

The Benefit of Dexamethasone in the Treatment of Bacterial Meningitis

Clinical Question: Does dexamethasone prevent death or neurological morbidity in adult patients with acute bacterial meningitis?

Article: Dexamethasone in adults with bacterial meningitis. De Gans, et al. *New England Journal of Medicine*. 2002;344:1549-1556.

Study Design: Randomized controlled clinical trial

301 patients with newly diagnosed meningitis by clinical features and at least one of the following: a positive cerebrospinal fluid Gram's stain, cloudy CSF, or more than 1000 leukocytes per cubic ml in the CSF were randomly assigned to an intervention. 144 patients were randomized to the placebo group where they received a sham medication in addition to amoxicillin or another empiric antibiotic. 157 patients were allocated to the dexamethasone group where 10 mg of dexamethasone was administered 15 to 20 minutes prior to or with the first dose of antibiotics and was continued every 6 hours for the next four days.

The primary outcome was based on the score obtained from the Glasgow Outcome Scale measured eight weeks after beginning treatment. A favorable outcome was defined as a score of 5, while an unfavorable outcome was any score between 1 to 4 (please see **Assessment of Outcome** on pg 1550).

Exclusion criteria included: age less than 17 y/o, history of hypersensitivity to *B*-lactam antibiotics or corticosteroids, pregnancy, cerebrospinal shunt, treatment with antibiotics in the last 48 hours, history of active TB or fungal infection, a recent history of peptic ulcer disease, head trauma, or neurosurgery.

1. Are the results of the study valid?

There was randomized assignment of the patients to both the treatment and placebo arm.

It appears that all patients entered into the trial were accounted for at the trial end (please see Figure 1 on page 1551).

Initially there were 157 patients randomized to the dexamethasone group. 11 patients were withdrawn early due to: 3 not meeting inclusion criteria, 4 with adverse events, 2 not being treated for 4 days (however they did receive the assigned study drug on the first day), and 2 more deteriorated and were treated with open label corticosteroid for various reasons. Furthermore 3 patients were lost to follow up at eight weeks (however their last Glasgow Outcome Score was carried forward and used in the final evaluation). And 11 patients died during therapy. In total, 143 patients received the experimental therapy and were followed for the entire 8 weeks. At the time of analysis, all 157 patients were included in an intention-to-treat basis.

In the placebo group, there were 144 patients. 11 patients were also withdrawn early due to: 1 not meeting inclusion criteria, 1 with an adverse event, 2 not being treated for 4 days, 1 withdrew consent, and 6 deteriorated for various reasons requiring steroid therapy. At the end of the trial, 119 patients received therapy and were followed for the entire eight weeks, 21 patients died, and 4 patients were lost to follow up but their final Glasgow Outcome Score was also carried forward. In the end, all 144 patients of the placebo group were used in the final calculations.

It appears that all patients and physicians were blinded with regards to the treatment groups.

At the start of the trial both groups were similar with regards to clinical characteristics and laboratory values, however it is important to note that more patients in the Dexamethasone group had seizures (please see Table 1 on pg 1552).

It is difficult to determine whether the two groups were treated equally. Due to the fact that numerous hospitals were used (in different countries), and there was a variation in their presenting Glasgow Coma

Scales, it is likely that there were some inter and intra-group differences in their therapy (i.e. different antibiotics, levels of care, etc). Also due to a change in protocol some patients received steroids/placebo with antibiotics and some received the experimental therapy before the antibiotics. Also it appears that all patients did not receive the same uniform laboratory analysis (i.e. not all patients received gram staining, culture of CSF, or examination for papilledema, etc.). This fact may have led to an initial selection bias in the patients. Finally, the paper makes no mention of physical/occupational therapy or rehabilitation. A patient's access to these programs may influence their 8 week Glasgow Outcomes Scale.

Follow-up was over 8 weeks which is adequate but not ideal. One could argue that a patient with a severe neurological insult requiring ICU care and an extended hospital stay may not be fully "rehabbed" at the final 8 week evaluation.

2. Assessment of Results: (Please see Table 2 on pg 1553)

301 patients were analyzed with regards to: death, unfavorable outcomes, and neurological sequela. The easiest data to report is the fact that dexamethasone had no effect on neurological deficits including hearing loss at eight weeks (problems with this data analysis include that not all patients received audiometric testing and also if steroids decrease mortality as the paper reports those people surviving may be more likely to have some continued neurological problems).

With regards to unfavorable outcomes the paper reports that the dexamethasone group had significantly less unfavorable outcomes than the placebo group (15 percent vs. 25 percent; relative risk 0.59; 95 percent confidence interval, 0.37 to 0.94; P=0.03). Problems with this data include that: 7 patients were lost to follow-up and their last observation was carried forward. And the paper makes a blanket statement that dexamethasone reduces unfavorable outcomes in all patients with bacterial meningitis. However upon further review this appears relevant only for *Streptococcus pneumoniae* meningitis. This fact will be discussed further with regards to the mortality rate.

The literature reports that the proportion of patients who died was significantly smaller in the dexamethasone group than in the placebo group (7 percent vs. 15 percent; relative risk, 0.48; 95 percent confidence interval, 0.24 to 0.96; P=0.04). When reviewing the data this seems true only for *Streptococcus pneumoniae* meningitis, with regards to the other bacteria including *N. meningitides* (which made up approximately 30% of the sample size) it appears that dexamethasone had no effect on mortality.

	Steroid Group (# Deaths/Total Patients)	Placebo Group (# Deaths/Total Patients)
All Cases	11 / 157	21 / 144
<i>S. pneumoniae</i>	8 / 58	17 / 50
Cases Excluding <i>S. pneumoniae</i>	3 / 99	4 / 94

(For *S. pneumoniae*) ARR= 21% NNT=4.8 RRR=62

3. Will the results help me in my patient care?

Overall this trial seems fairly well done. It appears that these results can be applied to our population base but one should keep in mind that the population was slightly biased towards males of Northern European descent. Clinically relevant outcomes were measured appropriately including: mortality, complications, neurological deficits and "unfavorable outcomes". However one must realize that even though a score of 1 to 4 on the Glasgow Outcome Scale gave the patient an unfavorable outcome, it is important to realize that there is a large clinical difference between a permanent vegetative state (score=2) and a disability preventing a person from returning to work but still capable of living on their own (score=4). Also there appears to be no difference between the complications rate in the two groups with regards to gastrointestinal bleed, hyperglycemia, herpes zoster, and fungal infection. However, I feel the results may be overly generalized to all patients with bacterial meningitis when it appears the beneficial effect is more prominent in people with pneumococcal meningitis. Perhaps steroids should be reserved only for patients with Gram positive diplococci in the CSF or perhaps steroids should be initially given to everyone and then stopped if pneumococcus is not found. Further studies will be required to investigate this.