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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 end points, 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%.[1,2] Since 1986 there has been a 16% annual increase in the incidence of systemic tuberculosis, mainly-but not exclusively-related to the HIV epidemic.[3] Raviglione has rated South-East Asia as the region with the highest rate for TB in the world.[4] 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.[1] 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 periarteriitis.[7] Although mycobacterium tuberculosis is the causative agent, the initial inflammatory reaction seen in tuberculous meningitis is part of a hypersensitivity reaction[8], which even despite effective bacterial eradication can result in ongoing brain tissue damage.[9]

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[5], modify the periarteriitis and cause a decrease in CSF cytokine levels.[10,11] 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.[12] 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.[13] 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.[14] A further benefit of steroids may be suppression of hypersensitivity reactions induced by drugs such as rifampicin.[13]

Records in the literature can be found ranging from those supporting the use of steroids [15-19] to those with documenting no benefit or even potential toxicity.[20-23] Concern has been expressed that steroids might improve mortality rate but increase the number of disabled survivors.[24] 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.[25] 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)[26] 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[27] 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 Kumarvelu and Ahuja[28] 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[29] 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[4], 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[30], and whether raised intracranial pressure caused by obstructive hydrocephalus is actively treated.[31] 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[32] 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

1. Barnes PF, Bloch AB, Davidson PT, Snider DE. Tuberculosis in patients with human immunodeficiency virus infection . N Engl J Med 1991; 324:1644-50.
2. Haas DW, Des Prez RM. Tuberculosis and acquired immunodeficiency syndrome: a historical perspective on recent developments. Am J Med 1994; 96: 439-50.
3. Infections of the Nervous System. In: Adams RD, Victor M and Ropper AH, eds. Principles of Neurology. McGraw Hill, 1997: 717-20
4. Raviglione MC, Snider DE Jr, Kochi A. Global epidemiology of tuberculosis. Morbidity and mortality of a worldwide epidemic. JAMA 1995: 273: 220-6
5. Moench Th. Tuberculous meningitis. In: Johnson R and Griffin JW, eds. Current Therapy in Neurologic Disease. 4th Edition. B.C. Decker, 1993: 118
6. Alzeer AJ, Fitzgerald JM. Corticosteroids and tuberculosis: risks and use as adjunct therapy. Tuber Lung Dis 1993; 74: 6-11.
7. Dastur DK, Lalitha VS. The many facets of neuro/ tuberculosis: an epitome of neuropathology. In: Zimmermann HM, ed. Progress in Neuropathology. New York, NY. Grunde and Stratton, 1973: 351-408.
8. Rich AR, McCordock HA. The pathogenesis of tuberculous meningitis. Bull Johns Hopkins Hosp 1933; 52: 5-37.
9. Auerbach O. Tuberculous meningitis: a correlation of therapeutic results with the pathogenesis and pathologic changes. Part II: pathologic changes in untreated and treated cases. Am Rev Tuberc 1951; 64: 419-29.
10. Taylor HG, Samanta A. Treatment of vasculitis. Br J Clin Pharmacol 1993; 35: 93-104.
11. Mustafa MM, Lebel MH, Ramilo O et al. Correlation of interleukin –1beta and cachectin concentrations in cerebrospinal fluid and outcome from bacterial meningitis. J Pediatr. 1989; 11: 208-13.
12. Feldman S, Behar AJ, Weber D. Experimental tuberculous meningitis in rabbits: II Effect of hydrocortisone on the hypersensitivity reaction of the meninges. Arch Neurol 3: 420-4.
13. Allen MB, Cooke NJ. Corticosteroids and tuberculosis. BMJ 1991: 303: 871-2.
14. Kaojarern S. Supmonchai Kingfah, Phuapradit P. Mokkhavesa C, Krittiyanunt S. Effect of steroids on cerebrospinal fluid penetration of antituberculous drugs in tuberculous meningitis. Clin Pharmacol Ther 1991; 49: 6-12.
15. Voljavec BF, Corpe RF. The influence of corticosteroid hormones in the treatment of tuberculous meningitis in Negroes. Am Rev Respir Dis 1960; 81: 539-45
16. Kendig EL, Choy SH, Johnson WH. Observations on the effect of cortisone in the treatment of tuberculous meningitis. Am Rev Tuberc 1956; 73: 99-109
17. Johnson JR, Furstenberg NE, Patterson R et al. Corticotropin and adrenal steroids as adjuncts to the treatment of tuberculous meningitis. Ann Intern Med 1957; 46: 316-31
18. Ashby M, Grant H. Tuberculous meningitis treated with cortisone. Lancet 1955; 1: 65-6.
19. Humphries M. The management of tuberculous meningitis. Thorax 1992; 47: 577-81
20. Weiss W. Flippin HF. The prognosis of tuberculous meningitis in the isoniazid era. Am J Med Sci 1961; 242: 423-30
21. Weiss W. Flippin HF. The changing incidence and prognosis of tuberculous meningitis. Am J Med Sci 1965; 250: 46-59
22. Lepper MH, Spies HW. The present status of the treatment of tuberculosis of the central nervous system. Ann N Y Acad Sci 1963; 106: 106-23
23. Hockaday JM, Smith HMV. Corticosteroids as an adjunct to the chemotherapy of tuberculous meningitis. Tubercle 1966; 47: 75-83
24. Freiman I, Geefhuysen J. Evaluation of intrathecal therapy with streptomycin and hydrocortisone in tuberculous meningitis. J Pediatr 1970; 76: 895-901.
25. Girgis NL, Farid Z, Kilpatrick ME, Sultan Y, Mikhail IA. Dexamethason adjunctive treatment for tuberculous meningitis. Pediatr Infect Dis J 1991; 10: 179-83.
26. Escobar JA, Belsey MA, Duenas A, Medina P. Mortality from tuberculosis meningitis reduced by steroid therapy. Pediatrics 1975; 56: 1050-5
27. Schoeman JF, Van Zyl LE, Laubscher JA, Donald PR. Effect of corticosteroids on intracranial pressure, computed tomographic findings and clinical outcome in young children with tuberculous meningitis. Pediatrics 1997; 99: 226-31.
28. Kumarvelu M, Ahuja GK. Randiomized controled trial of dexamethasone in tuberculous meningitis. Tuber Lung Dis 1994; 75: 203-7.
29. Chotmongkol V. Jitpimolmard S, Thavornpitak Y. Corticosteroid in tuberculous meningitis. J Med Assoc Thai 1996; 79: 84-90.
30. Humphries MJ, Teoh R, Lau J, Gabriel M. Factors of prognostic significance in Chinese children with tuberculous meningitis. Tubercle 1990; 71: 161-8.
31. Chitale VR, Kasalival. Our experience of ventriculo-arterial shunt using Upadhyaya valve in cases of hydrocephalus associated with tuberculous meningitis. In: Rickham PP, Hecker WC, Prevot J,

eds. Progress in Pediatric Surgery. Baltimore, MD: Urban and Schwarzenburg. 1982: 224-31.
32. McAllister WAC, Thompson PJ, Al-Habet SM. Rifampicin reduces effectiveness and bioavailability of prednisolone. Br Med J. 1983; 286: 923-5