Tuberculous meningitis and corticosteroids: a review

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Abstract

Despite advanced chemotherapy the mortality rate for tuberculous meningitis (TBM) remains high (20-50%) and neurological sequelae can be devastating. Brain damage is the consequence of marked tendency towards granulation, organization and fibrosis of the basilar exudate, which causes raised ICP and obstructive hydrocephalus. Corticosteroids have been proposed as adjunct therapy to reduce complications. A literature search was conducted to determine evidence of the usefulness of steroids in the management of TBM. 11 clinical studies were found, 5 prospective, the rest retrospective studies. Patient numbers varied from 21 to 280. There were large variations in the definition of endpoints, which ranged from ocular complications, survival rate, intellectual outcome, activities of daily living to intracranial pressure and computed tomographic findings. The majority of patients included in the studies were of the pediatric age group. In the pediatric age group, there was evidence for the usefulness of steroids for both lower mortality rates and neurological sequelae. For adults, there were only two prospective studies, one with 42 patients, the other with 59 patients. Corticosteroids were only beneficial for some endpoints.

As evidence in the adult patient group is still conflicting, larger trials are needed to determine whether steroids will have an established role in the standard therapy of TBM, for both HIV and non-HIV patients.

Key words: Tuberculous meningitis, steroids, mortality, neurological sequelae, literature search

INTRODUCTION

With the resurgence of Tuberculosis (TB) in this decade, neurologists are increasingly facing the therapeutic challenge of tuberculous meningitis (TBM). Between 1984 and 1986, the incidence of pulmonary TB in the US increased by 3% and the incidence of extrapulmonary TB increased by 20%. Since 1986 there has been a 16% annual increase in the incidence of systemic tuberculosis, mainly-but not exclusively-related to the HIV epidemic. Raviglione has rated South-East Asia as the region with the highest rate for TB in the world. 49% of the 3.8 million cases of TB reported in the world in 1990 were from South East Asia. The overall incidence of TB in patients with AIDS is 500 times higher than in the general population. Although only 2% of tuberculosis cases among HIV-negative patients are complicated by meningitis, for HIV-infected patients with tuberculosis the risk of TBM is 10%.5

TB of the CNS is the most serious form of extrapulmonary TB. Despite effective chemotherapy the mortality rate remains high (20-50%) and the neurological sequelae can be devastating. 6 Brain damage in TBM is the consequence of a marked tendency towards granulation, organization and fibrosis of the basilar exudate that causes raised intracranial pressure, cranial nerve palsies, obstructive hydrocephalus and periarteritis. 7 Although mycobacterium tuberculosis is the causative agent, the initial inflammatory reaction seen in tuberculous meningitis is part of a hypersensitivity reaction, which even despite effective bacterial eradication can result in ongoing brain tissue damage.

For these reasons, corticosteroids with their anti-inflammatory properties have been proposed in the management of TBM. Steroids have inhibitory effects on monocytes, macrophages, as well as T and B-lymphocytes, reduce brain edema, modify the periarteritis and cause a decrease in CSF cytokine levels. Experiments have shown that intracisternally injected, heat-killed tubercle bacilli cause no leptomeningeal inflammatory reaction in rabbits sensitized to tuberculoprotein when these animals were pretreated with intrathecal hydrocortisone acetate. Since corticosteroids may adversely suppress or modify cell-mediated immunity, their

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usage can be controversial. Reassuringly, steroids apparently do not delay the elimination of the TB organism. But there has also been the concern that while inflamed meninges enhance the penetration of antituberculous drugs into the CSF, corticosteroids might impede CSF penetration and so delay the beneficial effect of treatment. A recent study involving 8 patients with TBM could not detect adverse effects of concomitant use of steroids on the CSF penetration of streptomycin, rifampicin, isoniazide and pyrazinamide. A further benefit of steroids may be suppression of hypersensitivity reactions induced by drugs such as rifampicin.

Records in the literature can be found ranging from those supporting the use of steroids to those with documenting no benefit or even potential toxicity. Concern has been expressed that steroids might improve mortality rate but increase the number of disabled survivors. However, most of these reports are either case reports or retrospective studies. We did a survey in South East Asia to determine how common steroids are used as adjunct therapy in TBM. 52 questionnaires were sent out to the main neurological centers or general hospitals in South East Asia. Questions were aimed at determining if steroids were routinely used in TBM for paediatric and/or adult patients, and if yes, in what stages it was given and at what dosage. The response rate (in terms of returned questionnaires) was 39%. The results showed that in the paediatric age group steroids were given routinely in 97% and were most commonly given in stages 2 and 3. In adults with TBM however steroids were given much less common (75%), and when given also in stages 2 and/or 3. The most common dosage was Prednisolone 2mg/kg in the paediatric age group and 1mg/kg for adults.

What evidence is there from the literature on the basis of prospective controlled randomised clinical studies that would indicate that steroids should be part of standard therapy in TBM?

We conducted a Medline search of the recent literature (English only) (1966-1998). The search revealed 5 prospective randomised, controlled clinical studies. The largest prospective study involved 280 paediatric patients. Significantly lower mortality rates as well as lower temporary and permanent neurological sequelae were reported for the group treated with dexamethasone. In a smaller prospective study (99 paediatric patients) sequential analysis of matched pairs was performed and a significantly lower mortality rate found for those on prednisone (both low 1mg/kg and high dose 10mg/kg over 30 days), but with no difference for neurological sequelae. A recent study from South Africa not only used clinical parameters for definition of end points, but also included computed tomographic scanning and intracranial pressure monitoring. 141 children with TBM were evaluated. Corticosteroids (4mg prednisolone/kg/day) significantly improved the survival rate and the intellectual outcome. Serial CT scanning showed enhanced resolution of the basal exudate and tuberculomas in the steroid treated group. However, steroids did not significantly decrease the incidence of permanent motor deficits, raised ICP or the incidence of basal ganglia infarction.

However, these studies only included paediatric patients, and the evidence for the overall benefit of steroids in TBM in the paediatric age group cannot necessarily be extrapolated to adult neurological patients. Only 2 prospective clinical studies for adults were found. A study by Kumaravelu and Ahuja found a trend toward increased survival in patients who received steroids, but the small number of 42 patients in their study prevented them from reaching conclusions of statistical significance. A study from Thailand with 59 patients concluded that steroids did not have any beneficial effect on mortality, severe brain lesions, increased intracranial pressure or cranial nerve palsies.

Whereas the above studies show good evidence for the beneficial effect of steroids in the treatment of TBM in children, the controversy about the use of steroids in adult patients remains. This is also reflected in our survey of centres in south east Asia where steroids were used routinely in children (97%), but less so in adults (75%). Scarce data in the adult population emphasizes the need for randomized clinical trials in determining the value of steroids in adult patients with TBM. As South East Asia has a high incidence of TB, a multi-center study in this region would certainly be worthwhile. Because of the underlying immunological disturbance among those with HIV, HIV positive and negative patients with TBM should be investigated separately. The two most important predictors of TBM outcome are disease stage at admission, and whether raised intracranial pressure caused by obstructive hydrocephalus is actively treated. Proper randomization would need to take these variables into account as well as good definition of end points inclusive of
mortality, morbidity, intellectual outcome, ICP and CT findings with adequate numbers of patients and controls. Adequate dosage of steroids needs to be determined since a study showed that rifampicin decreases the bioavailability of prednisolone by 66% and increased plasma clearance of the drug by 45%.

Certainly, steroids alone will not be the solution for decreasing mortality and morbidity in TBM. Early case detection and early diagnosis of complications using repeated CT scanning and CSF pressure monitoring with active management (including neurosurgical intervention) need to be the cornerstones next to standard medical therapy.

REFERENCES


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