Systematic review of dexamethasone as an adjuvant therapy for bacterial meningitis in children

Revisão sistemática do uso da dexametasona como terapia adjuvante na meningite bacteriana em crianças

Revisión sistemática del uso de la dexametasona como terapia adyuvante en la meningitis bacteriana en niños

João Antonio G. G. Prats[1], Alan Jelaleti Gaspar[1], Ana Bárbara G. Ribeiro[1], Gabriel Domingos De Paula[1], Luciana Vicente de S. P. V. Boas[2], Fernando Pereira de Sá[3]

ABSTRACT

Objective: To analyze the best available evidence from the last 15 years on the benefits of adjuvant therapy with dexamethasone for bacterial meningitis in children.

Data sources: Randomized controlled trials comparing dexamethasone to placebo and/or other adjuvant therapies in patients with bacterial meningitis diagnosed by biochemical, cytological and/or microbiological data. Studies with patients from 29 days to 18 years of age, from 1996 to 2011, were searched at Medline, Lilacs and SciELO databases. The evaluated outcomes were mortality and development of neurological and/or hearing impairment. Studies related to tuberculous meningitis were excluded.

Data synthesis: With the specified criteria, five published studies were identified corresponding to four study protocols. None of the studies showed differences between dexamethasone and placebo for the evaluated outcomes. All analyzed studies had high methodological quality (Jadad *et al* score=5).

Conclusions: Current evidence is insufficient to support routine adjuvant therapy with dexamethasone to reduce mortality, hearing impairment, or neurological sequelae in pediatric patients with non-tuberculous bacterial meningitis.

Key-words: meningitis, bacterial; dexamethasone; deafness; mortality.

RESUMO

Objetivo: Analisar a melhor evidência disponível nos últimos 15 anos com relação aos benefícios da terapia adjuvante com dexametasona na meningite bacteriana em população pediátrica.

Fontes de dados: Das bases de dados Medline, Lilacs e SciELO, foram analisados ensaios clínicos randomizados de 1996 a 2011, os quais comparavam a dexametasona ao placebo e/ou a outra terapia adjuvante em pacientes com meningite bacteriana diagnosticada laboratorialmente por critérios quimiocitológicos e/ou bacteriológicos, na faixa etária de 29 dias aos 18 anos. Os desfechos avaliados foram mortalidade e ocorrência de sequelas neurológicas e/ou auditivas. Foram excluídos estudos relacionados à meningite tuberculosa.

Síntese dos dados: Com os critérios utilizados, foram identificadas cinco publicações correspondentes a quatro protocolos de estudo. Nenhum dos estudos mostrou diferenças entre a dexametasona e o placebo para os desfechos avaliados. Os estudos analisados tiveram alta qualidade (escore de Jadad *et al*=5).

Conclusões: As evidências encontradas na literatura são insuficientes para indicar de forma rotineira o uso da dexametasona como terapia adjuvante para redução de mortalidade, perda auditiva e sequelas neurológicas em pacientes pediátricos com meningite bacteriana não tuberculosa.

Palavras-chave: meningite bacteriana; dexametasona; surdez; mortalidade.

Instituição: Centro Universitário Lusíada (UNILUS), Santos, SP, Brasil
[1]Acadêmicos do Curso de Ciências Médicas do UNILUS, Santos, SP, Brasil
[2]Mestre em Pediatria pela UNILUS; Professora da Disciplina de Pediatria do Curso de Ciências Médicas do UNILUS, Santos, SP, Brasil
[3]Especialista em Pediatria; Professor da Disciplina de Pediatria do Curso de Ciências Médicas do UNILUS, Santos, SP, Brasil

Endereço para correspondência:
João Antonio G. G. Prats
Rua Oswaldo Cruz, 179 – Boqueirão
CEP 11045-101 – Santos/SP
E-mail: jaggp89@gmail.com

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RESUMEN

Objetivo: El presente estudio tiene por objetivo el análisis de la mejor evidencia disponible los últimos 15 años respecto a los beneficios de la terapia adyuvante con dexametasona en la meningitis bacteriana en población pediátrica por medio de revisión sistemática.

Fuentes de datos: De las bases de datos Medline, Lilacs y ScieLO, se analizaron ensayos clínicos aleatorios de 1996 a 2011 que comparaban la dexametasona al placebo y/u otra terapia adyuvante, en pacientes con meningitis bacteriana diagnosticada laboratorialmente por criterios quimiocitológicos y/o bacteriológicos, en la franja de edad de 29 días a 18 años. Los desenlaces evaluados fueron mortalidad y ocurrencia de secuelas neurológicas y/o auditivas. Se excluyeron estudios con meningitis tuberculosa.

Síntesis de los datos: Con los criterios utilizados, se identificaron cinco publicaciones correspondientes a cuatro protocolos de estudio. Ninguno de los estudios mostró diferencias entre la dexametasona y el placebo para los desenlaces evaluados. Todos los estudios analizados tuvieron alta calidad (escore Jadad=5).

Conclusión: Las evidencias encontradas en la literatura son insuficientes para indicar, de modo rutinario, el uso de la dexametasona como terapia adyuvante para reducción de la mortalidad, pérdida auditiva y secuelas neurológicas, en pacientes pediátricos con meningitis bacteriana no tuberculosa.

Palabras clave: Meningitis bacteriana; dexametasona; sordera; mortalidad.

Introduction

Bacterial meningitis (BM) is a severe infection of the central nervous system which affects especially children. Although vaccination strategies, antibiotic treatment and adequate hospital care can strongly reduce its negative consequences, BM remains the cause of substantial morbidity and mortality both in developing and developed countries[1-3].

In Brazil, according to the Disease Reporting System (Sistema de Agravos de Notificação), almost 65,000 children had meningitis from 2007 to 2010, 3,770 of which died, characterizing a 5.8% mortality[4]. Long-term morbidity, especially morbidity related to persistent neurological sequelae, happens in approximately 15% of patients[5]. Sensorineural hearing loss, seizures, motor deficits, hydrocephaly and mental impairment[6-9], as well as less evident changes such as cognitive, behavioral and academic problems are observed in children who had BM[10,11].

Studies on dexamethasone as adjuvant therapy for the reduction of morbidity and mortality of BM began by the end of the 1980s, driven by experimental research in which corticosteroids were capable of reducing meningeal inflammation in animal models[12,13]. Its use in pediatric clinical practice was based on the results of the first clinical trials published in the late 1980s and early 1990s, which had very positive results, reducing hospitalization time, improving clinical parameters and reducing the occurrence of auditory and neurological sequelae in up to 24%[14,15].

However, several studies were published on this subject since then, with quite conflicting results. There is a disagreement between the results of the last meta-analyses[16,17]. They included studies with adults and/or age group cohort which encompass both children and adults or do not include the pediatric population in its totality. Moreover, these meta-analyses are also heterogeneous in relation to studies included and periods and groups analyzed. The last clinical trial published on the use of dexamethasone as adjuvant therapy for bacterial meningitis in children is from 2010[18] and, since then, there has been no revision with exclusive focus on this population.

This study analyzes the best available evidence from the last 15 years on the benefits of dexamethasone as adjuvant therapy for BM in the pediatric population through a systematic revision of primary studies with the higher level of evidence, i.e., randomized clinical trials[19].

Methods

A systematic review of the medical literature from the last 15 years (1996-2011) was performed in the primary database Medline, using MeSH descriptors and performing combinations of the descriptors "Meningitis, Bacterial", "Dexamethasone", "Child", "Child, Preschool", "Infant", "Adolescent" and "Randomized Controlled Trials". A supplementary search of the Latin-American literature was performed in the databases Lilacs and ScieLO to identify relevant studies not included in the primary search, using the same descriptors.

In the review were included: Randomized clinical trials that compared dexamethasone with placebo and/or other adjuvant therapy in patients with bacterial meningitis diagnosed via lab tests using biochemical, cytological and bacteriological criteria in the age group from 29 days to 18

years and that assessed as outcomes mortality and the occurrence of neurological and/or hearing sequelae.

Excluded from the review were studies which included newborns, particularly due to the different meningitis-causing agents in this age group[20]; studies with patients who had *Mycobacterium tuberculosis* meningitis, due to the heterogeneity of the affected population and of the clinical, diagnostic and prognostic characteristics of meningitis caused by this agent[21].

Studies were selected from the results of a comprehensive search, initially filtered for the studies' publication date. Abstracts were then studied to check if they met the inclusion and exclusion criteria. After this stage, complete versions of included abstracts were assessed to complete the selection process.

Criteria proposed by Jadad *et al*[22] were used to assess the quality of clinical trials. Two authors independently set the score for each of the studies selected. Disagreements were solved in consensus meetings.

Results

Through the initial search 35 studies were obtained, 14 of which were excluded for being published before 1996. 16 other studies were excluded at the abstract assessment stage: one was not a randomized clinical trial; four did not assess the outcomes mentioned in this review; five included patients with tuberculous meningitis; one included patients with meningococcal sepsis; four included adults; and one included newborns in the studied population. In total, five studies were selected after reading the abstracts. Of these, complete versions were obtained. No article was excluded after reading the complete version. However, there were two publications which were subsequent analyses of the same study protocol[18,23]. These articles were analyzed as a group, comprising a total of 5 publications and 4 study protocols. The selection flow chart is in Figure 1. Supplementary search in Latin-American databases resulted in no additional study.

The characteristics of the studies included in the final analysis described below are summarized in Table 1.[22-26] In 2007, Peltola *et al* published the results of a multicenter study conducted in ten Latin American countries from 1996 to 2003, including 654 children aged 2 months to 16 years with bacterial meningitis, no previous history of traumatic brain injury (TBI) and no recent neurosurgery, neurological disease, immunosuppression or hearing impairment known[23]. The diagnosis was defined by positive cerebrospinal fluid (CSF) culture for typical BM causative agent, characteristic biochemical and cytological findings on positive CSF and blood cultures, characteristic CSF biochemical and

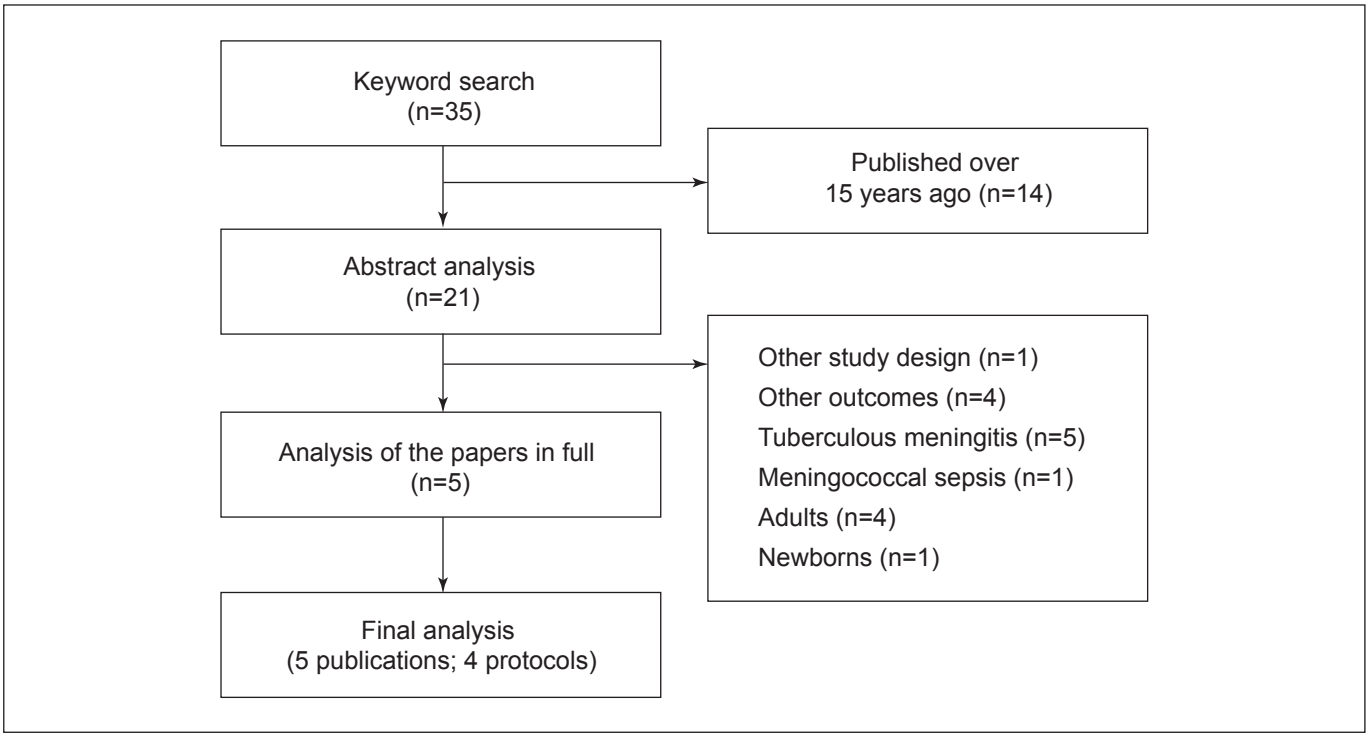

Figure 1 - Flow chart for the selection and detailing of excluded studies

Table 1 - Summary of the characteristics of analyzed studies

Author and year	Population	Diagnosis	Blinding	Antibiotics	Study groups	Studied outcomes	Jadad score[22]	Results	Notes
Peltola et al[23,18]	N=654 2 months to 16 years 6 countries – Latin America	Bacteriological or biochemical and cytological	Placebo and drug with the same appearance	Ceftriaxone	Dexa + Placebo vs. Dexa + Glycerol vs Placebo + Glycerol vs. Placebo + Placebo	Mortality, severe neurological sequelae or severe hearing loss; Degree of hearing loss	5	No difference between groups for any of the outcomes	Results were independent from etiological agent and of antibiotic administration time
Sankar *et al*[24]	N=58 2 months to 12 years Pediatric hospital - India	Bacteriological or biochemical and cytological	Placebo and drug with the same appearance	Ceftriaxone	Dexa + Placebo vs. Dexa + Glycerol vs. Placebo + Glycerol vs. Placebo + Placebo	Neurological and hearing sequelae	5	No difference between groups for any of the outcomes	No sample calculation
Molyneux *et al*[25]	N=598 2 months to 13 years Hospital - Malawi	Bacteriological or biochemical and cytological	Placebo and drug with the same appearance	Crystalline penicillin + chloramphenicol	Dexa vs. Placebo	General, in-hospital and after-discharge mortality, neurological and hearing sequelae	5	No difference between groups for any of the outcomes	26% of patients with HIV (similar number in both groups)
Qazi *et al*[26]	N=89 2 months to 12 years Pediatric hospital - Pakistan	Bacteriological or biochemical and cytological	Placebo and drug with the same appearance	Ampicillin + Chloramphenicol; Cefotaxime if resistance is documented	Dexa vs. Placebo	Mortality, neurological and hearing sequelae	5	There was no statistical difference between groups for any of the outcomes	

HIV: Human immunodeficiency virus; Dexa: dexamethasone

cytological findings associated to positive latex agglutination test or signs and symptoms consistent with meningitis associated with at least three of the following criteria: CSF pleocytosis (>1000cells/mm^3); hypoglycorrhachia (<40mg/dL), hyperproteinorrhachia (>40mg/dL), increased C-reactive protein serum (>40mg/L). Double blinding was performed through the use of identical bottles for drugs and placebo, coded for the study group in question. Each patient received an agent intravenously and another orally. The placebo for intravenous dexamethasone was physiologic saline solution and for oral glycerol was carboxymethylcellulose. Patients were block-randomized, divided into 4 groups: one group received intravenous dexamethasone (IV) and oral placebo (n=166), other received IV dexamethasone and oral glycerol (n=159), another group received oral glycerol and IV placebo (n=166), and the last received only placebo, both oral and IV (n=163). The doses used were: 0.15mg/kg of dexamethasone every 6 hours for 48 hours and 1.5ml/kg (with a maximum of 25ml) every 6 hours of 85% glycerol. Both agents were administered 15 minutes prior to antibiotic therapy. All patients were using 80–100mg/kg/day of ceftriaxone, in a single daily dose, for 7 to 10 days. The primary outcomes analyzed were: mortality, incidence of severe neurological sequelae and severe hearing loss (better ears inability to detect sounds to 80dB, determined by traditional audiometry with evoked potential). Loss to follow-up was less than 20% and the study showed excellent methodological quality (Jadad score=5). As for the results, there was no statistical difference in mortality between the four groups. As for neurological sequelae or severe hearing loss, there was no difference between the dexamethasone group and the placebo group. The two groups using glycerol demonstrated a lower incidence of severe neurological complications compared to the other two groups (p=0.022) and a significant reduction in combined mortality and severe neurological sequelae (p=0.016). It is noteworthy that, when analyzing only the cases with confirmed etiologic agent, glycerol lost statistic significance, leaving only a trend (p=0.081). In 2010, Peltola *et al* published the detailed results of the audiological study of 383 patients in the study[18]. This reduction in the number of studied patients was due to mortality (83 patients), to the fact that 155 patients had only been tested for severe hearing loss (80 dB) and that 33 had not been tested properly. Dexamethasone, glycerol or a combination of both agents were not capable of preventing hearing loss in pediatric patients with BM. Interestingly, this occurred regardless of the causative agent or time of administration of the antibiotic (either before or after administration of ceftriaxone).

Also in 2007, Sankar *et al* conducted in the Department of Pediatrics of a teaching hospital in northern India a study of 58 patients, aged 2 months to 12 years old, admitted between June 2002 and September 2003 with bacterial meningitis[24]. The study excluded patients with a prior diagnosis of neurological deficit, ventriculoperitoneal shunt, severe malnutrition, immunocompromised, those with chronic diseases and with a history of trauma. The diagnosis was confirmed by positive results in CSF and blood cultures positivity in latex agglutination test, biochemical and cytological CSF analysis suggestive of BM. Patients were randomized by a randomization list. Blinding was performed by using encoded packets and drugs identical to placebo. Patients were divided into four groups to receive: Glycerol orally or by nasogastric tube (NGT) associated with intravenous placebo (n=13), IV dexamethasone associated with NGT or oral placebo (n=12); oral or NGT glycerol plus IV dexamethasone (n=20); oral or NGT placebo associated with IV placebo. All patients received intravenous ceftriaxone (100mg/kg/day) for at least seven days. Survivors were assessed at discharge and after one month for the analysis of the following outcomes: neurological and hearing sequelae. The study showed loss to follow-up <20%, high methodological quality (Jadad score=5), but did not describe the sample calculation. As for the results, there were no statistical differences in the incidence of neurological or hearing sequelae among the four groups.

Molyneux *et al* published in 2002 data from their study assessing the efficacy of dexamethasone compared to placebo as adjuvant therapy in 598 patients with BM aged 2 months to 13 years old in a hospital in Malawi[25]. Patients who had received broad-spectrum antibiotics in the last 24 hours were excluded. The diagnosis of BM was defined as the presence of >100 leukocytes with a predominance of granulocyte in CSF, positive CSF bacterioscopy or positive CSF or blood culture. Patients were block-randomized to receive dexamethasone (0.4mg/kg every 12 hours for 2 days) or placebo 5 to 10 minutes before the first dose of antibiotics. Double blinding was performed with drugs and placebo of identical appearance, coded for the groups. All patients received penicillin (200,000UI/kg/day) and chloramphenicol (100mg/kg/day) for 7 to 10 days. The primary outcome assessed was mortality and secondary outcomes included neurological sequelae, assessed one and six months after discharge. Loss to follow-up was less than 20%. The methodological quality of the

trial was high (Jadad score=5). Results showed there was no statistical difference between dexamethasone and placebo for mortality or the incidence of neurological sequelae. There was no difference in mortality, incidence of neurological sequelae and deafness, even in the analysis of etiologic agents. The exception is pneumococcus, which presented a higher incidence of neurological deficits in patients who received dexamethasone (p=0.01).

In another study published in 1996, Qazi *et al* analyzed 89 patients aged 2 months to 12 years with BM, selected from April 1990 to March 1992 in a pediatric hospital in Pakistan[26]. Children with kidney or liver disease, diseases of the central nervous system (epilepsy, hydrocephaly, previous history of meningitis, hearing loss, mental impairment) or a history of trauma were excluded. The diagnosis of BM was defined as positive CSF bacterioscopy, latex agglutination test positive in CSF or presence of two biochemical and cytological CSF abnormalities (>1000 polymorphonuclear; proteinorrhachia >1g/L, glycorrhachia <50% of glucose). Double blinding was performed with drug and placebo of identical appearance, coded for groups. Randomization was performed with computerized list and divided patients into two groups. 10 to 15 minutes before the first dose of antibiotics the groups were given either IV dexamethasone (0.6mg/kg/day in four doses) (n=48) or IV placebo (same volume as dexamethasone) (n=41), for four days. All patients received ampicillin (300mg/kg/day in 4 doses) and chloramphenicol (100mg/kg/day in 4 doses) for at least 10 days, switching to cefotaxime (200mg/kg/day in 4 doses) in the case of a microorganism resistant to the first two drugs. Outcomes analyzed included mortality and the incidence of neurological and hearing sequelae one year after discharge. There was no statistical difference between groups for any of the outcomes considered.

Discussion

Regarding the outcomes studied (mortality, neurological damage and hearing loss), none of the clinical trials presented benefits of the use of adjuvant therapy with dexamethasone in pediatric patients with bacterial meningitis. The studies analyzed were of high quality, all of them with a of Jadad *et al* score equal to 5, which characterizes an adequately randomized study, with effective double-blinding and description of losses to follow-up, making the results significant from a methodological point of view[22]. The total number of patients included in the study was 1399, of whom 531 received only dexamethasone and 510 only placebo. All patients received antibiotic therapy, albeit with some differences in medications, and follow-up losses were less than 20% in all studies analyzed. Thus, there is insufficient evidence in the literature to indicate routine use of dexamethasone as adjuvant therapy in BM. Its use seems to only have been justified in some older clinical trials and observational studies[14,15,27,28].

The first clinical trials by Lebel *et al*[14] and Odio *et al*[15], respectively published in 1988 and 1991, included a total of 301 pediatric patients and demonstrated benefits of 12% reduction in hearing loss in the study by Lebel *et al* and 24% reduction in auditory and neurological sequelae in Odio *et al*. The studies compared the use of dexamethasone to placebo and the aforementioned reductions would justify the use of dexamethasone as adjuvant BM therapy for children. However, in these studies, there was no difference in mortality between groups and the percentage of meningitis caused by *Haemophilus influenzae* type b (Hib) was greater than 80% in both.

Yet another clinical trial, conducted in 1995 and involving 173 children aged from eight weeks to 12 years, showed no differences between dexamethasone and placebo for neurologic, hearing and developmental sequelae[29]. In this study, only 60% of meningitis cases were caused by Hib.

As for observational studies, a Brazilian retrospective analysis of medical records of 179 children between 6 months and 5 years with BM, treated in 1991 and 1992, showed a 14% reduction in mortality and the incidence of neurological and hearing sequelae with the use of dexamethasone as adjuvant therapy[27]. When considering only cases of Hib meningitis, sequelae reduction increased to over 20%. Another retrospective study of 180 children with pneumococcal meningitis treated from 1993 to 1996 in the United States showed no benefit from the use of dexamethasone[30].

One explanation for the lack of positive results in more recent clinical trials might be an epidemiological shift that occurred in recent years. The high incidence of meningitis caused by *Haemophilus influenzae* type b, a virulent germ with a high rate of complications, was reduced sharply after several years of large-scale vaccination. Its incidence decreased by 55% in the U.S. only[31]. The studies discussed above corroborate the hypothesis of this epidemiological shift by demonstrating benefits of dexamethasone in those patient populations with a high percentage of Hib meningitis and the absence of protective effects in pneumococcal meningitis. Besides the Hib vaccine, the introduction of the pneumococcal conjugate vaccine in the 2000s was responsible for an

almost 60% decrease of cases of pneumococcal meningitis in children under 18 years, from 1998 to 2005, in a U.S. epidemiological study[32]. Therefore, it is plausible that the major contribution of prevention strategies has minimized the effectiveness of adjuvant dexamethasone and that it has lost its role in the current epidemiological context of BM in the pediatric population.

None of the studies considered in this review has shown, however, any increase in neurological and/or hearing complications or mortality with the use of dexamethasone. Only the study by Peltola *et al*[23] demonstrated increased risks of gastrointestinal bleeding, but without influencing the outcomes considered. Thus, one cannot advocate dexamethasone as adjuvant therapy for BM in children due to lack of evidence for its use. There is no sufficient data, however, to contraindicate it. An emphasis on prevention strategies and early diagnosis and referral, as well as new studies, seems to be more important in the current reality.

This review included only four studies. Of those, the one by Sankar *et al*[24] had a very small sample, without an adequate sample power, which could limit comparisons using this study and make its results not really significant. The populations of the different studies were quite heterogeneous, one from Latin America, two from Asia and one from Africa, thus limiting the extrapolation of results. Regarding the study of Molyneux *et al*[25], the high prevalence of HIV infection (approximately 26%), although similar between the two groups, dexamethasone and placebo, could act as a confounding factor. In a subgroup analysis published separately from their own study, Molyneux *et al*[33] demonstrated that mortality was higher in BM patients with HIV seropositivity ($p<0.00001$), although HIV status did not make a significant difference in the incidence of neurological sequelae. It is noteworthy that the effectiveness of dexamethasone in HIV patients was not a primary outcome for the study and, therefore, the value of this data is limited. Other studies assessed did not include data on HIV seropositivity, although, in the studies by Peltola *et al*[23] and Sankar *et al*[24], patients with known immunosuppression were excluded.

In applying these results, it should be emphasized that only four randomized clinical trials were found after a careful review of the literature of the past 15 years. Therefore, there is still a need for well-designed clinical trials, randomized, double-blind, preferably multicenter, with samples of adequate size, with little or no loss to follow-up and standardized methods of measurement and outcome analysis to properly assess the use of adjuvant dexamethasone for BM in children in the current epidemiological context.

The low number of studies found could be explained by the large decrease in the incidence of bacterial meningitis[32], especially in developed countries, reducing its epidemiological importance. This low incidence could also explain the existence of several studies with small samples and containing adults and children in the same group. Low risks and the absence of evidence to contraindicate the use of dexamethasone also certainly help to reduce the number of clinical studies on the drug.

The development of new strategies to reduce BM mortality and sequelae in children is of major importance since the costs of long-term morbidity greatly outweigh the costs of diagnosing and treating this pathology[34]. In the study by Peltola *et al*[23], glycerol groups showed severe neurological sequelae reduction compared to placebo and dexamethasone. This finding is relevant for future research on the role of this agent for BM in children, even if, after adjusting for the etiology of confirmed cases, the benefit of glycerol lost statistical significance.

Results show that the evidence found in the literature are insufficient to indicate, on a routine basis, the use of dexamethasone as adjuvant therapy to reduce mortality, hearing loss and neurological sequelae in pediatric patients with non-tuberculous meningitis. An emphasis on prevention strategies and early diagnosis and referral, as well as new studies, seems to be more important in the current epidemiological context.

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