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Clinical Study

High dose *versus* low dose steroids in children with tuberculous meningitis

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ABSTRACT

Guidelines for the best steroid dose in children with tuberculous meningitis (TBM) have not been established. We enrolled 63 children with TBM and divided them into three steroid dose groups: Group 1 (prednisolone 2 mg/kg/day over 4 weeks), Group 2 (prednisolone 4 mg/kg/day over 1 week and 2 mg/kg/day for the next 3 weeks) and Group 3 (prednisolone 4 mg/kg/day over 4 weeks). All patients received standard antituberculous therapy. Optic atrophy, tuberculoma, hydrocephalus, mental retardation, spasticity, hearing impairment, vasculitis and mortality outcomes were compared. Optic atrophy was higher in Group 3 compared to Group 1 (odds ratio [OR] = 2.8) and Group 2 (OR = 2.8), although Group 3 had a high incidence of optic atrophy at diagnosis. Tuberculomas were more frequent in Group 1 (OR = 2.4) and Group 3 (OR = 3.0) as compared to Group 2. Infarcts were more common in Group 3 than in Group 1 (OR = 1.9) and in Group 2 (OR = 3.5). Hearing loss was higher in Group 2 as compared to Group 1 (OR = 2.88) and Group 3 (OR = 4.8). Evolving hydrocephalus was higher in Group 3 as compared to Group 2 (OR = 2.8) and Group 1 (OR = 3.1). Mental retardation was higher in children in Group 3 (OR = 1.6) and in Group 2 (OR = 1.9) as compared to Group 1. Spasticity was higher in Group 3 (OR = 2.0) and in Group 2 (OR = 1.4) as compared to Group 1. There was no difference in mortality between the groups. We conclude that prednisolone at a dose of 4 mg/kg/day for 1 week followed by 2 mg/kg/day for 3 weeks is associated with fewer tuberculomas and infarcts but a higher incidence of hearing loss. A prolonged period of high dose steroids increases the risk of optic atrophy and hydrocephalus. Prednisolone at a dose of 2 mg/kg/day is associated with lower risk of mental retardation and spasticity.

1. Introduction

The incidence of tuberculous meningitis (TBM) varies from 1–4% of total in-patient admissions across India [1,2]. The reported mortality rate in TBM is 15–75% [1,2]. Adverse sequelae occur in 10–85% of patients [3,4]. These include mental retardation, epilepsy, neurological deficit in the form of hemiplegia, quadriplegia, cranial nerve palsy (commonly cranial nerves VII, III and VI), blindness, deafness, behavioural problems, hydrocephalus, and hypothalamic disturbances in the form of precocious puberty and diabetes insipidus [2]. Though the beneficial effects of steroids have been documented in TBM, to our knowledge there is no direct evidence to guide selection of the dose of prednisolone to be used [5–7]. Doses of steroids in studies have varied from 1 mg/kg/day to 4 mg/kg/day for intervals of 3–4 weeks [7–9]. Our study evaluated the efficacy of steroids in various doses and durations in TBM patients.

2. Methods and materials

This randomised study was conducted between 2009–2011 after attaining approval from the Institutional Ethics Committee to evaluate the beneficial effects and side effects of three different dosages of prednisolone in TBM. Patients between the ages of 4 months and 14 years with TBM who were admitted to our hospital from May 2009 to May 2011 were included and randomized into three groups after initial dexamethasone (0.15 mg/kg/dose 8 hourly for 5 days) by a blinded health care worker randomly picking up chits of Group 1, Group 2 or Group 3. Group 1 received prednisolone of 2 mg/kg/day over 4 weeks which was then tapered over the next 4 weeks. Group 2 received prednisolone of 4 mg/k/day over 1 week and 2 mg/k/day for the next 3 weeks which was then tapered over the next 4 weeks. Group 3 received prednisolone of 4 mg/k/day over 4 weeks which was then tapered over the next 4 weeks.

Diagnosis of TBM was based on the British Medical Research Council for Tuberculosis (TB) criteria [10]. The staging of TBM was based on Doerr's criteria [11]. Baseline investigations including neurological imaging, ophthalmological examination, chest

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radiograph, Mantoux test using 5 tuberculin units, haemogram, and erythrocyte sedimentation rate were carried out in all patients. Cerebrospinal fluid TB culture was done if affordable. Induration of more than 10 mm was taken as a positive Mantoux test. All patients were screened for human immunodeficiency virus infection using an enzyme-linked immunosorbent assay. A detailed history was taken and all patients underwent a clinical examination. Status of Bacillus Calmette–Guérin vaccination was noted in all patients. Associated pulmonary TB was noted.

All patients were treated with four-drug antituberculous therapy (ATT) in the form of isoniazid, rifampicin, pyrazinamide, and streptomycin for the initial 2 months of the study period as per the Indian Academy of Pediatrics 2010 Guidelines, followed by isoniazid and rifampicin for 10 months. Compliance was ensured with pill recall at each visit to the clinic. In patients with drug resistant TB, ATT was given as per the sensitivity report. Patients with hydrocephalus and raised intracranial pressure not responding to medical management underwent a shunt surgery or insertion of a reservoir.

Repeat neurological imaging was done after 3 months of therapy to look for new changes, including an increase in the size of a previous tuberculoma or appearance of a new tuberculoma, increase in hydrocephalus, or appearance of a new infarct. All patients also underwent ophthalmological evaluation at the end of 3 months to assess for papilledema, blindness and optic atrophy. A hearing assessment was also carried out at the end of 3 months. Further neurological imaging was done as and when required if there were signs of raised intracranial pressure or to assess the size of tuberculomas in the 26 patients who had them. The follow-up period ranged from 6 months to 18 months. The mean and standard deviation follow-up duration was 10.8 ± 1.6 months in Group 1, 9.6 ± 2.0 months in Group 2 and 11.6 ± 3 months in Group 3. Neurological deficit in the form of decerebrate posturing, spasticity, dystonia, and hemiparesis were noted. Adverse effects of steroids such as hypertension, opportunistic infections, cataracts and cushingoid features were monitored and the steroid dosage was reduced if the child developed steroid toxicity. Shunt complications, in the form of shunt block, infection and the need for revision surgery in each group were assessed.

At the end of the ATT treatment period, patients were evaluated for visual impairment and hearing loss as well as comorbid conditions including spasticity, mental retardation and mobility. Mortality was calculated in each group.

The clinical features of TBM were noted at the different stages of TBM. Baseline clinical and radiological parameters were assessed in all three groups to remove selection bias. The effect of steroid dose on outcomes such as tuberculoma, infarct, hydrocephalus, hearing impairment and visual impairment was compared using the chi-squared test or Fischer's exact test and odds ratios (OR) calculated using the Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) software.

3. Results

A total of 63 patients with TBM were included in this study, of which 29 (46%) patients were randomised to be in Group 1, 16 (25%) were in Group 2 and 18 (28%) were in Group 3 (Fig. 1). The baseline clinical, laboratory and radiological features were similar in all three groups (Table 1).

The clinical and radiological outcomes of all patients in the three groups are depicted in Table 2. Optic atrophy was higher in Group 3 compared to Group 1 (OR = 2.78) and Group 2 (OR = 2.75). Incidence of new tuberculoma and worsening of existing tuberculomas was higher in Group 1 compared to Group 2 (OR = 2.4), and higher in Group 3 compared to Group 2 (OR = 3.0), but was similar in Group 1 and 3 (OR = 0.8). New infarcts were seen more in Group 3 than in Group 1 (OR = 1.9) and Group 2 (OR = 3.5). However, the OR of infarcts was higher in Group 1 compared to Group 2 (OR = 1.82). Hearing loss was higher in Group 2 as compared to Group 1 (OR = 2.88) and as compared to Group 3 (OR = 4.8). Evolving hydrocephalus was higher in Group 3 than in Group 2 (OR = 2.75) and in Group 1 (OR = 3.05). Incidence of mental retardation was higher in children in Group 3 as compared to Group 1 (OR = 1.57) and in children in Group 2 as compared to Group 1 (OR = 1.88). Spasticity was higher in Group 3 as compared to Group 1 (OR = 2) and in Group 2 as compared to Group 1 (OR = 1.4). There was no difference in mortality between the three groups. Six children (9.5%) had drug induced hepatitis during the study period, of which four children received steroids at 2 mg/kg/day, and two received steroids at 4 mg/kg/day (one each in Group 2 and Group 3). All six patients had to be administered ofloxacin, streptomycin, ethambutol while rifampicin, isoniazid and pyrazinamide were stopped until the hepatitis resolved. Five children had multidrug resistant TB and one child had extensively drug resistant TB. Two of these patients were in Group 1, three were in Group 2 and one was in Group 3.

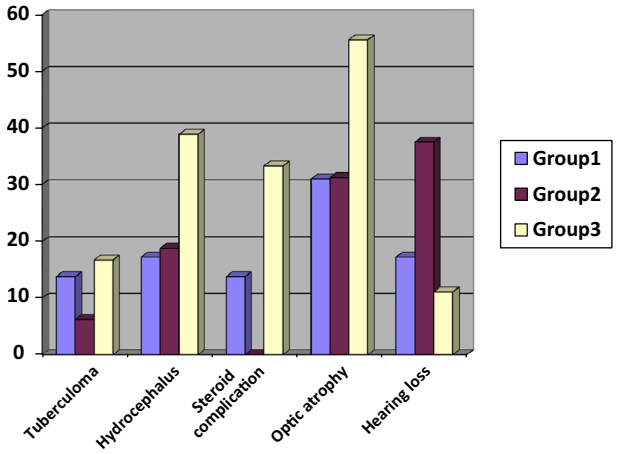

Fig. 1. Outcome of the three groups of paediatric tuberculous meningitis patients, treated with different prednisolone regimens. (This figure is available in colour at www.sciencedirect.com)

Table 1a
Baseline clinical, radiological and laboratory profiles in the three groups of paediatric tuberculous meningitis patients, treated with different prednisolone regimens

	Group 1	Group 2	Group 3	*p* value
Male:Female	13:16	8:8	7:11	0.8
Fever	25 (86.2%)	16 (100%)	17 (94.4%)	0.2
Altered sensorium	17 (58.6%)	14 (87.5%)	13 (72.2%)	0.1
Convulsion	20 (68.9%)	8 (50%)	10 (55.5%)	0.4
Headache	8 (27.6%)	5 (31.3%)	2 (11.1%)	0.3
TBM stage				0.8
I	2 (6.9%)	1 (6.2%)	0	
II	12 (41.4%)	6 (37.5%)	7 (38.9%)	
III	15 (51.7%)	9 (56.3%)	11 (61.1%)	
Focal neurological deficit	11 (37.9%)	5 (31.2%)	9 (50%)	0.5
Dystonia	6 (20.7%)	5 (31.2%)	3 (16.7%)	0.5
Decerebrate posturing	5 (17.2%)	3 (18.7%)	1 (5.5%)	0.4
Optic atrophy	3 (10.3%)	1 (6.2%)	5 (27.8%)	0.1
Hydrocephalus	18 (62.1%)	14 (87.5%)	11 (61.1%)	0.1
Tuberculoma	13 (44.8%)	3 (18.7%)	8 (44.4%)	0.2
Infarct	7 (24.1%)	6 (37.5%)	5 (27.8%)	0.6
BCG scar	24 (82.7%)	10 (62.5%)	16 (88.9)	0.1
Positive Mantoux test	13 (44.8%)	9 (56.2%)	14 (77.8%)	0.08
Associated pulmonary TB	7 (24.1%)	6 (37.5%)	6 (33.3%)	0.6

All data are presented as n (%) unless otherwise stated.
BCG = Bacillus Calmette-Guérin, TB = tuberculosis, TBM = tuberculous meningitis.