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SHORT REPORT

Sex-based differences in the response to dexamethasone in bacterial meningitis: Analysis of the European dexamethasone in adulthood bacterial meningitis study

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Inflammatory markers have been found at higher concentrations in women than men with bacterial meningitis. To investigate sex-based differences in the response to dexamethasone, we performed a *post hoc* analysis of a double-blind, randomised multicentre trial of dexamethasone (10 mg, 4 times daily for 4 days) *vs* placebo in adults with bacterial meningitis. The primary outcome measure was the Glasgow outcome scale score at 8 weeks and interaction tests were used to examine subgroup differences. Between June 1993 and December 2001, 301 patients (56% male) were randomly assigned to a treatment group: 157 received dexamethasone and 144 placebo. Although dexamethasone reduced the risk of unfavourable outcome to a greater extent in women (relative risk [RR] 0.42, 95% confidence interval [CI] 0.21–0.86, P = .02) than men (RR 0.79, 95% CI 0.41–1.51, P = .55), on interaction testing (ratio of RR women:men 0.53, 95% CI 0.20–1.39, P = .19) patient sex was not a significant modifier of the effect of dexamethasone.

KEYWORDS
corticosteroids, infectious diseases, inflammation, neurology

1 | INTRODUCTION

Bacterial meningitis is a serious and life-threatening disease, and, despite advances in prevention and treatment,[1] it remains a cause of substantial morbidity and mortality worldwide.[2] Experimental models have demonstrated that outcome in bacterial meningitis is related to the severity of subarachnoid inflammation, which is improved by administration of corticosteroids, particularly dexamethasone.[3-5] Since the publication of a large multicentre European randomised controlled trial which showed treatment with corticosteroids improves outcome in adults with community-acquired bacterial meningitis,[6] dexamethasone has become an established adjunctive treatment, with several meta-analyses and implementation studies supporting its use in high-income countries.[7-9]

Patient sex influences a wide range of biological processes, including immune responses, which contribute to differences in the prevalence and pathogenesis of infectious, inflammatory and

The authors confirm that the Principal Investigator for this paper is Prof. Diederik van de Beek and that he had direct clinical responsibility for patients.

autoimmune diseases.[10-13] In a nationwide prospective cohort study investigating sex-based differences in community-acquired bacterial meningitis, male sex was found to be independently associated with a poor prognosis, despite the fact that women had a more severe illness on admission.[14] Women in this cohort exhibited higher serum inflammatory markers and appeared to have superior benefit from treatment with corticosteroids, although no significant interaction between sex and dexamethasone was found. However, since the study took place following widespread implementation of dexamethasone use in the Netherlands, only a small portion of patients were untreated. In addition, as this was an observational study, treatment effects must be carefully interpreted.

We therefore analysed sex-based differences in outcome and treatment effect of adjunctive dexamethasone therapy using data from the European Dexamethasone in Adulthood Bacterial Meningitis trial.[6]

What is already known about this subject

- Outcome in bacterial meningitis is associated with subarachnoid inflammation, which is improved by treatment with corticosteroids.
- Dexamethasone is a proven adjunctive therapy for adults with community-acquired bacterial meningitis.
- Higher inflammatory markers have been found in female than in male patients with bacterial meningitis.

What this study adds

- Risk reduction with dexamethasone therapy appears to be more pronounced in women, but formal testing did not demonstrate a significant modification of the effect of dexamethasone by patient sex.
- Future drug trials should ideally be powered to detect anticipated interactions between patient sex and treatment.

2 | METHODS

We performed a *post hoc* analysis of a prospective, randomised, double-blind, multicentre trial in Europe, the enrolment for which took place between June 1993 and December 2001. Details of the study design, procedures, treatment, outcome assessment and statistical analysis, as well as the full list of participating centres and investigators can be found elsewhere.[6] In brief, patients were eligible for the study if they were aged 17 years or older, had suspected meningitis in combination with cloudy cerebrospinal fluid (CSF), presence of bacteria in CSF Gram staining, or a CSF leucocyte count >10^9/L. Exclusion criteria were as follows: a history of hypersensitivity to β-lactams or corticosteroids; pregnancy; presence of a cerebrospinal shunt; treatment with oral or parenteral antibiotics in the preceding 48 h; a history of active tuberculosis or fungal infection; a recent history of head trauma, neurosurgery, or peptic ulcer disease; and enrolment in another trial at the time of the study. The study was conducted in accordance to the principles contained in the Declaration of Helsinki and was approved by the Medical Ethics Committee of the Academic Medical Centre, Amsterdam, The Netherlands, and by the institutional review board of each participating hospital.[6] All patients or their legally authorised representatives gave written informed consent prior to enrolment.

Patients were randomly assigned to receive either dexamethasone (10 mg every 6 h intravenously for 4 days, before or with the first dose of antibiotics) or placebo. Investigators were blinded to treatment assignments, which were concealed except in the event of an emergency. Patients were initially treated with amoxicillin (2 g given intravenously every 4 h) for 7–10 days. Routine blood and CSF studies and cultures were performed prior to antibiotic treatment and initial regimen was maintained or changed according to aetiology and clinical response. The protocol was later amended to allow investigators to follow local guidelines for administering empirical antibiotic therapy. The primary outcome measure was the score on the Glasgow outcome scale at 8 weeks, with a score of 5 indicating a favourable outcome and score of 1–4 indicating an unfavourable outcome.[15]

Analysis of outcomes was performed on an intention-to-treat basis with the use of a last observation-carried-forward procedure. Continuous variables are expressed as median (interquartile range) and were compared using the Mann–Whitney *U* test; the Fisher exact test was used to study categorical variables. Severity of illness was calculated based on available clinical and laboratory data using the Dutch meningitis risk score.[16] Treatment effect is expressed as relative risk (RR) for treated *vs* untreated patients (with an RR < 1.0 indicating a beneficial effect). Forest plots were used to display treatment effects across subgroups and were created using Review Manager (RevMan), version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). A test for interaction, as described by Altman and Bland,[17] was performed to determine whether effect sizes differed significantly between men and women, and adjustment for potentially confounding variables was performed using logistic regression analysis.

All statistical tests were 2-tailed, and analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (Armonk, NY: IBM Corp.), with a *P*-value <.05 considered statistically significant.

2.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.[18]

TABLE 1 Baseline characteristics and clinical and laboratory admission findings of the study population (n = 301)

Characteristic [a]	Men (n = 169)	Women (n = 132)
Age (y), median (IQR)	42 (26–61)	48 (32–63)
Duration of symptoms before admission (h), median (IQR)	24 (12–55)	24 (12–48)
Range	1–336	1–168
Seizures prior to admission, No. (%)	15 (9)	7 (5)
Findings on admission		
Score on the Glasgow coma scale (median, IQR)[b]	12 (9–14)	12 (9–14)
Coma (defined as a score under 8), n (%)	31 (18)	17 (13)
Papilledema, n/n evaluated (%)	4/91 (4)	11/84 (13)
Cranial nerve palsy, n/n evaluated (%)	19/121 (16)	13/96 (14)
Hemiparesis, n/n evaluated (%)	9/166 (5)	13/128 (10)
CSF white cell count (/mm^3), median (IQR)[c]	4533 (1500–11 098)	3333 (1377–9949)
CSF opening pressure (cmH_2O), median (IQR)[c]	38 (28–50)	30 (24–50)
Dutch meningitis risk score, median (IQR)[d]	16 (6–26)	15 (9–26)
CSF culture, n (%)[e]		
Streptococcus pneumoniae	57 (34)	51 (39)
Neisseria meningitidis	54 (32)	43 (33)
Other bacteria	18 (11)	11 (8)
Negative	38 (23)	27 (20)
Positive blood culture, n/n evaluated (%)	73/148 (49)	59/116 (51)

CSF = cerebrospinal fluid; IQR = interquartile range

[a]Percentages may not add to 100% due to rounding.

[b]Glasgow coma scale scores range from 3 to 14, with 14 indicating a normal level of consciousness (abnormal flexion was omitted from the scale).

[c]CSF white cell count was evaluated in 167 male and 129 female patients, opening pressure in 84 males and 73 females.

[d]The Dutch meningitis risk score is a validated bedside risk score based on routinely collected data, resulting in a nomogram from which risk for adverse outcome can be predicted; scores can range from 0–65, with associated risk estimates for an unfavourable outcome varying between 3.2 and 96%, respectively.

[e]CSF culture was performed in 167 male and 132 female patients.

3 | RESULTS

In total, 301 patients were included in the trial, 157 (52%) of whom were randomly assigned to receive dexamethasone. There were 89 (57%) male patients in the dexamethasone group and 80 (56%) in the placebo group. Baseline characteristics and clinical and laboratory admission findings of male and female patients included in the study can be found in Table 1. Overall, there were no statistically significant differences between sexes regarding these features. However, within the placebo group, women were older than men (median 52 *vs* 41 years, P = .005). Furthermore, there was a difference in the age of female patients between the 2 treatment groups (median 52 years for women in the placebo *vs* 44 years for women in the dexamethasone group, P = .02).

Classic symptoms and signs of meningitis were present the majority of patients, in similar proportions in both sexes. Neck stiffness was reported in 146 of 160 (91%) males and 121 of 125 (97%) females, and 144 of 169 (85%) men and 101 of 131 (77%) women had fever. Headache was present in 94% of cases in both sexes (142 of 151 males and 106 of 113 females). An altered mental status (defined as a Glasgow coma scale score below 14) was found in 114 (67%) men and 84 (64%) women. Mean Glasgow coma scale score on admission did not differ between sexes or across treatment groups. Fifty percent of men and 45% of women exhibited the classic trial of fever, neck stiffness, and altered mental status.

Lumbar puncture was performed in all patients and CSF cultures were positive in 77% of male and 80% of female cases. *Streptococcus pneumoniae* was the most frequent pathogen in both sexes. Based on the Dutch meningitis risk score,[16] there were no significant differences between sexes regarding severity of illness on admission (median 16 in men *vs* 15 in women, P = .47).

During clinical course, impairment of consciousness was documented in 19 of 80 (24%) men in the placebo group and 9 of 89 (10%) in the dexamethasone group (P = .02), while 17 of 64 (27%) women treated with placebo and 9 of 68 (13%) treated with dexamethasone developed this complication (P = .08). Cardiorespiratory failure was

seen in 14 (18%) and 11 (12%) male patients in the placebo and dexamethasone groups, respectively (P = .39), and in 15 (23%) women treated with placebo and 5 (7%) treated with dexamethasone (P = .01). Ten (12%) male patients treated with placebo and 4 (4%) treated with dexamethasone exhibited seizures (P = .09), whereas in female patients this number was 7 (11%) and 4 (6%), respectively (P = .36).

On 8-week follow-up, the number of patients with an unfavourable outcome was significantly lower in the dexamethasone compared with the placebo group (15 *vs* 25%, RR 0.59; 95% CI 0.37–0.94; P = .03). In subgroup analyses by sex (Figure 1), treatment with corticosteroids decreased the rate of unfavourable outcome from 31 to 13% in females (RR 0.42, 95% CI 0.21–0.86, P = .02) and from 20 to 16% in males (RR 0.79, 95% CI 0.41–1.51, P = .55). However, tests of interaction were not statistically significant (ratio of RR women:men 0.53, 95% CI 0.20–1.39, P = .19), and when comparing the proportion of unfavourable outcome between sexes in each treatment arm separately, we could not find a significant difference in either (P = 0.13 in the placebo and P = .82 in the dexamethasone group).

In pneumococcal meningitis (Figure 2), dexamethasone reduced the rate of unfavourable outcome in women from 56 to 17% (RR 0.30, 95% CI 0.12–0.78, P = .008) and death from 41 to 12% (RR 0.31, 95% CI 0.10–0.97, P = .03), whereas this reduction was less pronounced in men (from 48 to 32% unfavourable outcome, RR 0.68, 95% CI 0.35–1.29, P = .28; and from 22 to 18% fatality rate, RR 0.81, 95% CI 0.28–2.35, P = .32). Nevertheless, there was no statistically significant interaction between sex and dexamethasone (ratio of RR women:men for unfavourable outcome 0.44, 95% CI 0.14–1.38, P = .16; for death 0.55, 95% CI 0.11–2.75). Further analysis splitting female patients intro pre- and postmenopausal age groups did not yield significant results, and interaction terms remained nonsignificant after adjusting for age using logistic regression analysis.

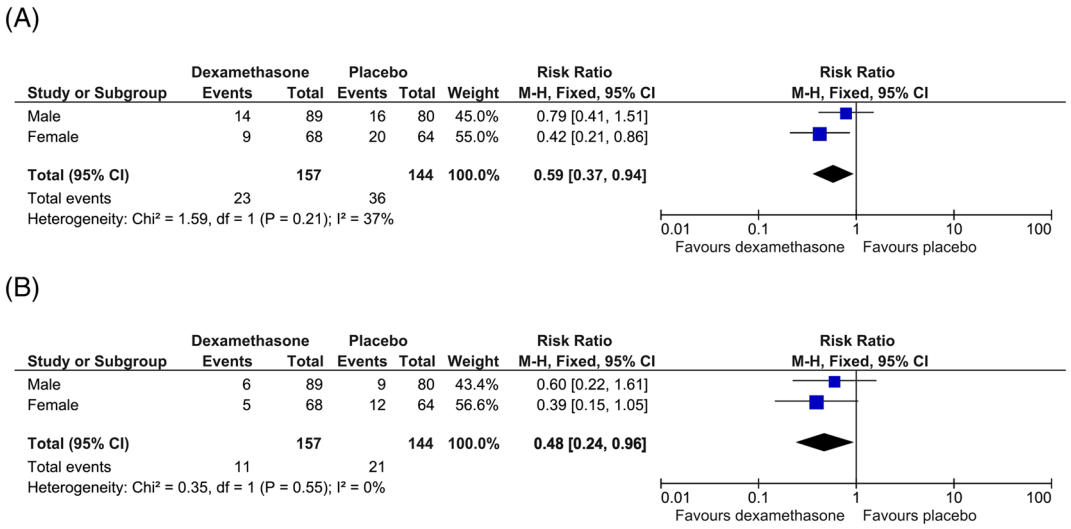

FIGURE 1 Risk of unfavourable outcome (A) and death (B) in male and female patients with bacterial meningitis according to treatment assignment. CI = confidence interval; M-H = Mantel–Haenszel method

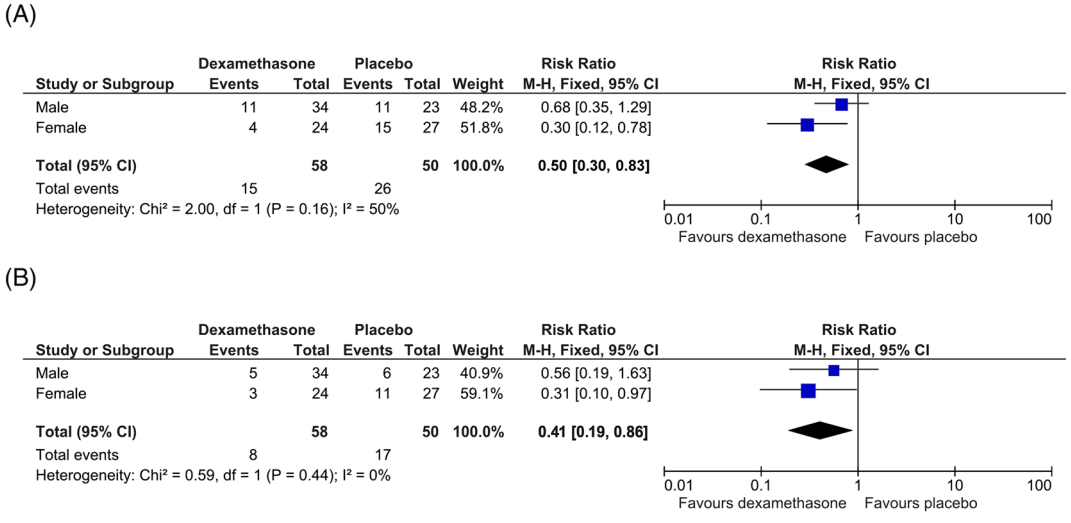

FIGURE 2 Risk of unfavourable outcome (A) and death (B) in male and female patients with pneumococcal meningitis according to treatment assignment. CI = confidence interval; M-H = Mantel–Haenszel method

4 | DISCUSSION

Dexamethasone is currently used as a proven adjunctive treatment for adults with community-acquired bacterial meningitis and should be prescribed without consideration for patient sex.[19,20] Although our analyses suggest a sex-based difference in response to dexamethasone, formal testing did not reveal a statistically significant interaction between patient sex and dexamethasone on the risk of unfavourable outcome or death. This is in line with a meta-analysis of individual patient data from 5 randomised placebo-controlled trials, which included 2029 patients of all ages (58% male) and showed no evidence of heterogeneity between sexes in the effect of dexamethasone on death or neurological sequelae.[9]

Furthermore, unlike a previous study where male sex was independently associated with unfavourable outcome,[14] in this trial, a multivariable logistic regression analysis of baseline variables, as described in the original publication, identified coma on admission, hypotension and pneumococcal meningitis, but not sex, as predictors of poor prognosis. It should be noted, however, that the 2 populations are considerably different, with the younger age and higher proportion of meningococcal cases among patients included in this trial likely to be responsible for a lower severity of illness.

It is widely recognised that females exhibit more robust innate and adaptive immune responses to self and foreign antigens than males,[10,21] which is thought to be due to hormonal, genetic and environmental influences.[10,22] Inflammation appears to be a common underlying feature of many disorders that disproportionally affect women[23] and glucocorticoids are a cornerstone in the treatment of many inflammatory disorders.[24] Men and women can also differ in drug pharmacokinetics and pharmacodynamics,[25] and clinical efficacy of glucocorticoid treatment depends on these parameters.[26-32] Consequently, it is reasonable to expect there could be a sex-related difference in the effect of drug treatment, specifically that a stronger immune reaction might render women more responsive to anti-inflammatory therapies.

The results of our analysis are consistent with previous observational findings,[14] supporting the notion of a sex-based difference in the magnitude of the effect of dexamethasone. Even though a significant effect modification could not be confirmed, this is not surprising; since the trial was powered to determine the overall effect of treatment,[6] subgroup analyses are naturally underpowered, limiting their ability to detect subgroup-treatment interactions. A large multinational randomised controlled trial would be necessary for this purpose,[7] but is unlikely to be performed. It took almost 9 years to complete the European Dexamethasone Trial, and since its publication the incidence of community-acquired bacterial meningitis has gradually declined in Europe and the USA,[2,33-35] such that an even lower inclusion rate would be expected.

By contrast, in the intervening years, the relative contribution of pneumococcal cases to adult bacterial meningitis has increased, and affected patients are older and more likely to be immunocompromised; treatment options, including intensive care medicine, have also improved, as has the overall outcome,[2,33-36] and therefore the possibility that subgroup analyses of older data may not accurately reflect differences between men and women in the current patient population is a potential limitation.

Moreover, *post hoc* analyses must always be carefully interpreted, as they are prone to finding false results. An imbalance of prognostic factors between subgroups, negating the benefit of randomisation, was also a matter of concern, as was the possibility selection bias. To control for selection bias, we compared the baseline characteristics of patients enrolled in this study with data from 345 men and 351 women included in a prospective nationwide cohort of adults with acute bacterial meningitis, collected between 1998 and 2002[37]; there were no significant differences between the 2 studies with respect to the Glasgow coma scale score on admission.

In conclusion, despite an apparently more pronounced risk reduction in women than in men, we did not find the effect of adjunctive dexamethasone treatment to be significantly modified by patient sex. Although these results do not support a change in treatment practices, they provide insight into sex-based differences in the response to anti-inflammatory therapy in bacterial meningitis; in addition, they should influence the design of future drug trials, which should take patient sex into account and, whenever possible, be adequately powered to detect anticipated treatment-subgroup interactions. Further research into the pathogenesis of sex-based differences in inflammatory reaction in bacterial meningitis, including the role of sex steroid hormones, is needed.

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

S.P.D. analysed and interpreted data and wrote the first draft of the manuscript. M.C.B. interpreted data and revised the manuscript for important intellectual content. D.v.d.B. designed the study, interpreted data, revised the manuscript for important intellectual content and is the principal investigator of the study. All authors reviewed and approved the final version of the article.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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