of these, two studies were excluded because they were classified as Jadad < 3 ^{5,8}. Thus, this review included data from eight primary studies,

totaling 1,460 patients (743 in the dexamethasone group and 717 in the control group).

All studies adequately described the sequence of patient allocation, as well as the description of blinding and follow-up losses. Thus, they received a Jadad score of 5.

The patients' ages ranged between two months and 16 years of age. The antibiotic schemes included cefotaxime 200 mg/kg/day², ampicillin 200 mg/kg/day + sulbactam 100 mg/kg/day⁶, ampicillin 300 mg/kg/day + chloramphenicol 100 mg/kg/day⁷, benzathine/penicillin 200,000 IU/kg/day + chloramphenicol 100 mg/kg/day⁹, and ceftriaxone 80-100 mg/kg/day^{3,4,10,11}. The dose of dexamethasone ranged from 0.6 to 0.8 mg/kg/day for 2-4 days.

The diagnosis was confirmed by culture of the CSF in all tests. Regarding the etiologic agents, 180 cases (12%) were caused by *Neisseria meningitidis*, 429 cases (29%) by *Streptococcus pneumoniae*, 535 cases (37%) by *Haemophilus influenzae* type B, 239 cases (16%) had no isolated agents, and 77 cases (5%) had other microorganisms as infection agents.

MORTALITY

The mortality rate in the study group was 18.0% (134 of 743 patients), whereas in the control group it was 17.6% (126 of 717 patients). There was no statistical difference between the groups ($p = 0.86$; $I^2 = 0\%$; Figure 1).

NEUROLOGICAL SEQUELAE

The incidence of neurological sequelae in the intervention group was 16.8% (104 of 618 patients), whereas in the control group it was 18.5% (110 of 595 patients). There was no statistical difference between the groups ($p = 0.41$; $I^2 = 18\%$; Figure 2).

AUDITORY SEQUELAE

The incidence of auditory sequelae in the intervention group was 28.2% (174 of 618 patients), whereas in the control group it was 29.9% (178 of 595 patients). There was no statistical difference between the groups ($p = 0.48$; $I^2 = 45\%$; Figure 3).

POWER (TYPE II ERROR)

None of the primary studies included in this review had power $> 80\%$ capable of demonstrating differences between groups.

DISCUSSION

Corticosteroids have been widely used in pediatric patients with bacterial meningitis, but literature is conflicting about the actual benefits of these drugs in reducing mortality and, mainly, auditory and neurological sequelae.

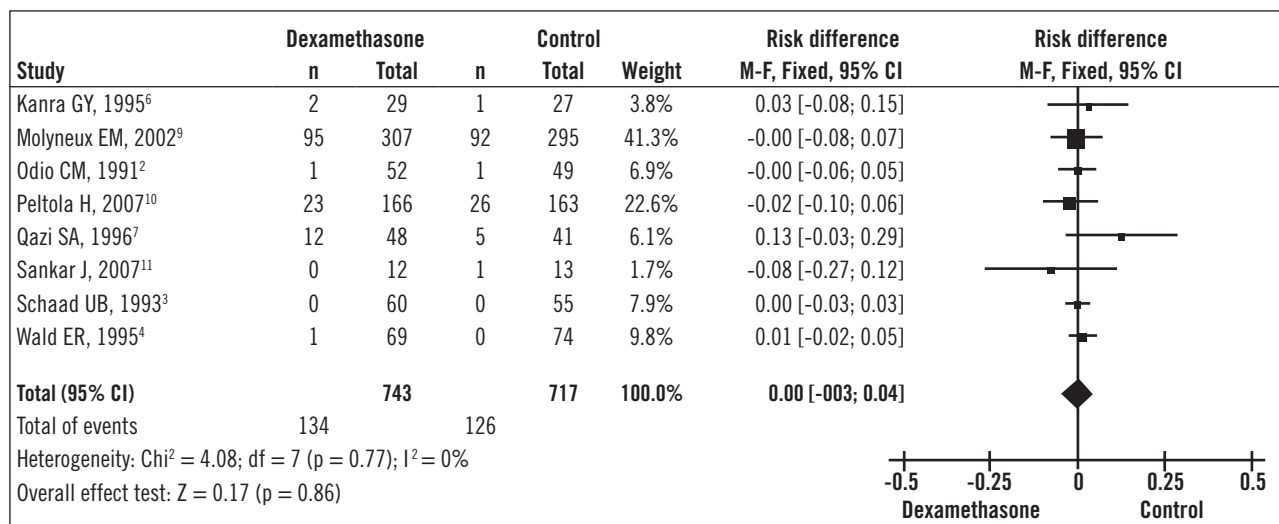


Figure 1 – Meta-analysis of the incidence of mortality evaluating the association of dexamethasone with antibiotic therapy in pediatric patients with bacterial meningitis.

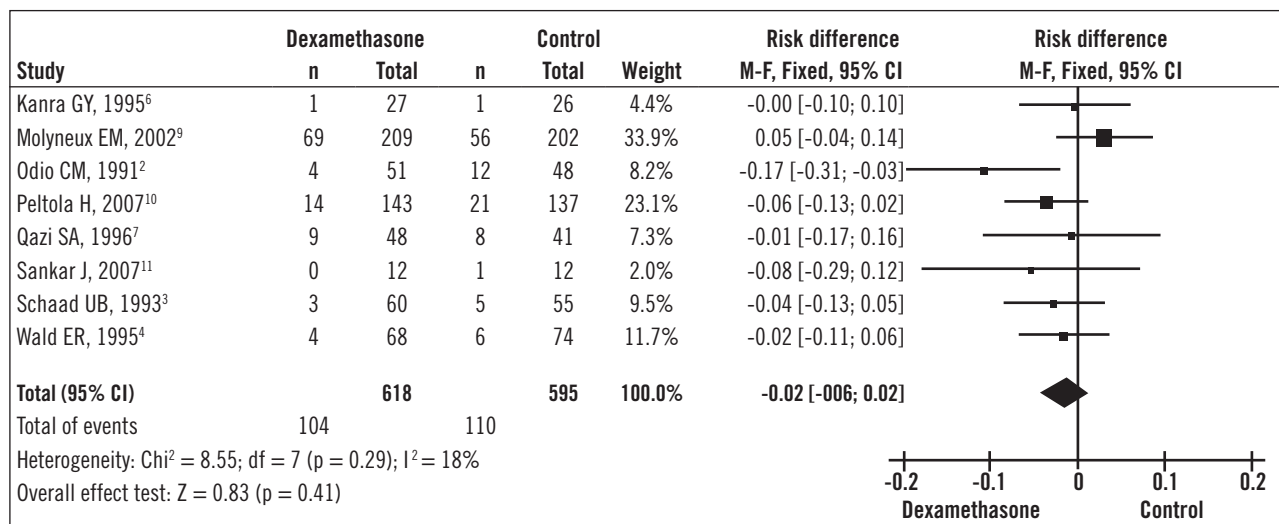


Figure 2 – Meta-analysis on the incidence of neurological sequelae evaluating the association of dexamethasone with antibiotic therapy in pediatric patients with bacterial meningitis.

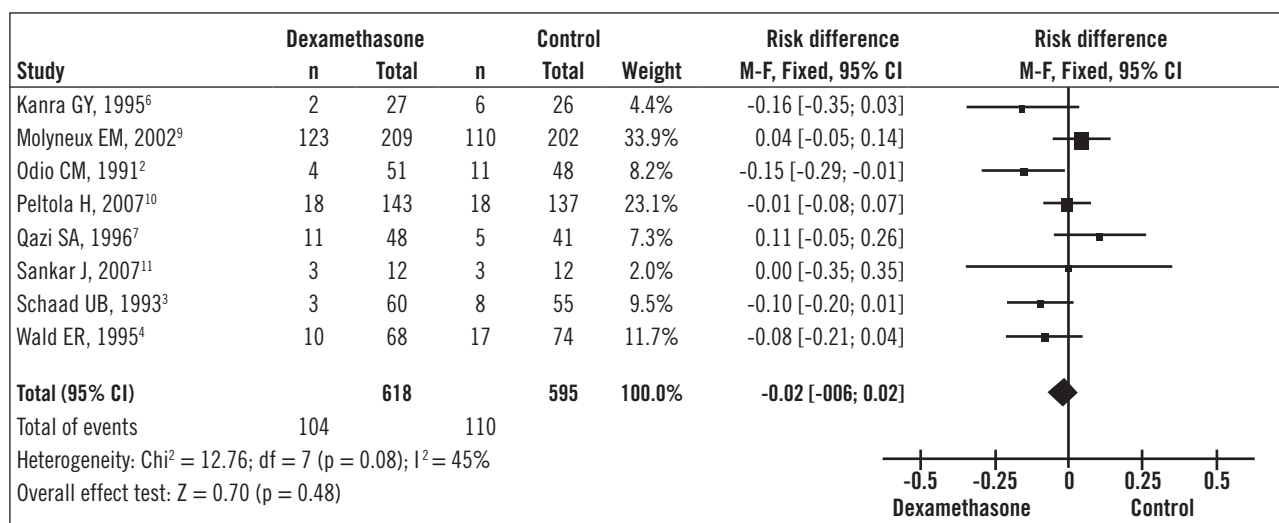


Figure 3 – Meta-analysis on the incidence of auditory sequelae evaluating the association of dexamethasone with antibiotic therapy in pediatric patients with bacterial meningitis.

The rationale for the use of corticosteroids is the inhibition of inflammatory cytokines in the CSF fluid and, when administered 15-20 minutes before the antimicrobial agents, the inhibition of the inflammatory response after bacterial lysis by these drugs. However, experimental studies *in vitro* have demonstrated that corticosteroids may be toxic to cultures of cortical and hippocampal neurons. In animals, hippocampal and striatal neurons are particularly vulnerable to dexamethasone. Corticosteroid therapy increases hippocampal apoptosis and also learning deficit¹². Several studies published in recent years have evaluated the benefit of dexamethasone in patients with bacterial meningitis, but the adjunct use of steroids remains controversial. Two meta-analyses of placebo-controlled studies have reached different conclusions. Havens et al.¹³ demonstrated that dexamethasone did not reduce mortality or neurologic abnormalities at hospital discharge and late follow-up, whereas Geiman and Smith¹⁴ found that dexamethasone did not reduce mortality, but decreased neurological sequelae and bilateral hearing loss up to six weeks after discharge. The difference in neurological sequelae in the groups treated with dexamethasone was maintained six months after discharge.

Some explanations for the inconsistent results are discussed in the literature, and include: (i) different patient populations, (ii) various antibiotic regimens, (iii) lack of standardization of diagnostic tests to evaluate hearing loss in infants, and (iv) duration of disease and antimicrobial treatment before admission.

None of the included studies had sufficient power to detect a significant difference in mortality and morbidity between patients treated with adjunct dexamethasone and those treated with placebo.

These data should be considered by pediatricians, intensivists, neurologists, and all those who treat patients with meningitis regarding the decision-making of prescribing or not prescribing corticosteroids.

CONCLUSION

Based on the results of this review, it can be inferred that there are no benefits in the association of corticosteroids with the standard treatment of bacterial meningitis in pediatric patients.

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