Am. J. Trop. Med. Hyg., 101(5), 2019, pp. 1083–1086
doi:10.4269/ajtmh.19-0416

Intravenous Steroid Days and Predictors of Early Oral Steroid Administration in Tuberculous Meningitis: A Retrospective Study

Vimal Kumar Paliwal,[1]*† Animesh Das,[1]† Sucharita Anand,[1] and Prabhakar Mishra[2]

[1]*Department of Neurology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India;* [2]*Department of Biostatistics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India*

Abstract. Intravenous (IV) dexamethasone is recommended for 14 days in stage 1 and 28 days in stage 2/3 tuberculous meningitis (TBM). We used a different steroid protocol. We shifted TBM patients to oral steroids after 48 hours of sustained improvement on IV steroids (oral group). Patients who worsened after shifting to oral steroids were reinitiated on IV steroids. Once they showed a consistent improvement for 48 hours, the IV steroids were overlapped with oral steroids for 7–10 days to taper off IV steroids (overlap group). We compared total IV steroid days in our patients with the recommended treatment and identified predictors that favored the oral group. This was a retrospective study. We included 98 patients with TBM (66 in the overlap group and 32 in the oral group) from January 2013 to July 2018. The median IV steroid days were 9 days (interquartile range of 4–12; 2–3.5 days in the oral group and 10–11.5 days in the overlap group). The mortality rate was 6.1%. The logistic regression model showed that TBM patients with basal exudate, tuberculoma, and modified Rankin scale (mRS) < 3 had a higher probability for going to the oral group. We conclude that total IV steroid days can be reduced in TBM patients by our method of steroid use. Presence of basal exudates and tuberculoma may favor early shifting from IV to oral steroid, whereas higher mRS may require a relatively longer course of IV steroid.

INTRODUCTION

Corticosteroids are a cornerstone in the management of tuberculous meningitis (TBM). Studies have showed that corticosteroids reduce the number of deaths and prevent disabling neurological deficits in patients with TBM.[1] The current study is strongly influenced by a Vietnamese study by Thwaites et al.[2] The steroid protocol followed by Thwaites et al. is widely used in clinical practice. For stage 1 TBM (British Medical Research Council staging of TBM), Thwaites et al. used intravenous (IV) dexamethasone for 2 weeks, and for stage 2 and 3 TBM, they used IV dexamethasone for 4 weeks. Intravenous dexamethasone was followed by oral dexamethasone for 4 weeks in stage 1 to stage 3 TBM patients (Supplemental Table 1). However, this fixed regimen for IV steroids for 2–4 weeks requires a long hospital stay. Because TBM mostly affects people from poor socioeconomic background, many of these patients cannot afford a long hospital stay.

Hence, we followed a different protocol to rapidly taper IV steroid use in patients with TBM (Supplemental Table 1). We shifted patients from IV to oral steroids after they achieved a sustained improvement in headache, vomiting, and at least a two-point improvement in Glasgow Coma Scale for a minimum of 48 hours. This group of patients is referred to as the oral group. After shifting to oral steroids, if patients had reappearance of headache, vomiting, or deterioration in consciousness, they were again initiated on IV dexamethasone until a consistent improvement for at least 48 hours on IV steroids was observed. At this point, IV dexamethasone was overlapped with oral steroids. As the dose of IV dexamethasone was reduced every 2 days, oral steroid dose was up-titrated. At no point, the total dose of IV plus oral steroids was beyond the bioequivalent dose of 0.4 mg/kg/day of dexamethasone. The overlap period usually lasted 10 days. This group was referred to as the overlap group. We found that this overlap method invariably improved the acceptability of oral steroids. The oral steroids were then continued for 4–6 weeks depending on the clinical response.

Objectives of the study were as follows:

1. To determine the total IV steroid days in TBM patients and compare them with the recommended IV steroid days
2. To determine the predictors that favor the oral group

METHODS

Our institute's Ethics Committee approved this retrospective study.

Inclusion criteria. Patients admitted in the neurology ward of Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, between January 2013 and July 2018 who fulfilled the widely accepted diagnostic criteria for TBM[3] were included in the study.

Exclusion criteria. Patients who received oral steroids alone and patients who received oral steroids before IV steroids were excluded from the analysis. Patients with coinfection with HIV disease were also excluded.

Data collection and interpretation. Baseline characteristics of the patients, including demographic profile, clinical features, cerebrospinal fluid (CSF) findings, and radiological characteristics, were retrieved from the hospital information system. The case file of each patient that included detailed clinical examination findings, daily vital charts, treatment charts, and details of peripheral referrals during the hospital stay was also reviewed for any missing information. Depending on the method of shifting the patients from IV to oral steroids, the patients were divided into two groups:

1. Overlap group
2. Oral group

*Address correspondence to Vimal Kumar Paliwal, Department of Neurology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Raebareli Rd., Lucknow 226014, India. E-mails: dr_vimalkpaliwal@rediffmail.com or drvimalkpaliwal@gmail.com
† These authors contributed equally to this work.

Total IV steroid days in both the groups were noted. Both the groups were compared for clinical features, CSF parameters, and radiological findings to determine the factors favoring the oral group.

Patient follow-up data. The outpatient follow-up details till November 2018 of each patient were reviewed. The time of follow-up of each patient was calculated from the day of discharge and classified as follows:

1. ≥ 1 year
2. Six months to < 1 year
3. Less than 6 months
4. Lost to follow-up (patients not in touch for 3 months or more)

Some patients were readmitted to treat complications of TBM. Number of deaths during initial or subsequent hospitalization was noted. The readmission rate, surgical complication rate, and number of patients with the neurological sequelae during the follow-up period were also noted.

Statistical analysis. Baseline characteristics of the patients were expressed as mean ± SD/median (interquartile range [IQR])/number (percentage), as applicable. Medians were compared by the Mann–Whitney U test, whereas proportions were compared by the ci-squared test. Univariate and multivariate binary logistic regression analyses were used to determine the predictors favoring the oral group with respect to the overlap group and calculate odds ratio and adjusted odds ratio with corresponding 95% CI. Variables determined after the logistic regression were scored and used to predict the proportion of patients (with different scores) going to either group. A *P*-value < 0.05 was considered as statistically significant. Statistical Package for Social Sciences version 23 (SPSS-23, IBM, Chicago, IL) was used for statistical analysis.

Sample size estimation. We arrived at a sample size of 27 in each group by using the difference in the mean admission days in the overlap and oral groups. However, we found more than 27 eligible patients for either group after a retrospective analysis of 5-year data.

TABLE 1

Comparison of clinical, radiological, and biochemical characteristics

Variable	Overlap group (*n* = 66)	Oral group (*n* = 32)	*P*-value
Age (years)	31.08 ± 16.48	26.56 ± 12.84	0.177
Gender (male)	41 (62.1%)	15 (46.9%)	0.153
Duration of symptoms (days), median (range)	45 (20–90)	45 (15–90)	0.849*
Seizures	30 (45.5%)	19 (60.9%)	0.196
Altered sensorium	40 (60.6%)	10 (31.3%)	**0.006**
Headache	55 (83.3%)	29 (91.3%)	0.539
Vomiting	47 (71.2%)	24 (75%)	0.694
Fever	60 (90.9%)	26 (81.3%)	0.198
Weight loss	14 (21.2%)	12 (37.5%)	0.087
Vision	3 (4.5%)	2 (6.3%)	0.660
Cranial nerve palsy	26 (39.4%)	7 (21.9%)	0.085
Movement disorder	1 (1.5%)	1 (3.1%)	1.0
Focal weakness			0.364
Hemiparesis	12 (18.2%)	3 (9.4%)	**0.033***
Paraparesis	12 (18.2%)	4 (12.5%)	
Monoparesis	2 (3.0%)	0	
Ataxia	4 (6%)	1 (3.1%)	
mRS at admission, median (IQR)	3 (2–4.25)	2 (1–3)	
Stage of tuberculous meningitis			
Stage 1	6 (9.1%)	10 (31.3%)	0.005
Stage 2	20 (30.3%)	12 (37.5%)	
Stage 3	40 (60.6%)	10 (3.3%)	
mRS at discharge, median (IQR)	3 (1–4)	2 (1–3)	0.068*
CSF sugar (mg/dl), median (range)	41 (24–64)	48.5 (33.5–63.25)	0.413*
CSF protein (mg/dl), median (range)	126 (89–195)	133 (62–288.75)	0.853*
CSF cells (/cumm), median(range)	100 (30–270)	95 (29–210)	0.714*
Tuberculoma	35 (53.0%)	27 (84.4%)	**0.003**
Hydrocephalus	18 (27.3%)	8 (25%)	0.246
Basal exudate	17 (25.8%)	20 (62.5%)	**< 0.001**
Optochiasmatic arachnoiditis	4 (6.06%)	0	0.3
Infarcts	23 (34.9%)	6 (18.8%)	0.102

CSF = cerebrospinal fluid; IQR = interquartile range; mRS = modified Rankin scale.
* Mann–Whitney U test and chi-squared test used (significant at *P* < 0.05).

RESULTS

A total of 146 patients received treatment for TBM during the period of study. Thirty-five patients who received oral prednisolone followed by IV dexamethasone and 13 patients who received only oral prednisolone were excluded from the analysis. Finally, 98 patients were included in the study. The overlap group had 66 patients, whereas the oral group had 32 patients (Supplemental Figure 1).

The mean age of the patients was 29.6 ± 15.47 years (males 57.1%). The clinical characteristics of patients are detailed in Table 1. The median IV steroid days were 9 days (IQR of 4–12) in all patients: 2–3.5 days in the oral group and 10–11.5 days in the overlap group. The median steroid days in the patients were less than the recommended IV steroid days, with the difference ranging from 4 to 26 days across three TBM stages (Table 2). The median IV steroid days in the oral group were significantly less than that in the overlap group (Table 3).

We compared the clinical, radiological, and biochemical characteristics between the two groups (Table 1). Binary logistic regression analysis was used to identify the predictors for the oral group (with the overlap group as the reference group). In univariate analysis, we found significant differences in the number of patients with altered sensorium, modified Rankin scale (mRS) score at admission, stage of TBM, and the presence of tuberculoma and basal exudates (*P*-value < 0.05) (Table 4). In multivariate analysis, mRS score at admission

TABLE 2

Intravenous steroid days compared between the overlap group and oral group vs. IV steroid days as recommended among different tuberculous meningitis stages

Tuberculous meningitis stages	Median number of IV steroid days in study groups, median (interquartile range)	Number of IV steroid days as recommended	Difference (%)
	Overlap group (*n* = 66)		
Stage 1	10 (8.25–22.50)	14	4 (28.6%)
Stage 2	10 (7.25–17.75)	28	18 (64.3%)
Stage 3	11.5 (8.25–21.00)	28	16.5 (58.9%)
	Oral group (*n* = 32)		
Stage 1	2 (2–3)	14	12 (85.7%)
Stage 2	3.5 (3–5.75)	28	24.5 (87.5%)
Stage 3	2 (2–4)	28	26 (92.9%)

IV = intravenous.

TABLE 3
Comparison of median number of IV steroid days between the overlap group and oral group

Stage of tuberculous meningitis	IV steroid days, median (interquartile range)		
	Overlap group	Oral group	*P-value
Stage 1	10.0 (8.25–22.25)	2 (2–3)	**< 0.001**
Stage 2	10.0 (7.25–17.75)	3.5 (3–3.75)	**< 0.001**
Stage 3	11.5 (8.25–21.0)	2 (2–4.5)	**< 0.001**

Intravenous = IV.
* Mann–Whitney U test used (significant at $P < 0.05$).

and the presence of tuberculoma and basal exudates were found to be statistically significant ($P < 0.05$) (Table 4). Patients who showed basal exudates and tuberculomas on MRI were 5.42 times and 4.39 times, respectively, more likely to go to the oral group (*P* 0.001 and *P* 0.013, respectively). Patients with higher mRS score at admission were more likely to receive IV–oral steroid overlap (*P* 0.015). The mRS score of ≤ 3.5 had a sensitivity of 75% and a specificity of 47% with an area under the curve (AUC) of 0.63 (0.51–0.75) for going to the oral group. The mRS score of ≤ 3 and the presence of basal exudates and tuberculoma were included in the scoring system to predict direct transfer to the oral group, yielding a total score of 0–5 (based on regression coefficients of the logistic regression model) (Table 5). The prediction model had an AUC of 0.79 (95% CI: 0.69–0.88), with a *P*-value of < 0.001 (Supplemental Figure 2). If we take a cutoff of sum score ≥ 2.5, the sensitivity for going to the oral group will be 87.5% and specificity will be 51.5%. The probability of going to the oral group increased with an increase in the score (Supplemental Figures 3 and 4).

Sixty-four patients had a follow-up for 1 year or more. Twenty-two patients completed a follow-up of 6 months to < 1 year. These two groups constituted 87.8% of the patients in the study. Twelve patients had less than 6 months of follow-up. Eight patients were lost to follow-up at the time of analysis. All eight patients belonged to the "6 months to < 1-year follow-up group." Five patients were in the overlap group, whereas three patients were in the oral group.

There were overall six (6.1%) deaths. The follow-up period and survival analysis have been shown in the Kaplan–Meier plot (Supplemental Figure 5). This was lower than the rates reported by previous studies, including the study by Thwaites et al. Twenty-five (25.5%) patients were readmitted for management of complications or for other reasons during the follow-up period. Neurological sequelae were seen in 48.0% of patients (Supplemental Table 2). Duration of hospital stay was significantly lower in the oral group. The readmission rate, mortality rate, and surgical complication rate were similar in the two groups (Supplemental Table 3).

DISCUSSION

In this study, we found that IV steroid days can be reduced from "Thwaites's protocol" of 14 days in stage 1 and 28 days in stage 2/3 TBM. By reducing the total IV steroid days, total hospitalization days can be reduced without any increase in the mortality rate (Supplemental Table 3).[2–8] In our study, 67.4% patients received an overlap of IV and oral steroids for successful tapering of IV steroids. The overlap of oral steroids with IV dexamethasone worked possibly by covering the critical period required for IV steroids and also by gradually acclimatizing the patients to a lower bioavailability of steroids from oral prednisolone. The early shift from IV to oral steroids helped in delineating a subgroup of patients who required IV steroids for a brief period of up to 3.5 days. After multivariate logistic regression analysis, the patients with tuberculoma and basal exudates had a higher probability for early and direct shift to oral steroids, whereas patients with a higher mRS score at admission had a higher probability for a longer IV steroid course. Patients with a higher mRS score usually represent stage 3 TBM. They are the sickest of TBM patients, and therefore, the results of the logistic regression model appear logical.

The role of steroids in the treatment of TBM is well documented. However, because of the paucity of controlled trials, the dose, formulation, and mode of delivery of steroids are sparingly discussed.[9,10] People have used different formulations and doses of steroids in TBM (K. Prasad, unpublished data).[2,11–14] We used IV dexamethasone and oral prednisolone. We excluded 13 patients who received only oral prednisolone and showed improvement at their first visit to the hospital. This indicates that TBM patients show a variable immunological response to *Mycobacterium tuberculosis* bacilli, and there is a need to determine factors that could facilitate a customized treatment approach, especially for the use of steroids.

TABLE 4
Binary regression analysis of variables achieved after univariate analysis

Variable	Binary logistic regression analysis			
	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*P*-value	Adjusted odds ratio (95% CI)	*P*-value
mRS score at admission	0.72 (0.53–0.97)	0.033	0.64 (0.45–0.92)	**0.015**
Altered sensorium (yes)	0.30 (0.12–0.72)	0.008	–	–
Tuberculoma	4.78 (1.64–13.94)	0.004	4.39 (1.37–14.10)	0.013
Basal exudate	4.80 (1.95–11.86)	0.001	5.42 (1.95–15.12)	0.001
Stage of tuberculous meningitis		0.009	–	–
Stage 1	6.67 (1.96–22.73)	0.002	–	–
Stage 2	2.40 (0.89–6.50)	0.085	–	–
Stage 3	Reference group		–	–

mRS = Modified Rankin scale. Outcome variable (oral vs. overlap), overlap group used as reference category, $P < 0.05$ significant. Receiver operating characteristics curve: mRS score (area under the curve = 0.63, 95% CI: = 50.9–75.0, $P = 0.038$), at mRS score < 3 (sensitivity = 68.8% and specificity = 60.6%).

TABLE 5

Predictive scores for different variables determined after the binary regression analysis

	Category	Score
Modified Rankin scale at admission	≤ 3	1
	> 3	0
Basal exudate	Yes	2
	No	0
Tuberculoma	Yes	2
	No	0

Area under the curve of 0.79 (95% CI: 0.69–0.88) with a *P*-value of < 0.001. If sum score ≥ 2.5, sensitivity is 87.5% and specificity is 51.5%.

The strength of our study is that it provided a novel idea to use steroids in patients with TBM. Our "customized approach" for rapidly tapering IV steroids can be validated in a prospective study. One of the limitations of our study was that it was a retrospective study that relied on the data available from the hospital information system. The mortality data were calculated from the patient deaths that occurred during their initial or subsequent hospital admissions. A small group of eight patients was lost to follow-up. The lost-to-follow-up patients and the patients who have not completed 1 year of follow-up might have led to the underestimation of mortality rate. We had mRS scores of patients on admission and at the time of discharge, but mRS scores at 1 year were missing. Therefore, we could not estimate the disability score at 1 year.

We conclude that the duration of IV steroid use can be reduced in patients with TBM. Tuberculous meningitis patients with tuberculoma and basal exudates and less severe disease (stages 1 and 2) may be the candidates for early oral steroids. Patients with a higher mRS score (mostly stage 3 TBM) may require a longer course of IV dexamethasone. Our proposed predictive model needs to be externally validated. A brief period of overlap of IV and oral steroids may help in improving the acceptance of oral steroids in TBM patients.

Received May 31, 2019. Accepted for publication August 16, 2019.

Published online September 16, 2019.

Note: Supplemental files appear at www.ajtmh.org.

Acknowledgment: The American Society of Tropical Medicine and Hygiene (ASTMH) assisted with publication expenses.

Authors' addresses: Vimal Kumar Paliwal, Animesh Das, and Sucharita Anand, Department of Neurology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, E-mails: dr_vimalkpaliwal@rediffmail.com, animeshdas05@gmail.com, and sucharita.anand@gmail.com. Prabhakar Mishra, Department of Biostatistics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, E-mail: drpmishra@sgpgi.ac.in.

REFERENCES

1. Prasad K, Singh MB, Ryan H, 2016. Corticosteroids for managing tuberculous meningitis. *Cochrane Database Syst Rev 4:* 1–64.
2. Thwaites GE et al., 2004. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N Engl J Med 351:* 1741–1751.
3. Marais S, Thwaites G, Schoeman JF, Torok ME, Misra UK, Prasad K, Donald PR, Wilkinson RJ, Marais BJ, 2010. Tuberculous meningitis: a uniform case definition for use in clinical research. *Lancet Infect Dis 10:* 803–812.
4. Chiang SS, Khan FA, Milstein MB, Tolman AW, Benedetti A, Starke JR, Becerra MC, 2014. Treatment outcomes of childhood tuberculous meningitis: a systematic review and meta-analysis. *Lancet Infect Dis 14:* 947–957.
5. Wang JT, Hung CC, Sheng WH, Wang JY, Chang SC, Luh KT, 2002. Prognosis of tuberculous meningitis in adults in the era of modern antituberculous chemotherapy. *J Microbiol Immunol Infect 35:* 215–222.
6. Hosoglu S et al., 2002. Predictors of outcome in patients with tuberculous meningitis. *Int J Tuberc Lung Dis 6:* 64–70.
7. Karstaedt AS, Valtchanova S, Barriere R, Crewe-Brown HH, 1998. Tuberculous meningitis in South African urban adults. *QJM 91:* 743–747.
8. Lamprecht D, Schoeman J, Donald P, Hartzenberg H, 2001. Ventriculoperitoneal shunting in childhood tuberculous meningitis. *Br J Neurosurg 15:* 119–125.
9. Kalita J, Misra UK, Ranjan P, 2007. Predictors of long-term neurological sequelae of tuberculous meningitis: a multivariate analysis. *Eur J Neurol 14:* 33–37.
10. Sharma SK et al., 2017. Index-TB guidelines: guidelines on extrapulmonary tuberculosis for India. *Indian J Med Res 145:* 448–463.
11. World Health Organization, 2017. *Guidelines for Treatment of Drug-Susceptible Tuberculosis and Patient Care, 2017 Update*. Available at: http://apps.who.int/iris/bitstream/10665/255052/1/9789241550000-eng.pdf?ua=1. Accessed September 17, 2018.
12. Malhotra HS, Garg RK, Singh MK, Agarwal A, Verma R, 2009. Corticosteroids (dexamethasone versus intravenous methylprednisolone) in patients with tuberculous meningitis. *Ann Trop Med Parasitol 103:* 625–634.
13. Chotmongkol V, Jitpimolmard S, Thavornpitak Y, 1996. Corticosteroid in tuberculous meningitis. *J Med Assoc Thai 79:* 83–90.
14. Schoeman JF, Van Zyl LE, Laubscher JA, Donald PR, 1997. Effect of corticosteroids on intracranial pressure, computed tomographic findings, and clinical outcome in young children with tuberculous meningitis. *Pediatrics 99:* 226–231.