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Original Article

Comparison of dexamethasone regimens in tubercular meningitis (TBM): a randomized open label clinical trial

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Abstract

Introduction: Corticosteroids are used as adjunctive treatment in tuberculous meningitis (TBM). However, there is no universally accepted regimen, type, duration, or route of steroid administration.

Methodology: In a randomized open labelled pilot study, TBM patients were divided into overlap oral dexamethasone (OOD) and direct oral dexamethasone (DOD) arms. The total duration of steroid administration was 8 weeks. The primary outcome was symptomatic resolution at 1 month post randomization. The secondary outcomes were mortality and modified Rankin scale (mRS) at 3 and 6 months after initiation of steroids.

Results: Symptomatic resolution after one month of randomization in 53 randomized patients was similar in OOD (71.4% (15/21)) versus DOD ((85.0% (17/20)) arm (*p* value:0.45). Median mRS was also similar in OOD versus DOD (OOD: 2.5 (IQR: 1.0; 6.0) versus DOD: 1.0 (IQR: (0.0; 4.0); *p* value: 0.31)) arm at 6 months. The mortality at 6 months was 31.8% (7/22) in the OOD versus 20.0% (4/20) in the DOD arm (*p* value: 0.49).

Conclusions: In this open label pilot study, the outcomes were similar in OOD versus DOD arms in terms of symptomatic resolution at 1 month, and morbidity, and mortality at 3 and 6 months. Patients with stage I to III TBM may be given injectable steroids for 1 week after which they may be switched to oral steroid. This regime cannot be applied to stage IV TBM and patients with complications like optico-chiasmatic or spinal arachnoiditis or vasculitic infarcts.

Key words: tuberculous meningitis; dexamethasone; corticosteroid; comparison.

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Introduction

Tuberculosis (TB) is a devastating disease with significant morbidity and mortality in the lower middle-income countries (LMIC). The World Health Organization (WHO) TB statistics for India for 2016 listed an estimated incidence figure of 1.6 million new cases of TB annually [1]. Central nervous system (CNS) TB accounts for 5-10% cases of extrapulmonary TB and only 1% of all cases [2]. However, mortality from CNS TB of about 27% is the highest amongst all forms of TB [3].

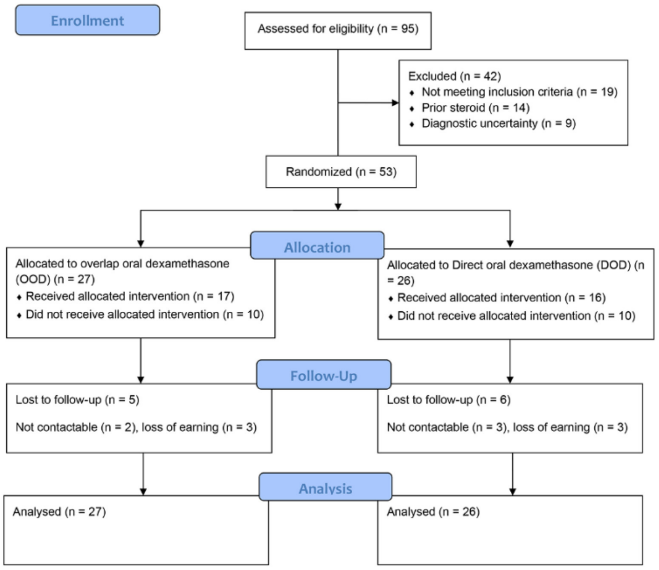
Corticosteroids are used as adjunctive treatment in tuberculous meningitis (TBM) to decrease inflammation, reduce oedema, intracranial pressure and inflammation [4,5]. There are no trials which demonstrate superiority of one steroid agent over the other, nor the superiority of any one route of administration in TBM [6]. In a randomized control trial, Thwaites *et al.* proposed a regimen of dexamethasone consisting of intravenous dexamethasone tapered over 4 weeks followed by oral dexamethasone tapered over another 4 weeks in stage II or III TBM patients [7]. Administering injectable steroid for 4 weeks is impractical in patients who recover neurologically within a week of treatment initiation. Also, due to high patient turnover, the steroid regime was switched to oral with satisfactory outcomes, although there was no evidence for the same. However, there are also instances of clinical deterioration upon switching of steroids directly from intravenous to oral route [8]. We therefore conducted a randomized control study to compare the overlapping intravenous to oral versus direct intravenous to oral dexamethasone treatment regimens. The hypothesis of the study was that in TBM patients the symptomatic resolution of symptoms would be similar in overlap oral dexamethasone (OOD) and direct oral dexamethasone (DOD) regimes.

Methodology

The study was a single centre, open label comparative study, conducted in the neurology department of a tertiary care centre in North India. Eligible patients were recruited according to the diagnostic criteria outlined by Ahuja *et al*. [8]. Patients were excluded if they had any of the following: alternative diagnosis (including non-tubercular infection, malignancy) made on cerebrospinal fluid (CSF) testing or imaging, and absolute contraindications to the use of steroids. Since the patients who were human immunodeficiency virus (HIV) positive were admitted to the medicine department (according to hospital policy), they were excluded from the study.

The study was an open label randomized control trial (RCT) with 1:1 concealed allocation. Sequentially numbered sealed opaque envelopes were used to conceal allocation of the participants into either group. Randomization sequence generation was done by permuted block randomization with a block size of four. The allocation concealment was ensured by the statistician (SND) who was not aware of the clinical status of the patients. The participants were divided into two arms: overlap oral dexamethasone (OOD) arm and direct oral dexamethasone (DOD) arm. The British Medical Research Council (MRC) staging of TBM was done to assess the severity of disease at presentation [9]. The regimens were based on Thwaites regimen (Supplementary Table 1) [7]. As no prior studies comparing regimens of dexamethasone had been carried out on TBM patients, a pilot study of 30 patients in each arm was planned. However, due to the large number of patients who had to be excluded from the study (Figure 1) and the completion of the permitted tenure of the study period, the study was terminated when 53 patients completed the follow-up duration of 6 months. All the patients received anti-tubercular treatment (ATT): 2 months of daily oral isoniazid (5 mg/kg), rifampin (10 mg/kg), pyrazinamide (25 mg/kg; maximum dose 2 g/day), and intramuscular streptomycin (15 mg/kg, maximum dose 1 g/day), followed by continuation of isoniazid and rifampin at the same daily doses in maintenance phase [10]. Any deviation in the treatment was left to the discretion of the treating neurologist, depending upon the clinical condition of the patient. In the event of clinical deterioration warranting stepping up of steroids or change in the regimen of ATT, the details and deviations from the protocol were noted. The primary outcome was resolution of clinical symptoms (headache, fever, altered consciousness) at 1 month after randomization. The symptoms were self-reported and requested from the patients and their caregiver(s) during in-person visit. This outcome was chosen because the most proximate effect of steroid regimen would reflect in this endpoint. The secondary outcome measures were mortality and modified Rankin score (mRS) at the end of 3 and 6 months. The assessment of the outcomes was done by the investigator (AS) who was aware of the treatment arm.

Figure 1. Study flowchart.



Ethical clearance for the study was obtained from the institutional ethics committee (IECPG-440/31.01.2018). Written informed consent was obtained for participation in the study. The study was registered in the clinical trials registry India (reference number CTRI/2018/01/011319).

Statistical analysis was performed using Chi square test and Fischer's exact test for categorical variables. Independent Student's t-test and Mann-Whitney U tests were used for continuous variables. Cochran-Mantel Haenszel (CHM) equation was used for calculating p value related to shift in mRS scores. The results were statistically significant if the p value was < 0.05. All analyses were done in STATA version 23.

Results

The patients were enrolled between 2018 and 2019. Out of a total of 95 patients screened for eligibility, 53 were randomized (Figure 1). The characteristics of randomized and non-randomized patients were similar (Supplementary Table 2). There were 37.0% (10/27) in OOD arm and 38.5% (10/26) patients in DOD arm who had protocol violation. These violations were in terms of doses of steroid (n = 3), reversion to injectable steroid

(n = 5) and switching to pulse methylprednisolone (n = 2) (Supplementary Table 3). 42 (79.2%) of randomized patients completed the 6 months follow up period (Figure 1). The median age of TBM patients was 23.0 (IQR: 18.0; 32.0) years (Table 1). Females constituted 54.7% of the patients. The baseline characteristics were similar. The median duration of symptoms was 15.0 (IQR: 10.0; 40.5) days. Fever and/or headache were the commonest symptoms. Majority of the patients were in stage II (54.7%). The baseline characteristics of the randomized and non-randomized patients were similar (Supplementary Table 2). Also, when the patients with and without protocol violation were compared, higher proportion of stage I and II TBM (milder disease) followed the allocated arm (Supplementary Table 3).

Table 1. Baseline clinical, laboratory, and neuroimaging characteristics of patients.

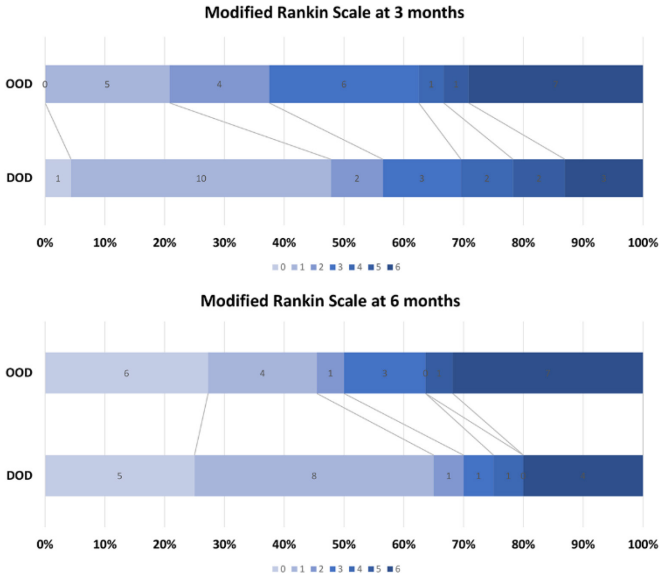
Variables (n = 53)	Overall (n = 53)	OOD arm, (n = 27)	DOD arm, (n = 26)	*p* value
Demographic and clinical features				
Age, years, median (IQR)	23.0 (18.0; 32.0)	23.0 (18.0; 28.0)	23.0 (20.0; 38.8)	0.37
Gender (female), n (%)	29 (54.7)	17 (63.0)	12 (46.2))	0.22
Clinical features, n (%)				
Fever	48 (90.6)	25 (92.6)	23 (88.5)	0.67
Headache	48 (90.6)	25 (92.6)	23 (88.5)	0.67
Vomiting	34 (64.2)	18 (66.7)	16 (61.5)	0.70
Altered sensorium	44 (83.0)	24 (88.9)	20 (76.9)	0.29
Seizures	17 (32.1)	9 (33.3)	8 (30.8)	0.84
Constitutional symptoms	43 (81.1)	24 (88.9)	19 (73.1)	0.18
Duration of symptoms, days, median (IQR)	15.0 (10;40.5)	30.0 (9.5; 73.0)	30.0 (15.0; 90.0)	0.31
Duration of altered sensorium, days, median (IQR)	4.0 (2.0;10.0)	4.0 (2.0; 12.5)	4.0 (2.0; 10.0)	0.94
Extra neural tuberculosis, n (%)	8 (15.1)	2 (7.4)	6 (23.0)	0.14
History of treatment of tuberculosis, n (%)	13 (24.5)	6 (22.2)	7 (26.9)	0.69
Glasgow coma scale, median (IQR)	11.0 (9.0;15.0)	11.0 (8.5; 14.5)	11.0 (9.0; 15.0)	0.40
Meningeal signs, n (%)	42 (79.2)	22 (81.5)	20 (76.9)	0.68
Cranial nerve palsies, n (%)	31 (58.5)	17 (63)	13 (52)	0.58
Focal motor deficits, n (%)	8 (16.0)	5 (25)	3 (22)	0.70
TBM stage at admission, n (%)				
Stage I	7 (13.2)	2 (7.4)	5 (19.2)	0.44
Stage II	29 (54.7)	16 (59.2)	13 (50)	
Stage III	17 (32.1)	9 (33.3)	8 (30.8)	
Modified Rankin Scale (mRS), median (IQR)	5.0 (3.0;5.0)	5.0 (4.0; 5.0)	5.0 (3.0; 5.0)	0.22
Laboratory parameters				
Total leucocyte count, per cc, mean (SD)	9933.6 (5061.4)	9190.0 (7810; 11700)	8635.0 (6475; 10727.5)	0.17
AST, IU/L, median (IQR)	37.0 (27.0;52.0)	40.0 (24.8; 54.0)	31.0 (19.7; 51.5)	0.31
ALT, IU/L, median (IQR)	36 (23.5;72.0)	39.0 (27.0; 91.0)	30.5 (16.5; 63.0)	0.21
Bilirubin, mg/dL, IU/L, median (IQR)	0.6 (0.5;0.9)	0.6 (0.4; 1.1)	0.7 (0.6; 0.9)	0.17
Cerebrospinal fluid analysis				
Total cell count, per cc, median (IQR), (n = 49)	80 (25;150)	65 (15; 150)	75 (15; 150)	0.84
Lymphocytes, %, median (IQR), (n = 49)	90.0 (65.0;100.0)	80 (40.0; 100.0)	90 (67.5; 100.0)	0.80
Glucose, mg/dL, median (IQR), (n = 49)	34.5 (22.5;56.0)	34.0 (19.0; 42.0)	38.0 (26.0; 56.0)	0.98
Protein, mg/dL, median (IQR), (n = 49)	158 (83;276)	161 (80-262)	95 (68.75-278.25)	0.47
GeneXpert positivity (n = 45)	18 (42.2)	9 (39.1)	9 (40.9)	0.90
Culture positivity (n = 31)	5 (16.1)	3 (17.6)	2 (14.3)	1.00
Neuroimaging features				
CT findings at baseline (N = 50)				
Hydrocephalous	34 (68.0)	19 (73.1)	15 (62.5)	0.42
Basal exudates and leptomeningeal enhancement	34 (68.0)	17 (65.4)	17 (70.8)	0.68
Infarcts	9 (18.0)	3 (11.5)	6 (25.0)	0.22
Tuberculomas	9 (18.0)	5 (19.2)	4 (16.7)	1.00
MRI findings at baseline (N = 32)				
Hydrocephalous	20 (62.5)	11 (68.8)	9 (56.3)	0.47
Infarcts	9 (28.0)	6 (37.5)	3 (18.8)	0.24
Tuberculomas	27 (84.4)	12 (75.0)	15 (93.8)	0.14
Basal exudates and /or leptomeningeal enhancement	32 (100.0)	16 (100.0)	16 (100.0)	-

ALT: alanine transferase; AST: aspartate Transferase; CT: computerized tomography; DOD: direct oral dexamethasone; IQR: interquartile range; MRI: magnetic resonance imaging; OOD: overlap oral dexamethasone; SD: Standard deviation; TBM: tuberculous meningitis.

Gene Xpert was positive in 42.2% (19/45) patients, and all were rifampicin sensitive. Culture for tubercle bacilli was positive in 16.1% (5/31) patients. The median total CSF count was 80.0 (IQR: 25.0; 150.0) cells with lymphocytic predominance (median: 90.0 (IQR: 65.0; 100.0) %). The median CSF glucose was 34.5(22.5; 56.0) mg/dL and the median CSF protein was 158.0 (83.0; 276.0) mg/dL.

Hydrocephalus and basal exudates with leptomeningeal enhancement were the commonest findings seen in CT head (68.0% (34) each). Higher proportion of tuberculomas and infarcts could be picked up by magnetic resonance imaging (MRI) brain image.

Figure 2. Modified Rankin scores (mRS) at three and six months in the overlap oral steroid (OOD) versus direct oral steroid (DOD) arm.



In-hospital disease and treatment related complications occurred most in the form of hydrocephalus (20.8%) and anti-tubercular treatment (ATT) drug induced liver injury (DILI) (28.3%) (Table 2). The in-hospital mortality was 7.5% (4/53). The primary outcome in the form of improvement in symptoms at cessation of steroids was present in 71.4% (15/21) patients in the OOD arm and 85.0% (17/20) in the DOD arm ($p = 0.45$).

Median mRS improved from the baseline of 5.0 (3.0;5.0) in both the treatment arms to 3.0 (1.0; 6.0) at 1 month follow up (Table 2). Shift in mRS scores at 3 and 6 months showed no significant difference (Figure 2). Mortality at 1 month was 19.5% (8/41) and increased to 26.2% (11/42) at 6 months. The difference in mortality between the 2 groups was not statistically significant (OOD arm: 31.5% versus DOD arm: 20.0% (p value: 0.49)).

Discussion

Corticosteroids, by means of their anti-inflammatory properties, may provide relief in symptoms and prevent complications [11]. In our study, 78% (32/41) patients followed up at 1 month showed resolution of clinical symptoms. Neither OOD nor DOD regimen significantly altered the proportion of patients who improved symptomatically. In a study by Malhotra *et al.,* dexamethasone was compared with pulse methylprednisolone with no difference in mortality [12].

The purpose of the study was to examine if direct conversion to oral steroids was equally efficient and if it would reduce hospital stay days. Although the duration of hospital stay was similar in both the groups,

Table 2. In hospital course and outcomes.

Variables (n = 53)	Overall (n = 53)		OOD arm (n = 27)		DOD arm (n = 26)	*p* value
Complications of treatment, n (%)						
VP shunt	11 (20.8)		5 (18.5)		6 (23.1)	0.75
Drug induced liver injury	15 (28.3)		6 (22.2)		9 (34.6)	0.32
Duration of hospital stay, median (IQR)	11.0 (7.0; 15.0)		11.0 (7.0; 18.0)		11.5 (7.0; 15.3)	0.44
Protocol violation	20 (37.7)		10 (38.5)		10 (38.5)	1.00
In hospital mortality	4 (7.5)		3 (11.1)		1 (3.8)	0.61
Improvement of symptoms, n (%)						
One month, (n = 41)	32 (76.2)	n = 21	15 (71.4)	n = 20	17 (85.0)	0.45
Three months, (n = 47)	37 (78.7)	n = 24	17 (70.8)	n = 23	20 (87.0)	0.29
Six months, (n = 42)	31 (73.8)	n = 22	15 (68.2)	n = 20	16 (80)	0.49
Modified Rankin scale, median (IQR)						
One month, (n = 41)	3.0 (1.0; 5.0)	n = 21	3.0 (2.0;5.0)	n = 20	2.0 (1.0;4.0)	0.28
Three months, (n = 47)	3.0 (1.0; 6.0)	n = 24	3.0 (2.0;6.0)	n = 23	2.0 (1.0;4.0)	0.14
Six months, (n = 42)	1.0 (0.0; 5.0)	n = 22	2.5 (1.0;6.0)	n = 20	1.0 (0.0;4.0)	0.31
Mortality, n (%)						
One month, (n = 41)	8 (19.5)	n = 21	5 (23.8)	n = 20	3 (15.0)	0.70
Three months, (n = 47)	10 (21.3)	n = 24	7 (29.2)	n = 23	3 (13.0)	0.29
Six months, (n = 42)	11 (26.2)	n = 22	7 (31.8)	n = 20	4 (20.0)	0.49

DOD: direct oral dexamethasone; IQR: interquartile range; OOD: overlap oral dexamethasone; VP: ventriculoperitoneal.

it was probably driven by the monitoring required as they were included in the trial. In real life, this may be a definite advantage. A retrospective cohort study found similar results, although the groups were not balanced at baseline [13]. Our study randomized patients to minimize selection bias. The study by Paliwal *el al.* also highlights the evidence-practice gap [13]. Our study attempted to generate higher level of evidence for the current practice.

Our study showed similar radiological resolution at the end of 1 and 6 months which is similar to the study by Schoeman *et al.* [14]. However, these studies have been conducted primarily in the pediatric population and larger studies in adults are required.

The strengths of our study were a randomized study design, concealed allocation of participants to either group, and sampling done from a representative population. The limitations were small sample size, open-label design, and loss to follow up and protocol violations. Although we excluded immunocompromised patients with HIV, we did not systematically investigate for impaired cell mediated immunity in all the patients. The CSF culture positivity was similar to the other studies done from this part of the world, ranging from 9-35% [15,16]. Our study also did not compare the original Thwaite's regimen with the OOD and DOD regimens. This was due to the pragmatic trial design and high patient load at our hospital. Stable patients could not be kept hospitalized for 4 weeks for injectable dexamethasone. Lastly, most of the patients in our study were stage II TBM. Extremely sick and TBM patients admitted in the ICU were largely excluded as most of these patients were not eligible for the study.

Conclusions

Our study showed that both the overlap and direct switch regimens of dexamethasone were similar in producing symptomatic resolution at 1 month. The mortality was comparable to prior studies [4,17]. The results are, however, applicable mainly in stage II and III TBM patients as these constituted most of our study population. Therefore, switching to DOD may be considered in these patients. This would reduce the hospital stay of these patients. TBM patients who are comatose or have severe complications (like vision loss, optico-chiasmatic arachnoiditis) were excluded from the study, so the results do not apply for them. Further studies with a larger sample size and longer follow-up will be required to draw further conclusions.

Ethical approval

Institutional ethics committee (IECPG-440/31.01.2018); CTRI registration (CTRI/2018/01/011319).

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Conflict of interests: No conflict of interests is declared.

Annex – Supplementary Items

Supplementary Table 1. Treatment arms according to grade of tuberculous meningitis (TBM).

	MRC stage II and III			MRC stage I		
	Thwaites regime*	**OOD arm**	**DOD arm**	**Thwaites regime**	**OOD arm**	**DOD arm**
Week 1	0.4 mg/kg IV (20-24 mg/day)	24 mg (6 mg IV QID)		0.3 mg/kg IV (15-18 mg/day)	16 mg (4 mg IV QID)	
Week 2	0.3 mg/kg IV (15-18 mg/day)	18 mg (6 mg IV BD + 6 mg oral OD) for 3 days → 18 mg (6 mg IV OD +6 mg oral BD) for 3 days	18 mg (6 mg oral TDS)	0.2 mg/kg IV (10-12 mg/day)	10 mg (4 mg IV BD +2 mg oral OD) for 3 days →10 mg oral single tablet	10 mg oral single tablet
Week 3	0.2 mg/kg IV (10-12 mg/day)	10 mg oral single tablet		0.1 mg/kg IV (5-6 mg/day)	6 mg oral single tablet	
Week 4	0.1 mg/kg IV (5-6 mg/day)	6 mg oral single tablet		3 mg/day	3 mg/day	
Week 5	4 mg/day	4 mg/day		2 mg/day	2 mg/day	
Week 6	3 mg/day	3 mg/day		1 mg/day	1 mg/day	
Week 7	2 mg/day	2 mg/day		Stop steroid		
Week 8	1 mg/day	1 mg/day				
Week 9	Stop steroid					

BD: twice daily (bis die); DOD: direct oral dexamethasone; IV: intravenous; MRC: Medical Research Council; OD: once daily; OOD: overlap oral dexamethasone; QID: four times a day (quater in die); TDS: three times a day (ter in die); *[7].

Supplementary Table 2. Characteristics of randomized versus non-randomized patients.

Variables	Randomized (n = 53)	Non-randomized (n = 42)	*p* value
Age	27(11.3)	29.2 (13.4)	0.39
Gender	29 (54.7)	24 (57.1)	0.81
Stage I and II TBM	36 (67.9)	28 (73.7)	0.55
In hospital death	5 (9.6)	8 (21.6)	0.14

TBM: Tuberculous meningitis.

Supplementary Table 3. Characteristics of patients who followed the randomized treatment versus patients who violated protocol.

Variables	Protocol followed (n = 33)	Protocol violated (n = 20)	*p* value
Age	27.8(11.4)	25.7 (11.4)	0.52
Gender	17 (51.5)	12 (60.0)	0.55
Stage I and II TBM	25 (78.8)	10 (50.0)	0.04
In hospital death	1 (3.2)	4 (20.0)	0.07

TBM: Tuberculous meningitis.