Does Dexamethasone reduce mortality or neurologic sequelae in bacterial meingitis?

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Introduction

- Bacterial meningitis(acute purulent infection within the subarachnoid space)
- Annual incidence in the U S A >2.5/lac population.
- Presentation :

  Classic Triad:

  - Fever
  - Headache
  - Nuchal rigidity
  - Nausea,vomiting & photophobia are also common .

- **Common organisms responsible:**
  - *Streptococcus pneumonae(~50%)*
  - *N.meningitides (~25%)*
  - *Group B Streptococci (~15%)*
  - *Listeria Monocytogenes (~10%)*
  - *H. influenzae (<10%).*

Complications :

- **Systemic:**
  - Septic shock
  - DIC
  - ARDS
  - Maculopapular rash & meningococcaemia.
- **Neurologic:**
  - Impaired mental status
  - Increased ICP & cerebral oedema
  - Seizures
  - Focal neurologic deficits (eg: cranial nerve palsy,hemiparesis)
  - Cerebro vascular abnormalities
  - Sensorineural hearing loss
  - Intellectual impairment.

Proposed mechnism of action of dexamethasone

- Bactericidal antibiotics leads to lysis of bacte rial cell wall components

Liberation of endotoxin,teichoic acid

Stimulates microglia & macrophage

IL-1,TNF-alpha in subarachnoid space

Ultimately leads to vasogenic,cytotoxic & interstitial oedema

Increased ICP

Coma

Dexamethasone inhibits synthesis of IL-1,TNF
Reduces CSF outflow resistance
Stabilizes blood brain barirer

CLINICAL TRIALS

- **In developed regions:**
  - Carried out by Jan De Gans PhD el
  - Prospective, randomized,double blind trial in 301 patients from Europe.
  - **Inclusion criteria :**
    - Suspected meningitis with one or more of the CSF analysis:
    - Cloudy fluid
    - Positive gram stain for bacteria
    - CSF WBC count >1000/ml

Continued…

- **Exclusion Criteria:**
  - Cerebrospinal shunts
  - Antibiotics in past 48 hours
  - Hypersensitivity to beta lactum antibiotics or corticosteroids
  - H/O active TB or fungal infection, head trauma , neurosurgery,PUD

OUTCOME MEASURES

- **Primary Outcome:**
  - All unfovourable outcome (GCS score-5=favourable, 1-4= unfavourable outcome).

- **Secondary endpoints:**
  - Hearing loss
  - Death
  - GIT bleeding
  - Fungal infection
  - Herpes zoster
  - Hyperglycaemia.

Result

- **Follow up:**
  - **at 8 weeks:**
    - All unfavourable outcomes (15% vs 25%,RR 0.59,95% CI 0.37–0.94,p=0.03)
    - Significantly reduced mortality (7% vs 15% with placebo,RR 0.48,95% CI 0.24–0.96,p=0.04)
    - In pneumococcal meningitis significant reduction in
      - Mortality(14% vs 34%)
      - All unfavourable outcomes(26% vs 52%,RR 0.48,95% CI 0.3–0.83,p=0.006)
    - Other types of bacterial meningitis had much lower rate of mortality or all unfavourable outcomes independent of dexamethasone therapy.

- **Follow up :**
  - **At 8 years**:
    - Long term effects of dexamethasone on neurologic sequelae in 87 of 99 eligible patients showed:
      - No difference between the treatments groups with regard to:
        - Persistent cognitive dysfunction
        - Hearing loss
        - Focal neurologic deficit.

In devloping regions:

- **Malawi trial:**
  - RCT in 465 patients received dexamethasone or placebo for 4 days plus I/v ceftriaxone .
  - **Follow up** :
    - At 40 days:
      - No significant mortality difference in dexamethasone vs placebo group
      - In all bacterial meningitis cases(56% vs 53%,OR 1.14,95% CI 1.79-1.64)
      - In pneumococcal meningitis(53% vs 50%,OR 1.10, 95% CI 0.68-1.77).
    - Long term follow up:
      - No significant outcome of disability,hearing loss or adverse events.

Vietnamese Trial

- Prospective, double blind trial of 300 patients with confirmed meningitis showed:
  - Significant reduction in:
    - mortality at 1 month(RR 0.43,95% CI 0.2-0.94)
    - Risk of death/disability at 6 month (OR 0.56,95% CI 0.32-0.98).

Meta-Analysis:

Design: 5 RCTpublished after 2001.

Setting: 2 RCT in Malawi;1 RCT in Europe;1 RCT in South-America;1 RCT in Vietnam

Patients: 2447 Patients with clinically suspected bacterial meningitis meeting CSF criteria.

Intervention: Dexamethasone(n=1019) 0.15mg/kg,4 times daily for 2 days or 10 mg 4 times daily for 4 days; or placebo(n=1010)

Follow-up: At hospital discharge,1 month,8 weeks.

Outcome: Death or severe neurologic sequelae(severe bilateral hearing loss).

Result

Dexamethasone vs placebo in bacterial meningitis

Outcomes	number of trials(n)	Dexamethasone	Placebo	At first follow-up	
				RRR(95%CI)	NNT(CI)
Death	5(2029)	26%	27%	2%(-13to16)	NS
Death,any neurologic sequelae, or any hearing loss	5(1987)	54%	57%	5%(-3to13)	NS
				At 1 mo	
Death,severe neurologic sequelae,or severe bilateral hearing loss	5(1995)	42%	44%	5%(-6to15)	NS

Summary & Recommendation :

- The efficacy of dexamethasone therapy in patients with bacterial meningitis varies between developed & developing countries & with offending organism.

- **Developed regions**:
  - Recmmended in all adults with known or suspected pneumococcal meningitis regardless of GCS score.
  - No proven benefit in patients with other bacterial meningitis(eg: meningococcus),so not recommended in such cases.
  - Recmmended dose: 0.15mg/kg every 6 hrly for 4 days
  - Should be initiated 15-20 mins before or at the same time of the 1st dose of antibiotics.

Developing Regions:

- Benefit of dexamethasone is less clear than for developed countries.

- **In high HIV prevalent regions:**
  - No apparent clinical benefit,not recommended.

- **In low HIV prevalent regions:**
  - Recommended in patients with strongly suspected or bacteriologically proven acute meningitis provided HIV infection is unlikely.
  - Recommended dose : 0.4mg/kg every 12 hrly for 4 days.

Antibiotic Regimen:

- **Two alternative regimen in all cases:**
  - I/V Ceftriaxone/Cefotaxime plus I/V Vancomycin add on Rifampicin if susceptibility studies show intermediate susceptibility (MIC >2mcg/ml).
  - I/V Ceftriaxone plus I/V Vancomycin plus Rifampicin pending studies of susceptibility.

Conclusion

- No overall benefit in terms of reduction of mortality or neurologic sequelae in comparison to placebo as showed from meta-analysis.

- Possible efficacy of dexamethasone in 3 important subgroup:
- Age more than 55 years.
- Who are not infected with HIV .
- Reduction in hearing loss in longterm follow up in survivors.

- Minimal adverse effect(eg-hyperglycemia) in steroid group.

- So,it is prudent to use it in suspected bacterial meningitis.

THANK YOU