

Feasibility and usefulness of tele-follow-up in the patients with tuberculous meningitis

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Background: Tuberculous meningitis (TBM) is the most severe form of tuberculosis and these patients need close follow-up because of a high frequency of complications. The coronavirus disease 2019 pandemic and lockdown resulted in an interruption in physical follow-up. In this situation, tele-follow-up may be helpful. We report the feasibility and usefulness of a telephonic follow-up in patients with TBM.

Methods: Patients with TBM managed by us from January 2017 to March 2020 were included from the TBM registry. Their presenting symptoms, and clinical and investigation findings were noted. We contacted these patients telephonically and their clinical status was obtained using a questionnaire. Based on the telephonic information, outcomes were categorized as death, poor or good. Patients with the new medical problems were advised as to relevant investigations and the reports were obtained through WhatsApp for prescribing treatment.

Results: The telephone numbers of 103 of 144 (71.5%) patients were viable. Twenty-seven (26.2%) patients died, 15 (19.7%) had a poor outcome and 61 (80.2%) had a good outcome. Twenty-five (32.9%) patients had new medical problems: 18 TBM related and 7 TBM unrelated. The medical problems of 23 patients could be managed telephonically and only 3 (4%) patients needed a physical visit. Sixty-five (85.5%) patients happily answered the questionnaire and willing responders needed a treatment modification more frequently than the reluctant responders ($p=0.008$). Patients on active antitubercular treatment needed treatment modification more frequently (80% vs 21.3%).

Conclusions: Tele-follow-up is feasible in 96% of TBM patients and is beneficial, cost effective and overcomes the barrier of distance.

Keywords: tuberculosis, tuberculous meningitis, Smartphone, telecare, infection

Introduction

Tuberculosis (TB) is a global health problem and its annual incidence is 110–165 cases/100 000 population in developing countries.¹ About 10% of TB is extrapulmonary and central nervous system (CNS) TB is the most severe form, resulting in high mortality (20–30%) and morbidity (56.1–78.5%).^{1–3} The disease course in tuberculous meningitis (TBM) following treatment is unpredictable in the initial few months. About two-thirds of TBM patients develop complications during the antitubercular treatment (ATT), including drug-induced hepatitis, hydrocephalus, granuloma, infarction, seizure, visual loss, cerebral salt wasting and syndrome of inappropriate antidiuretic hormone secretion (SIADH).^{4,5} These complications usually occur within a few weeks to 6 months after initiation of treatment.^{6,7} It is not possible to

keep these patients in the hospital for such a long time because of the limited health infrastructure, cost of hospitalisation and work loss of caregivers. In developing countries, repeat follow-up at closer intervals may not be possible and the dropout rate is higher.^{8,9} Moreover, the poor transportation system results in an interruption in follow-up, causing a treatment gap and complications.¹⁰

During the coronavirus disease 2019 (COVID-19) pandemic and lockdown in India, not only the COVID-19 infection resulted in suffering and deaths, but non-COVID patients also faced difficulties in physical consultations with their treating physicians. Many patients with TBM are bedridden and non-communicative, and there is restricted travel across the states. In this situation, tele-follow-up may be helpful in identifying and solving

their problem and recording their outcome. In chronic diseases such as Alzheimer's disease, stroke, epilepsy and renal transplant, telemedicine has emerged as an alternative method of follow-up.^{11,12} There is no study evaluating the feasibility of tele-follow-up in the management of CNS infection, especially in TBM. In this communication we report the feasibility and usefulness of tele-follow-up in a cohort of TBM patients. We also evaluated the variables of those patients needing a change in medication, investigation or readmission.

Methods

This study was conducted in the Department of Neurology of a tertiary care teaching hospital in Lucknow, Uttar Pradesh, India. This hospital caters to patients from adjoining states, including Bihar, Madhya Pradesh, Chhattisgarh, West Bengal and Assam, as well as from the neighbouring country Nepal.

Inclusion criteria

The patients with TBM admitted to the neurology service under two investigators (JK and UKM) from 2017 to 2020 were included. The baseline details were obtained from a prospectively maintained TBM registry. The patients' phone numbers were retrieved from the hospital information source. Patients who died in the hospital were excluded.

Diagnostic criteria

The diagnosis of TBM was based on the clinical history of meningitis illness (fever for >2 weeks, headaches, vomiting), cerebrospinal fluid pleocytosis with elevated protein and computed tomography/magnetic resonance imaging (MRI) findings (exudates, hydrocephalus, granuloma or infraction). The presence of *Mycobacterium tuberculosis* in cerebrospinal fluid culture or smear, positive polymerase chain reaction (PCR) or extra-CNS bacteriologically confirmed TB was considered definite TBM. The absence of bacteriological confirmation was grouped as probable TBM.¹³ The baseline characteristics of the patients, including demographics (age, gender, residence), duration of illness, seizures, altered sensorium and focal neurological deficits were noted.

The severity of TBM

The severity of TBM at admission was graded as per the modified Medical Research Council (MRC) criteria:^{14,15} stage I, meningitis only; stage II, meningitis with a focal deficit or Glasgow Coma Scale (GCS) score of 11–14; stage III, meningitis with a GCS score <11.

Investigations

Blood counts, erythrocyte sedimentation rate in the first hour, haemoglobin, blood glucose, blood urea nitrogen, serum creatinine, sodium, potassium, transaminases, bilirubin, albumin, calcium and alkaline phosphate were measured. Chest radiograph, electrocardiogram and human immunodeficiency virus serology were done. Cranial MRI was done using a 3T MRI machine (GE

Medical System, Wauwatosa, WI, USA). T1, T2, fluid-attenuated inversion recovery, diffusion weighted imaging and T1 contrast images were obtained. The presence of exudate, hydrocephalus, infarction and tuberculoma was noted. Cerebrospinal fluid was analysed for cells, proteins, sugar, *M. tuberculosis* (smear and culture), polymerase chain reaction for *M. tuberculosis* and cryptococcal antigen.

Treatment

A four-drug ATT (rifampicin 10 mg/kg, ~450 mg; isoniazid 5 mg/kg, ~300 mg; ethambutol 15 mg/kg, ~800 mg; pyrazinamide 25 mg/kg, ~1500 mg daily) was prescribed. Prednisolone 40 mg/day was prescribed for 1 month then tapered over the next month. Aspirin 150 mg/day was also prescribed, except to those with coagulopathy, bleeding diathesis or peptic ulcer. Patients with seizures received levetiracetam and/or clobazam and those with hydrocephalus having features of elevated intracranial pressure had undergone ventriculoperitoneal shunt surgery.

Follow-up

We generally practice physical follow-up and TBM patients are advised to return at 1, 3, 6, 12 and 18 months after discharge. During the lockdown, there was no public transport and routine outpatients services were closed; therefore we had to plan for tele-follow-up.

Tele-follow-up

A neurology resident (PCP) and a PhD student (RS) contacted the patients or their relatives telephonically under the supervision of a senior neurologist (JK). A questionnaire was used (Supplementary Table 1). The duration from the initiation of ATT to the telephone call was noted. The patients were asked about the continuation of prescribed drugs at discharge or previous physical follow-up, the occurrence of any complications during the COVID-19 pandemic and accessibility to medical consultation at our institute or a nearby hospital. If they had a medical problem, necessary investigations were advised and the reports were received through WhatsApp. The medical problems were managed by changing or starting new medication if possible. The patients with more severe or complicated problems, such as recurrence of meningitis symptoms, seizure, paralysis or altered sensorium, were advised to attend our hospital. The new motor deficit, movement disorder and outcome measures were confirmed by video call. Pre-recorded videos of seizures or movement disorders were accessed through WhatsApp. The outcome was assessed by the modified Rankin Scale (mRS) score and was categorized as death, poor (mRS >2–5) or good (mRS ≤2). For defining the outcome, the duration from the initiation of ATT to the day of the telephone call was considered.

Statistical analysis

The normalcy of the continuous variable was assessed by the Wilk–Shapiro test. The telephonic response of the patient or caregiver was categorized into willing or reluctant groups. These two groups were compared in terms of age, gender, duration from the ATT to the phone call, sequelae and mRS score using χ^2

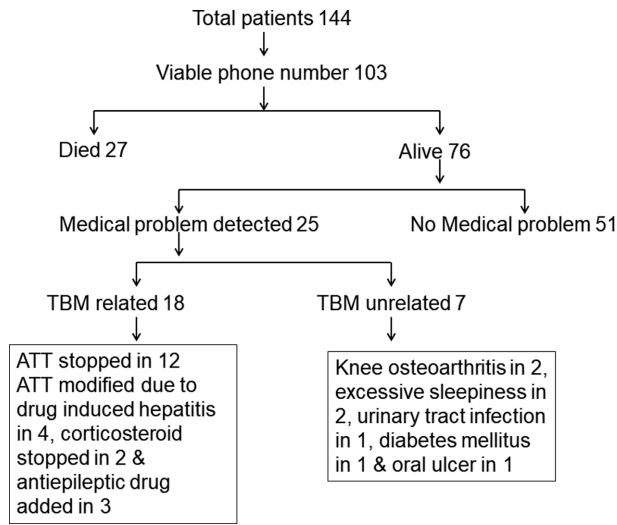


Figure 1. Number of patients in different groups.

for categorical and independent t-test for continuous variables. The Wilcoxon ranked sign test was used for skewed data using Bonferroni correction. The above-mentioned parameters were also compared between the treatment beneficiary (needing dose modification, discontinuation or addition of a new drug) and non-beneficiary (no change in treatment) groups. A variable with a two-tailed exact p-value <0.05 was considered significant. All the statistical analysis was done using the Statistical Package of Social Sciences version 20 software (IBM, Armonk, NY, USA).

Results

A total of 144 patients with TBM were admitted from January 2017 through March 2020. We started telephoning patients or their caregivers 6 months after the declaration of COVID-19 in India. The telephone numbers were not viable in 41 of 144 (28.5%) patients, therefore the information for 103 (71.5%) patients was collected. Thirty-two patients had definite and 71 had probable TBM. All the patients were literate and received a median of 12 y of schooling (range 4–17). Forty patients were urban dwellers and 36 rural. Twenty-nine patients and 47 caregivers responded to the questionnaire. Twenty-seven of 103 (26.2%) patients died a median of 24 months (range 6–36) after discharge from our hospital. The exact cause of death was unknown; however, caretakers stated that it was likely to be TBM related, because they had headaches, vomiting and altered sensorium. They died within 1 week of these symptoms without getting any medical treatment. The details of the patients are presented in Figure 1. During the 6 months of the pandemic, one patient had a mild COVID-19 infection and none died of COVID.

We generally prescribe 18 months of ATT to patients with TBM. Sixty-one patients completed 18 months of ATT at the time of the telephone call and 15 were still on ATT. Of the 76 surviving patients, medical problems were detected in 25 (32.9%): TBM related in 18 and TBM unrelated in 7 (oral ulceration in 1, excessive sleepiness in 2, arthralgia in 2, urinary tract infection in 1 and diabetes in 1). In the TBM-related cases, modification of ATT

Table 1. Clinical details of the patients with TBM (N=144)

Variables	Values
Viable phone number, n (%)	103 (71.5)
Alive, n (%)	76 (73.8)
Died, n (%)	27 (26.2)
Female, n (%)	35 (46.0)
Age (years), mean±SD	34.5±1.2
Follow-up duration (day of ATT to phone call in months), median (range)	24 (6–36)
Response, n (%)	
From patients	29 (38.2)
From caregiver	47 (61.8)
Reason for caregiver response, n (%)	
Paediatric	3 (6.3)
Logistic	42 (89.3)
Aphasic	2 (4.2)
Willing to give information, n (%)	65 (85.6)
Video call, n (%)	3 (3.94)
Treatment modification, n (%)	25 (32.9)
Physical visit to hospital, n (%)	3 (3.9)
Stage of TBM at admission, n (%)	
I	17 (22.3)
II	51 (67.1)
III	8 (10.5)
Abnormal MRI, n (%)	69 (90.8)
Exudate	33 (43.3)
Tuberculoma	48 (63.2)
Infarction	20 (26.3)
Hydrocephalus	18 (23.7)
Neurological sequelae, n (%)	31 (45)
Seizure only	15 (48.4)
Focal deficit only	4 (12.9)
Both seizure and focal deficit	12 (38.7)
Outcome, n (%)	
Death	27 (26.2)
Poor	15 (14.6)
Good	61 (59.2)

SD, standard deviation.

was needed in 12 patients, hepatotoxic drugs (isoniazid, pyrazinamide and rifampicin) were temporally withdrawn in 3 due to drug-induced hepatitis, an antiepileptic drug was added in 3 due to seizure recurrence and prednisolone was discontinued in 2 (Table 1).

Comparison of the willing and reluctant groups

A total of 65 (85.5%) patients or caregivers happily shared their medical information: 26 of 29 (89.6%) patients and 39 of 47 (83%) caregivers (p=0.42). Fifteen (19.7%) patients in the willing group were on ATT. Eleven (14.6%) patients were reluctant to share their information and all had completed 18 months of ATT. All the patients on active ATT were willing to share information, whereas 11 (18%) in the ATT completed arm were reluctant

Table 2. Comparison of various clinical variables between willing and reluctant groups

Parameters	Willing group	Reluctant group	p-Value
Age (years), mean±SD	34.62±16.29	29.82±11.00	0.34
Gender, n			
Male	38	3	0.99
Female	27	8	
Duration of ATT, n (%)			
>18 months	50 (82.0)	11 (18.0)	0.10
≤18 months	15 (100)	0 (0.0)	
Outcome, n (%)			
Good (mRS ≤2)	52 (85.2)	9 (14.8)	0.98
Poor (mRS >2)	13 (86.7)	2 (13.3)	
Treatment modification, n (%)			
Needed	25 (100)	0 (0)	0.008
Not needed	40 (78.43)	11 (21.56)	
Neurological sequelae, n (%)			
Yes	25 (83.3)	5 (16.7)	0.74
No	40 (87.0)	6 (13.0)	

SD, standard deviation.

Table 3. Comparison of patients on ATT (yet to complete 18 months of ATT) with those who completed >18 months of ATT at the time of the telephone call

Parameters	ATT completed group	On ATT group	p-Value
mRS, n (%)			
≤2	48 (78.68)	13 (21.31)	0.72
<2	13 (86.66)	2 (13.33)	
Treatment modification, n (%)			
Yes	13 (52.00)	12 (48.00)	0.001
No	48 (94.1)	3 (5.9)	
Neurological sequelae, n (%)			
Yes	23 (76.7)	7 (23.3)	0.56
No	38 (82.6)	8 (17.4)	

to share information. Those patients needing treatment modification either in ATT or for other medical illnesses were willing (100% vs 0%), whereas 11 of 51 (21.56%) patients not needing treatment modification were reluctant to share information ($p=0.008$). The age, gender, residence, severity of meningitis at admission and neurological sequelae were not related to willingness (Table 2).

Comparison of treatment beneficiary vs non-beneficiary patients

The telephone call resulted in treatment modification in 25 patients: TBM related in 18 and TBM unrelated in 7. The details are presented in Supplementary Table 2. Patients on ATT needed treatment modification more frequently than those who com-

pleted ATT (80.0% vs 21.3%; $p=0.001$). The treatment modification was mainly due to TBM or antitubercular drugs in the ATT-continued group. In the ATT-completed group, medical advice was needed for osteoarthritis, diabetes, oral ulcer, urinary tract infection and seizures. The time from the ATT to the phone call was not related to the disability ($p=0.72$) and neurological deficit ($p=0.56$) but was related to treatment modification (Table 3).

Outcome

At the time of the telephone call, the median follow-up duration was 24 months (range 6–36). Forty-two (40.6%) patients had a poor outcome, 27 (26.2%) of whom died and 15 (19.7%) had a poor (mRS >2–5) recovery. Sixty-one patients (59.2%) had a good (mRS ≤2) outcome. Neurological sequelae in the form of seizures

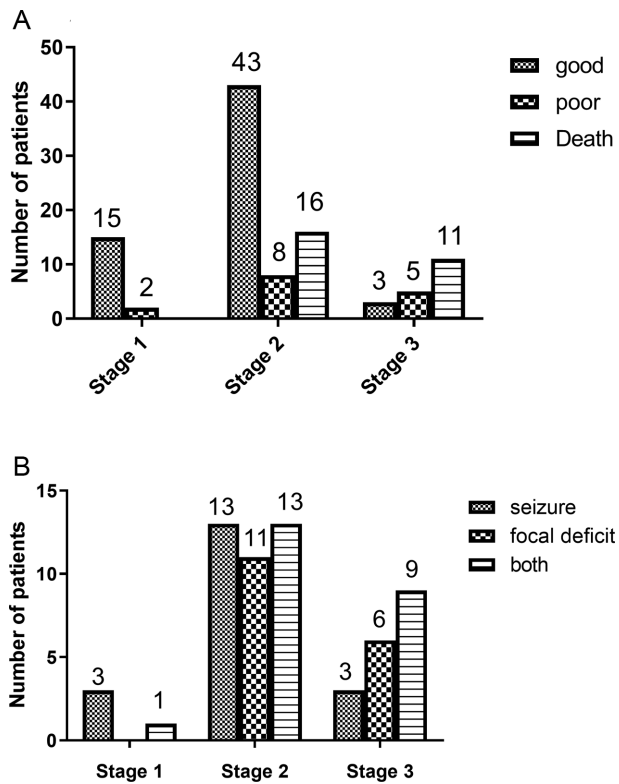


Figure 2. Relationship of stage of meningitis with (A) outcomes and (B) neurological sequelae. Outcomes were related to the stage of meningitis ($p < 0.001$) but neurological sequelae were not related to the stage of meningitis ($p = 0.20$).

were present in 15 (19.7%), a focal deficit in 4 (5.2%) and both in 12 (15.8%) patients. The stage of meningitis was related to outcome ($p < 0.001$) but not to sequelae ($p = 0.20$; Figure 2). The video call was done in three patients and investigations through WhatsApp were accessed in three patients. Three (4%) patients had to visit our hospital: two due to altered sensorium and one due to refractory seizures.

Cost of travel

In this cohort of patients, the distance from the patients' residence to our hospital ranged from 18 to 1400 km. If we consider the cheapest mode of travel (train) for the patient and for one accompanying person, the cost of travel ranged from 100 to 2800 rupees (median 900 rupees). During lockdown, public transportation was not available and the use of private transport would have incurred a many-fold increase in travel costs.

Discussion

This study has revealed the feasibility and usefulness of tele-follow-up of TBM patients after discharge from the hospital. About 33% of patients needed treatment modification and only 4% of patients needed to visit the hospital. All the patients shared the needed information; however, patients having medical problems or receiving ATT were happier to get the

telephone call and shared information more willingly. We used a smartphone for video calls, which has helped in assessing patients in real time, especially those with jaundice, oedema, seizures and movement disorders. The smartphone also helps in the transfer of investigation reports or pre-recorded videos to the treating physician. In our cohort, WhatsApp messages helped to diagnose drug-induced hepatitis, seizure and outcome. Conventional telemedicine needs a large amount of equipment, bandwidth and manpower. Indians are the largest users of smartphones and WhatsApp. There are about 450 million smartphone and 400 million WhatsApp users in India.^{16,17} Smartphones can be used for both synchronous and asynchronous tele-follow-up. In the synchronous teleconference, the patient and physician interact in real time. In asynchronous telecare, information is stored, processed and evaluated later.¹⁸ We have done real-time synchronous tele-follow-up in all patients, and in some patients stored video or investigations were transferred and analysed later; following which necessary treatment modification and advice were given.

The feasibility of telecare has been evaluated in various neurological disorders such as stroke, epilepsy, Parkinson's disease, dementia and other chronic neurological disorders.^{19,20} However, tele-follow-up and telecare have not been applied in patients with CNS infections. CNS infections, including TBM, neurocysticercosis, pyogenic meningitis, scrub typhus, viral encephalitis and fungal infections, are prevalent in developing countries.^{21–23} Patients with severe dengue, scrub typhus encephalitis, cerebral malaria and pyogenic meningitis need hospitalization, and surviving patients usually have a good recovery.^{24,25} On the other hand, 30–50% of patients with acute viral encephalitis have various neurological sequelae, including cognitive impairment, movement disorders, seizures and motor deficits. These patients could be followed up using various telecare modalities.

The role of telemedicine has been evaluated in patients with active pulmonary and extrapulmonary TB. Almost all the studies revealed similar levels of treatment adherence for patients via telemedicine and those examined in person by a public health worker.^{26–29} In Papua New Guinea, a web-based 'store and forward' telemedicine service was used to optimize the treatment of multidrug-resistance TB.³⁰ In a study of patients with active pulmonary TB, videophone technology was used for directly observed therapy (DOT) of 304 treatment doses. It revealed 95% treatment adherence in a cost-effective manner.²⁶ Guo et al.³¹ compared video DOT with DOT in person in 405 TB patients in each arm and reported comparable treatment adherence (96.1% vs 94.6%) and satisfaction. The video DOT group needed a shorter observed time per dose and incurred a lower cost.

Patients with TBM require hospital care at the initial stage for investigations. The patients with hydrocephalous and deteriorating consciousness may require a ventriculoperitoneal shunt. During the initial few months of ATT, TBM patients may develop various complications, including hepatitis, infarction, hydrocephalus, spinal arachnoiditis, paradoxical tuberculoma, cerebral salt wasting and seizures.³² Delayed sequelae (seizure, hydrocephalous and paraparesis), although uncommon, may occur as a result of fibrosis and adhesions.³³ In TBM, seizure as a sequela is five times more frequent in those with seizures in the acute

stage compared with those without.³⁴ We could detect medical problems in 21.3% (13/61) patients who completed 18 months of ATT.

In our cohort, about 30% of patients could not be contacted, as their telephone numbers were not viable. In India, telephonic follow-up studies of neurological patients have reported invalid phone numbers in 36.8% of patients.³⁵ Changing subscriber identity module (SIM) cards is a common practice in developing countries, especially in underprivileged areas. Often these people change SIM cards due to promotion strategies, low cost or extra features.³⁶

Limitations

This study is retrospectively designed due to the needs of the hour—lockdown, closure of outpatient services and limited emergency admission for fear of COVID-19. The data for the patients included herein regarding diagnosis, treatment and clinical parameters were retrieved from a prospectively maintained TBM registry. A future prospective study may be undertaken to compare the efficacy and cost effectiveness of physical follow-up and tele-follow-up.

Conclusions

Telephonic follow-up using a smartphone is feasible in patients with TBM and the majority of their medical problems could be sorted out. This might be a cost- and time-saving method for use in real-time physician–patient interactions.

Authors' contributions: JK was involved in the concept, planning and formulation of the study, data interpretation and finalizing the manuscript. PCP was responsible for the management of patients, data collection and statistical analysis. RS was responsible for data collection and statistical analysis. UKM was responsible for patient management and supervision of the study.

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Data availability: The data are available upon reasonable request from RS and PCP.

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