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Original article

Betamethasone and dexamethasone in adult community-acquired bacterial meningitis: a quality registry study from 1995 to 2014

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ABSTRACT

Acute bacterial meningitis (ABM) is a highly lethal disease. Available data support the use of corticosteroids in high-income countries, but the effect on mortality is still controversial. The effects of corticosteroids on mortality and sequelae were evaluated in the national Swedish quality registry. In total, during 1995–2014 1746 adults with ABM were included, of whom 989 were treated with corticosteroids (betamethasone, $n = 766$; dexamethasone, $n = 248$; methylprednisolone, $n = 2$), 498 were not given corticosteroids and in 259 patients data for corticosteroids were missing. Fatal outcome was observed in 8.9% of the patients in the corticosteroid-treated group vs. 17.9% in the non-corticosteroid-treated group (p <0.001), resulting in an odds ratio (OR) of 0.57 with a 95% confidence interval (CI) of 0.40–0.81 adjusted for age, sex, mental status, and door-to-antibiotic time. In patients with meningitis caused by *S. pneumoniae*, mortality was 10.2% in the corticosteroid-treated group and 21.3% in the non-corticosteroid-treated group (p <0.001) with an adjusted OR of 0.50 (95% CI 0.31–0.80). In ABM patients with non-pneumococcal aetiology the adjusted OR was 0.71 (95% CI 0.40–1.26). Lower mortality was observed in the corticosteroid-treated group with impaired mental status, whereas no significant difference was found in patients with unaffected mental status. The adjusted ORs for betamethasone and dexamethasone were 0.49 (95% CI 0.28–0.84) and 0.61 (95% CI 0.37–1.01), respectively. Corticosteroid treatment decreases mortality in ABM and should be administered initially with antibiotics in adult ABM patients with impaired mental status regardless of presumed aetiology. Betamethasone seems to be at least as effective as dexamethasone. **M. Glimåker, CMI 2016;22:814.e1–814.e7**

Introduction

Acute bacterial meningitis (ABM) is a life-threatening disease [1,2] in which early diagnosis and timely and effective antimicrobial therapy are the major determinants for outcome [3,4]. Adjunctive therapy with corticosteroids has been supported by animal studies showing reduced inflammation in the central nervous system (CNS) by dexamethasone [5]. On the other hand, there are experimental data showing that corticosteroids may potentiate ischemic injury to neurons and reduce meningeal permeability that could hamper the diffusion of antibiotics into the cerebrospinal fluid (CSF) [6,7].

Clinical benefit of adjunctive corticosteroid treatment has been established for meningitis in children caused by *H. influenzae*, with reduced risk of hearing deficits [8]. In a large European placebo-controlled multicentre trial of adults with ABM, administration of dexamethasone reduced the risk of death and adverse outcomes [9]. The beneficial effect of dexamethasone was most pronounced in pneumococcal meningitis with reduced mortality from 34% to 14%. There are, however, other controlled trials, mostly from low-income countries, that have not been able to confirm the efficacy of adjuvant corticosteroids [10–13]. Several important factors such as general health status, HIV-prevalence, disease severity, standards of diagnostics, and general care differ between high- and low-income countries, making comparisons difficult of results of ABM trials from different parts of the world.

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A recent meta-analysis of 25 trials investigating the effects of corticosteroids in ABM found that corticosteroids reduced hearing loss, irrespective of causative bacteria, and reduced mortality in pneumococcal meningitis, without increasing severe adverse events [14]. There was no benefit of corticosteroid therapy in low-income countries. The investigators concluded that the present evidence merits the use of corticosteroids in adults and children in high-income countries, although the strength of the evidence was suboptimal [15,16].

A sufficiently large randomized study to definitively answer the question of whether corticosteroids have a place in the treatment of ABM is unlikely to be performed in the foreseeable future [17]. A recent study indicates beneficial effects of dexamethasone [1], but there is still a need for implementing studies. The first Swedish national guidelines for the management of bacterial CNS infections were published in 2004 by the Swedish Association of Infectious Diseases, recommending adjuvant treatment with dexamethasone to be initiated before or together with the first dose of antibiotics, and continued for 2–4 days in all adults with ABM. Because, traditionally, betamethasone was used in most cases of brain oedema of non-ABM aetiology and dexamethasone has not been licensed in Sweden since 2002, betamethasone was recommended if dexamethasone was not available. Betamethasone is structurally very similar to dexamethasone, differing only by the configuration of a methyl group in position 16 [18]. The two substances have a high CNS penetration and similar anti-inflammatory potency [19]. Dexamethasone was available in some clinics until 2007 despite not licensed in Sweden since 2002. Thus, the two corticosteroids were used in parallel until 2007, but since then, dexamethasone has not been available in Sweden and therefore betamethasone has become the sole adjuvant corticosteroid for the treatment of ABM.

The primary aim of this retrospective quality registry study was to investigate the effects of adjuvant corticosteroids on mortality in adult ABM. Secondary aims were to evaluate the effects on hearing impairment and neurological deficits at follow-up and to compare outcomes depending on whether dexamethasone or betamethasone was used.

Materials and methods

The study comprised adult ABM patients (age ≥16 years) who were registered in the national Swedish quality registry for ABM during the period January 1995 to December 2014. Using conventional diagnostic criteria, ABM diagnoses were set by local specialists in infectious diseases at each of the 32 Swedish infectious disease clinics. The diagnoses were based on clinical criteria, CSF analysis, and microbiological tests on blood and CSF as previously described [3]. ABM was defined as community-acquired if the patients had not been hospitalized or had operations on the CNS within 30 days before admission.

In the registry, sex, age, aetiology, mental status on admission, corticosteroid and antibiotic treatment, door-to-antibiotic time, in-hospital mortality, neurological sequelae, and hearing deficits are routinely recorded. Mental status on admission was recorded in 956 patients, as the reaction level scale (RLS) [20] in 895 patients and as the Glasgow coma scale (GCS) in an additional 61 patients (Table 1). In the latter GCS was converted to RLS for standardized comparison [21]. Adequate antibiotic treatment was defined as intravenous β-lactam antibiotics for which the isolated bacteria were sensitive according to susceptibility testing at local laboratories and administered in meningitis dosages. In patients with unknown aetiology third-generation cephalosporin ± ampicillin or meropenem was considered adequate. Neurological and hearing deficits were registered at the follow-up 2–6 months after discharge. Neurological sequelae were specified as disabling headache, cognitive dysfunction/dementia, vertigo, or fatigue causing limitations of daily activity, epileptic seizures, ataxia, or persistent neurological deficits. Hearing disability was defined by the patient as new onset of impairment, and audiometry was performed when appropriate.

Adequate corticosteroid treatment was defined as dexamethasone 10 mg or betamethasone 8 mg every 6 hours intravenously, initiated within 1 hour from the start of antibiotics. Two patients who were given high doses (≥1 g) of methylprednisolone were also considered adequately treated with corticosteroids. The duration of corticosteroid treatment was not noted in the registry but the

Table 1
Characteristics of patients during the different study periods by groups with different corticosteroid treatment

	Beta-methasone; 1995–2007 (n = 278)	Dexa-methasone; 1995–2007 (n = 243)	Corticosteroid treatment[a]; 1995–2014 (n = 989)	No corticosteroid treatment; 1995–2014 (n = 498)	No data for corticosteroid treatment; 1995–2014 (n = 259)
Median age (interquartile range)	58 (42–68)	59 (43–71)	58 (42–68)	65 (51–75)	59 (39–70)
Males/females[b]	147/131	113/128	486/501	236/259	84/76
RLS on admission; number with available data	110	40	611	232	113
RLS 1 (%)	29 (26.4)	5 (12.5)	211 (34.6)	103 (44.4)	36 (31.9)
RLS 2–3 (%)	53 (48.2)	25 (62.5)	290 (47.5)	101 (43.6)	48 (42.5)
RLS 4–8 (%)	28 (25.5)	10 (25.0)	110 (18.0)	28 (12.1)	29 (25.7)
Time from admission to start of antibiotics; number with available data	244	206	856	394	182
≤1 hour (%)	88 (36.1)	61 (29.6)	324 (37.9)	75 (19.0)	53 (29.1)
>1 hour (%)	156 (63.9)	145 (70.4)	532 (62.1)	319 (81.0)	129 (70.9)
Aetiology					
S. pneumoniae (%)	163 (58.6)	141 (58.0)	547 (55.3)	221 (44.4)	125 (48.3)
N. meningitidis (%)	31 (11.2)	28 (11.5)	118 (11.9)	46 (9.2)	34 (13.1)
Other/unknown bacteria[c] (%)	84 (30.2)	74 (30.5)	324 (32.8)	231 (46.4)	100 (38.6)

RLS = reaction level scale. The RLS is as follows: 1, mentally alert; 2, drowsy or confused, responsive to light stimulation; 3, very drowsy or confused, responsive to strong stimulation; 4, unconscious, localizes but does not ward off pain; 5, unconscious, withdrawing movements on pain; 6, unconscious, stereotype flexion on pain; 7, unconscious, stereotype extension on pain; 8, unconscious, no response [20]. Conversion of Glasgow coma scale (GCS) to RLS is as follows: GCS 14–15 = RLS 1, GCS 12–13 = RLS 2, GCS 10–11 = RLS 3, GCS 8–9 = RLS 4, GCS 6 = RLS 5, GCS 5 = RLS 6, GCS 4 = RLS 7, and GCS 3 = RLS 8 [21].

[a] Treatment with betamethasone (n = 744), dexamethasone (n = 243), or methylprednisolone (n = 2).

[b] The sex of the patient was not noted in 104 patients (two with dexamethasone treatment, three without corticosteroids, and 99 with no data for corticosteroids).

[c] Streptococci (n = 115), *H. influenzae* (n = 98), *L. monocytogenes* (n = 77), *S. aureus* (n = 75), *Enterobacteriacae* (n = 33), other bacteria (n = 33), and unknown (n = 224).