EFFECTIVENESS OF MOXIFLOXACIN IN THE MANAGEMENT OF TUBERCULOUS MENINGITIS: A PILOT STUDY

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ABSTRACT

Objective: To determine the effectiveness of moxifloxacin as fourth drug in the management of tuberculous meningitis (TBM).

Methodology: This hospital based comparative clinical trial was done as pilot study from January 2016 to December 2017. The study was carried out on 43 patients with TBM. Moxifloxacin based regimen (group I) versus standard treatment for tuberculous meningitis (group II) were compared. Computer software, SPSS version 21.0, was used for data entry and analysis. Statistical significance was considered at p value <0.05.

Results: Out of 43 patients, there were 15 (34.9%) males and 28 (65.1%) females. Age of the patients ranged from 13 to 80 years (mean 31.418 ±18.62 years). Fever, headache, vomiting and altered level of consciousness was present in 38 (88.4%); neck stiffness in 39 (90.69%) and neurological deficit was present in 18 (41.9%) patients. Leptomeningeal enhancement was the most frequent radiological finding found in 13 (30.2%) patients. Overall improvement occured in 38 (88.37%) of patients. In group I, 21/22 (95.45%) patients and in group II, 17/21 (80.95%) patients improved, (p value 0. 158). Till 3rd day of commencement of treatment, 11/21 (52.38%) patients recovered in group I while 02/17 (11.76%) patients recovered in group II.

Conclusion: Moxifloxacin based regimen was associated with an early recovery (within 03 days of commencement of treatment) in a significant number of patients with TBM.

Key Words: Tuberculous meningitis, Treatment regimens, Fluoroquinolones, Moxifloxacin

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INTRODUCTION

Tuberculosis (TB) continues to be a global health issue with 1.5 million deaths annually. It is highly prevalent in third world countries including Pakistan[1].Tuberculous involvement of the central nervous system (CNS) represents about 1% of all new cases annually[2]. Tuberculous meningitis (TBM) is the subset of CNS TB and occurs in 4% cases of CNS TB[3]. It has a poor outcome with significant morbidity (hemiparesis, cranial nerve palsies and persistent vegetative states) and mortality in approximately 50% of its victims[4].

The spectrum of TBM includes meningitis or meningo-encephalitis, hydrocephalus, tuberculomas and cerebral vasculitis[5,6]. The clinical presentation ranges from headache, cranial nerve palsies, seizures to stupor and coma. Neck stiffness is an important clinical clue towards the diagnosis.

Currently, TBM is treated in the line of pulmonary TB with standard first-line drugs (combination of isoniazid, rifampin, pyrazinamide, ethambutol) and corticosteroids are added. A prolonged treatment duration of 9-12 months is recommended due to the serious risk of morbidity and mortality associated with TBM[7]. However, concerns are raised over the lack of evidence supporting the longer treatment duration for TBM[8,9] and whether same anti-TB drugs will be similarly suitable and successful in the treatment of TBM[4]. Replacement of ethambutol by streptomycin is recommended by World Health Organization (WHO) because of the ineffective cerebrospinal fluid (CSF) penetration of ethambutol[7]. Furthermore, ethambutol is not given in obtund-

ed patients and in children as these are unable to report the possible visual complications inherently associated with TBM per se or ethambutol use. On the other hand, streptomycin did not show good CSF penetration in the absence of inflammation[10] and serious adverse events like nephrotoxicity and ototoxicity are associated with it. Ototoxicity may be confused with underlying disease process. Moreover, streptomycin is given through intra-muscular injections which is painful and health care professional is required to inject it and therefore may result in decreased compliance[11]. These side effects of ethambutol or streptomycin are of concern in patients with TBM, as they cannot report their symptoms due to blurred sensorium; and are measurable only in clinically alert and communicating patient.

The newer generation fluoroquinolones, have shown excellent CSF penetration, safety profiles and strong activity against Mycobacterium tuberculosis. For these reasons, fluoroquinolones may be considered to have great potential for incorporation in TBM treatment regimens and good alternatives to ethambutol or streptomycin. Among the fluoroquinolones, moxifloxacin is found to have greatest in vitro and in vivo activity against M. tuberculosis, good penetration into the CSF, is relatively safe and better tolerated[12-14]. We, therefore, used moxifloxacin as fourth drug (replacing ethambutol or streptomycin) in the initial 02 months of intensive phase management of tuberculous meningitis in our study. The purpose of the current research was to determine the effectiveness of moxifloxacin as fourth drug in the management of TBM. It may help in providing the scientific basis and recommendations regarding the alternative regimens for TBM and may help in reducing the optic, otological and neurological disabilities associated with prior regimens of TBM.

METHODOLOGY

This hospital based comparative clinical trial was conducted as pilot study from January 2016 to December 2017. The study was carried out on 43 patients with TBM, who presented to the Department of Medicine, Lady Reading Hospital, Medical Teaching Institution, Peshawar. Patients of either gender, above 12 years of age with clinical, CSF and radiological features suggestive of TBM were included in the study. Exclusion criteria were known hypersensitivity to moxifloxacin; baseline serum alanine amino-transferase (ALT) level more than 05 times the upper limit of normal; pregnancy; failure to obtain CSF for analysis via diagnostic lumbar puncture; evidence of acute bacterial or viral meningitis; and those unwilling to participate or give informed consent. These factors would have influenced the study results and might lead to confounding and bias in the study. As this was a pilot study, so sample size was not calculated but 30 patients were considered as minimum for the study. The study participants (n=43) were randomized by lottery/draw method to either group I (moxifloxacin based regimen;n=22) or group II (standard treatment regimen; n=21). Patients were selected by non-probability convenient sampling method.

Operational diagnosis of TBM was based on the presence of a meningeal syndrome and typical CSF picture. It was supported by the neuro-imaging findings. Meningeal syndrome (meningitis or meningo-encephalitis) was defined as onset of illness of more than one week; low grade fever, headache, vomiting, confusion, seizures, altered level of consciousness, neck stiffness, hemiparesis and cranial nerve palsies. Typical CSF picture for TBM was defined as lymphocytic pleocytosis (increased number of cells which are predominantly lymphocytes), elevated protein and low CSF glucose concentration. Supportive findings on contrast enhanced neuro-imaging i.e. cerebral computed tomography (CT brain) and cerebral magnetic resonance imaging (MRI brain) include: leptomeningeal enhancement, tuberculomas, hydrocephalus, vasculitis and cerebral infarctions.

Ethical approval for the research was obtained from the Institutional Review Board (IRB) of the hospital. The purpose of our research was discussed with the patients or their close relatives. They were briefed that their rights will be taken into consideration and the information obtained will be solely used for research purpose. Confidentiality was assured and then an informed written consent in Urdu language was taken from the patients or their close relatives depending on the level of consciousness of the patients and the ability to give consent.

Patients meeting the inclusion criteria were admitted through the Emergency Department to the Medical Units of Lady Reading Hospital, Medical Teaching Institution, Peshawar. All patients were assessed clinically. A structured questionnaire covering demographics (age, sex, address, marital status, occupation, socioeconomic status and past or family history of tuberculosis) was utilized. They were thoroughly asked about pertinent presenting features (low grade fever, headache, vomiting, confusion, seizures, altered level of consciousness) and duration of illness. Focused clinical examination for presence of neurological deficit (neck stiffness, hemiparesis and cranial nerve palsies) was performed. Level of consciousness was assessed by Glasgow Coma Scale (GCS). Ocular examination was performed for pupillary changes and papilledema. The neurological status of patients with TBM was graded according to the modified British Medical Research Council (BMRC) grading system as grade 1 (GCS score 15 but with no focal neurological signs); grade 2 (GCS score 15 and presence of focal neurological signs or GCS score 11–14) and grade 3 (GCS score <10)[15].

Typical CSF picture for TBM was defined as lymphocytic pleocytosis, elevated protein and low CSF glucose concentration. Supportive findings on contrast enhanced neuro-imaging i.e. cerebral computed tomography (CT brain) and cerebral magnetic resonance imaging (MRI brain) include: leptomeningeal enhancement, tuberculomas, hydrocephalus, vasculitis and cerebral infarctions. Lumbar puncture was performed for CSF examination and analysis. Naked eye examination of CSF sample was done for appearance and any web formation. Opening pressure was measured at bedside. The collected CSF samples were then sent to the hospital lab for cytology, chemistry and staining (Gram, ZN staining). Contrast-enhanced neuro-imaging (CT scan and/or MRI brain) were performed for the diagnosis and assessment of complications of TBM (lepto-meningeal enhancement, hydrocephalus, tuberculomas or evidence of cerebral vasculitis/infarcts). Relevant investigations including complete blood count, blood glucose level, serum ALT, chest x-ray and 12-lead electrocardiogram (ECG), were carried out at Lady Reading Hos¬pital, Peshawar.

We compared moxifloxacin based regimen (combination of isoniazid, rifampin, pyrazinamide, moxifloxacin) with standard treatment (combination of isoniazid, rifampin, pyrazinamide, ethambutol) for TBM. Cortico-steroid (dexamethasone) was given to both groups accordingly. All anti-TB drugs were given in standard doses and moxifloxacin was given in 400 mg daily dose. All oral drugs were given once daily before breakfast. Those who could not swallow, drugs were given per nasogastric (NG) tube. Adherence was directly monitored by the researcher. Patients were observed and the effectiveness was calculated in terms of symptoms resolution, improvement in GCS score or neurological deficit. In selected cases neuro-imaging was repeated to look for reduction in lepto-meningeal enhancement or in number / size of tuberculomas and decrease in hydrocephalus. The day of recovery was recorded in patients in both groups. The collected data were entered into a predesigned proforma.

Computer software, SPSS version 21.0, was used for data analysis. For numerical variables (age, GCS score and day of recovery), mean ±SD was calculated; while for categorical variables (gender, clinical presentation and imaging features), frequencies and percentages were calculated. Improvement was compared between the two groups using chi square test. Statistical significance was considered at p value ≤0.05. All results were presented as tables.

RESULTS

There were 43 patients of TBM in the present study. Among them, there were 15 (34.9%) males and 28 (65.1%) females. Male to female ratio was 1:1.86.

Age of the patients ranged from 13 to 80 years with mean age of 31.418 ±18.62 years. It was more common in younger age group; 48.8% in <20 years of age and 76.7% in <40 years of age. Fever, headache, vomiting and altered level of consciousness was present in 38 (88.4%) while hemiparesis, aphasia and fits in 05 (11.6%) patients. Glasgow Coma Scale (GCS) score ranged from 3 to 15 with mean of 11. 63 ±3.23. Neck stiffness was present in 39 (90.69%) of patients. Neurological deficit was present in 18 (41.9%) patients as shown in Table 1.

Analysis of CSF showed increased white cell count (median 42 cells per µL, interquartile range IQR, 24–80), predominantly lymphocytic (median 88%, IQR 76–97), raised protein concentration (98 mg/L, IQR 72–156) and low glucose (median 34 mg/L, IQR 25-49). Leptomeningeal enhancement was the most frequent radiological finding in patients with TBM (30.2%). Relative frequencies of other radiological findings are shown in Table 2. Based on the neurological status of patients according to modified BMRC grading system, there were 08 (18.6%) patients in grade 1, 20 (46.5%) in grade 2 and 15 (34.9%) patients in grade 3. Cross tabulation of TBM grade and drug regimen is shown in Table 3.

Overall improvement was present in 38 (88.37%) of patients. In group I, 21/22 (95.45%) patients and in group II 17/21 (80.95%) patients improved, (p value 0. 158), as shown in Table 4. Days on which Improvement was observed, ranged from 1 to 8 days with mean of 4.90 ±2.24. Till 3rd day of commencement of treatment, 11/21 (52.38%) patients recovered in group I while 02/17 (11.76%) patients recovered in group II, as shown in Table 5.

DISCUSSION

Tuberculous meningitis (TBM) is the most severe and challenging of all forms of TB. It is reported that young adults are more commonly affected with TBM[16]. Similarly, 48.8% of our patients were less than 20 years of age and 76.7% were less than 40 years of age.

In our study, fever, headache, vomiting and altered level of consciousness was present in 88.4% of patients while hemiparesis, aphasia and fits occurred in 11.6% patients. Mean GCS score was 11.63 ±3.23, neck stiffness was present in 90.69% and neurological deficit in 41.9% of patients. These findings were comparable to the study by Ruslami et al[10] who reported headache in 97%, decreased consciousness 78% and fits in 7% of patients while a median GCS of 13 was observed and neck stiffness was noted in 95%, motor deficit (hemiparesis) in 50% and cranial nerve palsies were found in 38% of their patients.

Leptomeningeal enhancement was the most frequent radiological finding in our patients (30.2%), followed by tuberculomas (18.6%) and vasculitic infarcts

Table 1: Neurological deficit in patients with TBM (n=43)

Neurological Deficit	Frequency	Percentage
Hemiparesis	4	9.3
Cranial Nerve Palsies	5	11.6
Papilloedema	7	16.3
Ataxia	2	4.7
No Neurological Deficit	25	58.1
Total	43	100

Table 2: Radiological findings in patients with TBM (n=43)

Radiological findings	Frequency	Percentage
Leptomeningeal Enhancement Only	13	30.2
Hydrocephalus	5	11.6
Tuberculomas	8	18.6
Vasculitic Infarct	7	16.3
Leptomeningeal Enhancement + Hydrocephalus + Infarct	2	4.7
Tuberculomas + Infarcts	1	2.3
Normal Imaging	7	16.3
Total	43	100

Table 3: Neurological status of TBM patients in the 02 treatment groups (n=43)

BMRC Grade of Neurological Status	Drug Regimen		Total
	Moxifloxacin Based Regimen (Group I)	Standard Treatment Regimen (Group II)	
Grade 1	3 (6.98%)	5 (11.62%)	08 (18.6%)
Grade 2	8 (18.60%)	12 (27.90%)	20 (46.5%)
Grade 3	11 (25.58%)	4 (9.30%)	15 (34.9%)
Total	22 (51.16%)	21 (48.84%)	43 (100%)

Table 4: Improvement of patients in the 02 treatment groups (n=43)

Improvement	Drug Regimen		Total	P value
	Moxifloxacin Based Regimen (Group I)	Standard Treatment Regimen (Group II)		
Yes	21 (48.84%)	17 (39.53%)	38 (88.37%)	0.138
No	1 (02.32%)	4 (9.30%)	5 (11.62%)	
Total	22 (51.16%)	21 (48.84%)	43 (100%)	

Table 5: Recovery day in both groups (n=38

Neurological Deficit	Drug Regimen	
	Moxifloxacin Based Regimen (Group I)	Standard Treatment Regimen (Group II)
3rd Day	11 (52.38%)	02 (11.76%)
5th Day	16 (76.19%)	12 (70.58%)
7th Day	21 (100%)	16 (94.11%)

(16.3%). In 16.3% of cases the neuro-imaging was normal in our study. Wassay et al[17] reported tuberculomas in 50% and infarcts in 25% of patients. Neuro imaging may demonstrate different types of lesions ranging from leptomeningeal enhancement to development of new infarcts or tuberculomas in more than 50% of cases. The presence of hydrocephalus, infarction, tuberculomas and advanced age are associated with poor prognosis. Delay in the diagnosis of TBM and the failure to initiate therapy prior to the onset of coma are considered to be the strongest predictors of mortality in TBM[18].

In the present study, improvement was shown in 95.45% patients in group I and 80.95% patients in group II; with a p value 0. 158. The difference was statistically not significant. One reason might be the presence of more severely affected patients with neurological status of grade 3 according to modified BMRC grading system in the moxifloxacin based regimen as compared to the standard treatment regimen i.e. 11 (25.58%) Vs. 04 (9.30%) patients respectively. Importantly, moxifloxacin based regimen was associated with an early recovery in a significant number of patients with TBM as compared to the conventional regimen (52.38% Vs. 11.76%, within 03 days) and (100% Vs. 94.11%, within 07 days of commencement of treatment) respectively.

Currently, the model of pulmonary TB treatment is followed for treating patients with TBM and optimal treatment for TBM has not been well established. Modifications in TBM regimens are therefore much needed either in the form of shortened treatment duration or changes in drugs for the initial intensive phase[19,20]. In this regard, one possible approach is to use more effective and well tolerated anti-tuberculous drugs like fluroquinolones. Although phase II trials having fluroquinolones as first-line agents showed mixed results but three studies in which ethambutol was replaced by moxifloxacin reported increased number of early sputum negativity for tubercle bacilli[21]. Similarly, Fouad et al showed that replacing ethambutol with moxifloxacin 400 mg daily was well tolerated[22]. Moxifloxacin is a promising drug and has a good CSF penetration in patients with TBM[23,24]. Animal data regarding CSF penetration of moxifloxacin showed that in the absence of meningitis it has CSF/plasma ratio of 23-50% which increased to 50-78% in the presence of inflamed meninges[25,26]. The in vitro activity was also greatest for moxifloxacin, having an MIC(90) of 1 mg/[27,28].

The in vivo efficacy of moxifloxacin against Mycobacterium tuberculosis can be best shown by AUC/MIC ratio[29]. The highest bactericidal effect with a reduced probability of resistance to fluoroquinolones against various bacteria occurs at Cmax/MIC ratios of >8-10 and AUC_{24}/MIC ratios of >100-125 (where Cmax =peak serum concentration, AUC_{24} =24-hour area-under-the-curve and MIC =minimum inhibitory concentration). Based on these parameters, moxifloxacin was considered as the most active fluoroquinolone against tuberculosis at the usual recommended dose of 400 mg daily[30]. However, interactions with other drugs may alter its pharmacokinetic properties[31,32]. Rifampicin if given together with moxifloxacin may lead to 31% decreased plasma concentrations of moxifloxacin. However, the relevance of this interaction in clinical practice is unclear[33], because another research showed that increasing the dose of rifampicin and moxifloxacin were not associated with increased toxicity[34].

In an Indonesian randomized trial, higher intravenous dose of rifampicin in combination with moxifloxacin was used. More than 50% reduction in mortality was reported[10]. They argued that increasing the dose leads to higher availability of rifampicin in blood and CSF by a factor of 3 with resultant increased therapeutic response[35]. On the other hand, a trial in Vietnam compared the standard regimen for TBM with an intensified treatment regimen comprising of higher dose rifampicin and levofloxacin in adult patients with TBM. It was found that the latter regimen was not associated with improved survival or other treatment benefits[36]. However, it was suggested that the lack of therapeutic benefits may be due to the "not high enough" chosen dose of rifampicin. Moreover, it was given orally and not intravenously, as in the study by Ruslami et al[10]. In the study by Thwaites et al[38], fluoroquinolones were found to add anti-TB activity to the existing standard treatment regimen. However, it was stressed that these need to be instituted early in the management of TBM for improved outcomes.

LIMITATIONS

Our study has several limitations. This study was conducted in a single center. It is essential for better policy making to observe the data from multiple centers with larger samples and for a longer time period. Moxifloxacin exhibits extensive inter-individual pharmacokinetic variability. Moreover, rifampicin may have interaction with moxifloxacin and thus higher dose of moxifloxacin may be needed which was not used in the current study. Serial lumbar punctures for cerebrospinal fluid analysis and repeat neuroimaging were not done, so biochemical and radiological response could not be documented.

CONCLUSION

There was no statistically significant difference between the moxifloxacin based regimen and conventional regimen regarding improvement in patients with TBM. However, moxifloxacin based regimen was associated with an early recovery (within 03 days of commencement of treatment) in a significant number of patients with TBM.

RECOMMENDATIONS

Moxifloxacin can be considered as a valuable addition to the existing therapeutic armamentarium of TBM management. It, therefore, can be considered as an attractive alternative option in TBM treatment. However, further research and larger scale studies are needed to devise optimum regimens against M. tuberculosis.

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CONTRIBUTORS

RM conceived the idea, planned the study, and drafted the manuscript. ZA and MARA helped acquisition of data and did statistical analysis. MA, AS, SH and EA helped acquisition of data. IA critically revised the manuscript and supervised the study. All authors contributed significantly to the submitted manuscript.