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Trial of dexamethasone treatment for severe bacterial meningitis in adults

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Introduction

Despite antibiotic therapy and intensive care, bacterial meningitis continues to be associated with unacceptably high morbidity and mortality. Neurologic and audiological sequelae has been reported in up to 38% of children with bacterial meningitis, mostly due to *Hemophilus influenzae* [1]. Neurologic sequelae are also frequent in

Abstract *Objective:* To evaluate the clinical benefit of early adjunctive dexamethasone therapy for severe bacterial meningitis in adults. *Design:* Multicenter, double-blind, randomized trial initiated in emergency or intensive care units in France and Switzerland. Within 3 h after initiation of an aminopenicillin therapy, patients received dexamethasone (10 mg q. i. d.) or placebo for 3 days. The primary end-point was the rate of patients cured without any neurologic sequelae on day 30.

Results: Sixty patients were enrolled, predominantly with a severe form since 85% required ICU stay and 43% mechanical ventilation. *Streptococcus pneumoniae* accounted for 31 cases and *Neisseria meningitidis* for 18 cases. The study had to be stopped prematurely because of a new national recommendation of experts to use third generation cephalosporin and vancomycin as a result of the increasing rate of penicillin-resistant *S. pneumoniae* in France. After the third sequential

analysis by the triangular statistical test, the difference of rate of cured patients without any neurologic sequelae was not statistically significant ($p = 0.0711$) between the dexamethasone group (74.2%; $n = 31$) and the placebo group (51.7%; $n = 29$). Furthermore, the former group was younger and less sick at inclusion.

Conclusion: Bacterial meningitis is still a severe disease in adults, since the overall observed rate of death or severe neurologic sequelae was 26.7%. The reported data are inconclusive regarding a systematic use of dexamethasone as an adjunctive therapy for bacterial meningitis in adults. Moreover this treatment impairs antibiotic penetration into the cerebrospinal fluid (CSF) that can lead to therapeutic failure, particularly in areas with high or increasing rates of penicillin-resistant *S. pneumoniae*.

Key words Bacterial meningitis · Adult · Dexamethasone therapy

adults, observed in 17% of cases after pneumococcal meningitis and 6% after *Neisseria meningitidis* meningitis and associated with mortality rates of 19% and 3%, respectively [2], with no significant reduction during the last decades. After reaching the subarachnoid space, bacteria or their components initiate an inflammatory process, of which the main recognized mechanisms are neutrophil and macrophage activation, and local pro-

duction of cytokines, platelet activating factor and toxic oxygen derivatives. Cerebral edema results from cytotoxicity, vasodilatation and increased blood brain barrier permeability and is responsible for neuronal cell dysfunction and destruction [3–5]. In animal models, corticosteroids significantly reduce the level of the inflammatory mediators and many of the pathophysiologic consequences of bacterial meningitis [6].

Since 1988, six well designed randomized clinical trials addressing the potential benefit of the adjunctive role of dexamethasone (Dxm) therapy in bacterial meningitis have been published [1, 7–11]. All but one involved children with *H. influenzae* as a predominant pathogen. Although these trials were not free of any bias, four of them demonstrated a significant reduction of hearing loss and neurologic sequelae [1, 7, 8, 10]. Moreover, in one study including 147 patients over 13 years old, Dxm was associated with an striking reduction in mortality in the subgroup of patients with pneumococcal meningitis [8]. However, the results of these trials must be used cautiously for the therapy of bacterial meningitis of adults, in whom the most commonly responsible organisms are *Streptococcus pneumoniae* and *N. meningitidis*.

The increasing prevalence of penicillin-resistant strains of *S. pneumoniae* in many countries add more complexity to the therapeutic problem. For the highly resistant strains, normal or even high doses of penicillin therapy do not achieve sufficient cerebrospinal fluid concentrations to exceed the minimum bactericidal concentration of these strains. In this setting, an alternative therapeutic approach has been proposed using broad-spectrum cephalosporins and/or vancomycin [12]. Although there has been concern that corticosteroids reduce the permeability of the blood-brain barrier and thus the penetration of antibiotics, the phenomenon was thought to have no clinical significance for susceptible strains of *S. pneumoniae*. However, Dxm has been demonstrated significantly to reduce the penetration and the rate of bactericidal activity of vancomycin in experimental meningitis induced by highly penicillin-resistant strains of *S. pneumoniae* [13].

The objective of the study was to assess the clinical benefit of an early Dxm adjunctive therapy in the management of severe bacterial meningitis in adults. Since a French consensus conference recently stated that an association of third generation cephalosporin and vancomycin should be first considered for the treatment of pneumococcal bacterial meningitis [14], the antibiotic design of this study was no longer regarded as adequate and the study had to be ended prematurely before definite conclusions could be reached.

Materials and methods

Patients selection

Eligible patients were adults 18–79 years of age, admitted to one of the 21 participant emergency departments or intensive care units, with clinical signs of presumed primary bacterial meningitis including fever over 38 °C, cloudy CSF or elevated white blood cell count in CSF with more than 50% polymorphonuclear cells, and in whom the first chosen empiric therapy was an aminopenicillin. Those who had previously received more than one dose of parenteral betalactam antibiotic or any other adequate treatment for more than 3 h, were excluded. Patients with septic shock, acute post-surgical or post-traumatic meningitis, brain abscess, history of hypersensitivity to betalactam antibiotics or to corticosteroids, or organ transplantation were excluded. The protocol was approved by the regional Ethical Committee and informed consent was obtained from patients or close relatives.

Design of the study

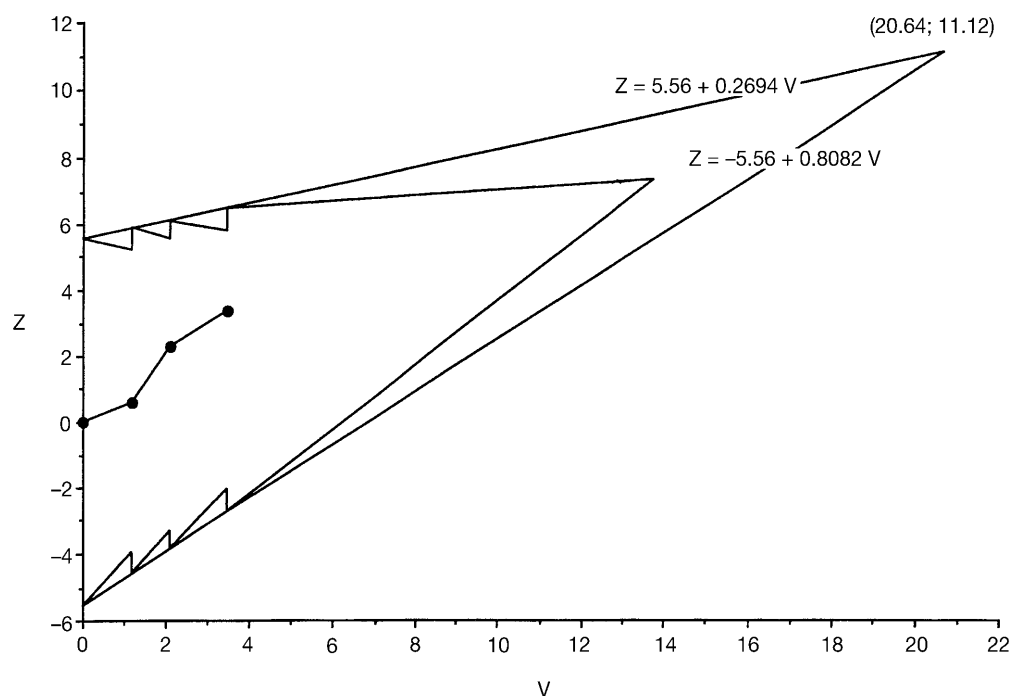
This was a placebo-controlled, randomized and double-blind study performed on two parallel groups which received either Dxm or a placebo for 3 consecutive days. Each therapeutic unit of Dxm was specially conditioned in a 10 mg/25 ml vial. The placebo was normal saline prepared in an identical manner. The patients received one intravenous injection of a therapeutic unit every 6 h during the first 3 days. The first dose was given within 3 h after the initiation of antibiotic therapy. Randomization was stratified and equilibrated by center. After the inclusion of a patient, the 3-day treatment was delivered from the hospital pharmacy. The complete similarity of the therapeutic units, placebo or Dxm, rendered the trial blind for the patients, nurses, pharmacists and physicians. The code was only broken by the methodologist at the end of the follow-up period of successive groups of 20 patients.

The empiric initial antibiotherapy for all the patients was intravenous amoxicillin (150–300 mg/kg per day). Then, the dose was adjusted by the physicians in charge of the patient, according to the bacterium isolated and its resistance profile. The duration of therapy was 10 days for *N. meningitidis* meningitis and 14 days for *S. pneumoniae*.

Follow-up and evaluation

The primary outcome measure was the rate of patients cured without any clinical neurologic sequelae 30 days after initiation of therapy (day 30). For this purpose, patients were clinically evaluated every day during the treatment; clinical examination, mental status by Glasgow coma scale, severity of disease by the Simplified Acute Physiologic Score (SAPS 1) [15], and Mini Mental Test were recorded on days 14 and 30. Each observation was reviewed by an expert committee which commented on the diagnosis and eventual sequelae of the bacterial meningitis, being unaware of the therapeutic allocation. Mild sequelae were defined as sensory deficit (visual disturbances, hearing loss), mild ataxia or memory deficit, associated with headache or not, which did not require prolonged hospitalization in an acute care facility. Severe sequelae were objective motor deficit and / or mental or consciousness changes that still required hospitalization of the patients.

Fig. 1 Sequential analysis of success rate by the triangular test. See the *Statistical Analysis* section in the text for explanation



Sample size calculation

Before the trial, the sample size was calculated according to the hypothesis of a success rate with placebo of 70% and a benefit to be detected with D_{xm} set at 15%. The type I and II error rates were chosen at the values of 0.05 and 0.10, respectively. With these conditions, the required sample size using a single-stage design and a one-sided test would have been 256. Anticipating that recruitment would be difficult, and in order to stop the study as soon as sufficient information had been collected, the study was planned with the triangular test [16].

Statistical analysis

Sequential analysis

Briefly, the triangular test uses a sequential plan defined by two perpendicular axes (Fig. 1). The horizontal axis corresponds to the statistic V , which represents the quantity of information accumulated, and the vertical axis to a second statistic Z , which represents the benefit from the tested treatment. The two straight boundaries of the test delineate a closed continuation region from the regions of non-rejection of the inefficacy hypothesis (below the bottom line) and of rejection of the inefficacy hypothesis (above the top line). The boundaries need to be adjusted at each analysis, thus defining a continuation region with a Christmas tree shape. At each analysis, the two statistics, V and Z , are calculated from all the data collected since the beginning and define a point on the plan. As long as the sample path, defined by consecutive points, stays within the boundaries, the study is continued. When the sample path crosses the boundaries, the study is stopped: crossing the bottom boundary causes the inefficacy hypothesis not to be rejected, while crossing the top boundary causes it to be rejected. After evaluation of each 20 patients, the sequential analyses were performed on the main end-point for efficacy with PEST statistical software (version 3) [17].

Final analysis

A conventional statistical analysis was performed on secondary end-points with the BMDP statistical software [18]. Student t -test was used for the comparison of quantitative variables and Pearson chi-square test or Fisher exact test for the comparison of qualitative variables. Values are expressed either as the mean \pm SD or as frequencies of observed values and corresponding percentages.

Results

Sixty-two adults were included in the trial. Two were excluded from analysis by the expert committee: one was thought to have an acute viral meningitis and received seven injections, the second was operated for a cerebral aneurysm on day 7 and received 11 injections. Thirty-one patients received dexamethasone and 29 received placebo (Table 1). Although the mean age was higher in the placebo group (50 ± 19 vs 40 ± 19 years; $p = 0.051$), the mean previous health status was not different as assessed by Knauss health status score and McCabe score. The overall severity of disease during the first day after admission, measured by SAPS I, was significantly greater in the placebo group (14.3 ± 5.7 vs 10.5 ± 6.4 ; $p = 0.018$). Most of the patients had to be admitted to an intensive care unit (25/29 and 26/31), requiring endotracheal intubation in 15 cases in the placebo group and 11 cases in the Dxm group ($p = 0.205$). The other nine patients (15%) were secondly transferred from the emergency departments to medical wards. On the day of enrollment, the Glasgow coma score was

Table 1 Characteristics (per treatment group) of 60 adult patients with bacterial meningitis

	Placebo group (n = 29)	Dxm group (n = 31)	p
Age (years) ± SD	50 ± 19	40 ± 19	0.051
Males	17 (59)	17 (55)	NS
Previous health status			
Good health (Knaus score)	24 (83)	27 (87)	NS
McCabe score ≥ 1	9 (31)	8 (26)	NS
Epilepsy	1 (3)	3 (10)	NS
Prior neurologic sequelae	0	2 (6)	NS
Causal agents			NS
S. pneumoniae	17 (59)	14 (45)	
N. meningitidis	7 (24)	11 (35)	
Unknown	3 (10)	5 (16)	
Other	2 (7)	1 (3)	
Health status at J1			
Glasgow coma scale	11.2 ± 3.4	12.2 ± 2.4	NS
SAPS I	14.3 ± 5.7	10.5 ± 6.4	0.018

11.2 ± 3.4 in the placebo group and 12.2 ± 2.4 in the treated group.

Streptococcus pneumoniae accounted for 31 cases (52%), *N. meningitidis* for 18 cases, *Streptococcus bovis*, *H. influenzae*, and *Listeria monocytogenes* for one case each. Five of the 27 tested strains of *S. pneumoniae* were of intermediate susceptibility to penicillin (0.1 µg/ml < MIC < 1 µg/ml), two in the Dxm group and three in the placebo group. The two patients in the placebo group whose therapy was switched to cefotaxime and to vancomycin plus rifampicin had severe neurologic sequelae. The patient in the treatment group whose therapy was switched to cefotaxime recovered, the other one had a mild but demonstrated hearing loss on aminopenicillin therapy. The mean delay between the first meningeal symptom and lumbar puncture was similar in the two groups (31 ± 29 vs 32 ± 19 h). The delay from lumbar puncture to the first injection of antibiotic was quite high, but similar in the two groups (placebo: 78 ± 80 min vs Dxm: 66 ± 74 min; *p* = 0.569). The first dose of Dxm was injected 97 ± 78 min after the initiation of antibiotic therapy. All the patients, except two who died before, completed the 3-day regimen of Dxm or placebo and received a mean 11.7 ± 2 doses per patient.

Outcome

Thirty days after inclusion, the physical and neurologic examination of survivors clearly distinguished six patients with mild neurologic sequelae from eight patients with severe sequelae, among whom three died before day 90 (Table 2). On day 30, 38 patients (63%) were cured without any neurologic sequelae. Figure 1 represents the triangular test and corresponding sample path.

Table 2 Outcome per treatment group of 60 bacterial meningitis in adults, 30 days after initiation of therapy

Outcome	Placebo group (n = 29)	Dxm group (n = 31)
Death ≤ day 30	5	3
Severe neurologic sequelae	5	3
Mild neurologic sequelae	4	2
Cured without neurologic sequelae	15 (52)	23 (74)*

* *p* = 0.0711

Table 3 Evolution of severity scores during therapy

	Placebo group (n = 29)	Dxm group (n = 31)	p
Glasgow coma score on:			
Day 1	11.2 ± 3.4	12.2 ± 2.4	NS
Day 2	11.8 ± 4.4	13 ± 3.7	NS
Day 4	12.6 ± 3.4	13.9 ± 2.8	NS
Day 7	13.5 ± 3.6	13.6 ± 3	NS
Day 14	14.0 ± 2.6	14 ± 2.3	NS
SAPS on:			
Day 1	14.3 ± 5.7	10.5 ± 6.4	0.018
Day 2	9.4 ± 6.7	5.7 ± 5.4	0.024
Day 4	7.9 ± 6	5 ± 5.6	NS
Day 7	6 ± 6.8	4.8 ± 6.2	NS
Day 14	4.4 ± 5.5	3.5 ± 5.5	NS

After the third analysis, no conclusion was available. Nevertheless, as stated above, the steering committee decided to stop the trial. Median success rates were estimated to be 52% and 74% for placebo and Dxm, respectively (unbiased estimate taking into account the sequential nature of the analyses). This difference was not significant (*p* = 0.0711). In the Dxm group, three patients died before day 30, on day 23 (*S. pneumoniae*), day 20 (germ not identified) and day 0 (*N. meningitidis*); this last patient died of shock not present at inclusion and received only one dose of steroid. Among the three patients with severe sequelae, one ultimately died on day 50. In the placebo group, five patients died before day 30, respectively on days 1, 2, 5, 6, 12, all after *S. pneumoniae* bacterial meningitis. Two other patients with severe sequelae died on days 39 and 43. There was no other clear-cut or significant difference between the two groups during the antibiotherapy period in the other clinical data, neurologic, mental or severity scores (Table 3).

Adverse effects of therapy

Five adverse effects possibly related to the tested therapy were observed, two in the Dxm group (pain at injection, transient hyperglycemia requiring insulin therapy over 3 days) and three in the placebo group (two gastric ulcers with overt hemorrhage, 1 herpes zoster).

Discussion

As confirmed by many reports, bacterial meningitis in adults, as in children, still has a very poor prognosis, since we found a 37% rate of mortality or overall neurologic sequelae and a 27% rate of mortality or very severe neurologic sequelae globally. The morbidity was also elevated, 85% of the patients had to be admitted to intensive care units and 43% had to be intubated. This emphasizes the actual need for trials to assess the potential clinical benefit of anti-inflammatory adjunctive therapy in this disease. The scarcity of such trials may be explained by difficulties in the realization, more than in the design, of the protocol. For ethical reasons, the protocol was designed not to interfere with the first antibiotic dose. It was accepted that the first injection of Dxm had to be given as long as 3 h after the initiation of antibiotic therapy, since randomization and delivery of treatment might create some additional delay. The mean observed delay was shorter, but longer than the delay mentioned in some pediatric studies [1, 8, 10]. If the major effect of Dxm is to antagonize an increase of cytokine CSF concentrations during the initial antibiotic therapy, as observed in pediatric patients with Gram negative (*H. influenzae*) meningitis [19], this delay may have resulted in a reduction in the corticosteroid efficacy.

Mortality and severe neurologic sequelae are more common in adults and represent more easily measurable end-points than hearing loss in children. However, the lower incidence of the disease in adults necessitates a multicenter study including the participation of the emergency department medical staff, and a prolonged period of inclusion. Over the study period, the protocol must first assume the bacteriologic efficacy of the antibiotic regimen and a relative homogeneity of the treatment. Empiric therapy by an aminopenicillin was an adequate choice at the beginning of the trial, but no longer acceptable by an expert consensus conference in 1996, because of the increasing rate of penicillin-resistant *S. pneumoniae* above 25% in French CSF isolates. Furthermore, the recommended empiric therapeutic option, third generation cephalosporin plus continuous infusion of vancomycin, is not compatible with Dxm therapy, since steroids significantly reduce the penetration of vancomycin into the CSF [13].

The premature end of the trial, and thus the low number of patients included, did not allow definite conclusions to be reached, despite the encouraging results of the sequential analysis. The triangular statistical test is particularly well adapted to this type of trial, since usually fewer patients than originally planned are required to reach statistical significance and the trial is stopped as soon as a conclusion is reached. In this trial, the observed non-significant reduction of mortality and neurologic sequelae rates in the Dxm-treated patients

was limited by the observed differences between the two groups. The Dxm group was significantly younger and less sick than the placebo group of patients. Since SAPS and Glasgow Coma Scale score were estimated by using the worst values observed during the first 24 h after admission and are not true pre-randomization scores, a potential rapid effect of Dxm cannot be discussed. With these limits, the adverse effects of a short 3-day corticosteroid regimen were very low.

Before conclusive trials have been obtained, a 3-day Dxm therapy may only be considered as an early rescue therapy of severe bacterial meningitis in adults [20]. Since *S. pneumoniae* is the predominant pathogen in these severe forms, it must also be reasonably assumed that Dxm would significantly reduce the penetration of antibiotics and could lead to therapeutic failure if the minimum inhibitory concentration of the strain is abnormally high. Decisions regarding the use of early Dxm therapy in the treatment of bacterial meningitis in adults needs careful consideration in areas with high incidences of penicillin-resistant *S. pneumoniae*. The priority is still the complete adequacy of an early anti-infective therapy. As long as more fundamental research has not provided antibiotics whose penetration into the CSF are not impaired by corticosteroids, Dxm therapy and trials will remain an unproved area.

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