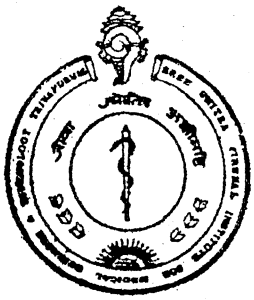


# SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY

THIRUVANANTHAPURAM - 695 011

# PROJECT REPORT

| | | |
|---|---|---|
| NAME | : | DR.ATRI CHAKRABORTTY |
| PROGRAMME | : | D.M. Neurology |
| MONTH & YEAR OF SUBMISSION | : | NOVEMBER 1998 |

SREE CHITHRA THIRUNAL INSTITUTE FOR
MEDICAL SCIENCES & TECHNOLOGY

# SHORT COURSE CHEMOTHERAPY IN TUBERCULAR MENINGITIS

ATRI CHAKRABORTTY

# PROJECT REPORT DONE

**TITLE**

## SHORT COURSE CHEMOTHERAPY IN TUBERCULAR MENINGITIS


NAME : **DR. ATRI CHAKRABORTTY**

PROGRAMME : **D.M. NEUROLOGY**


MONTH & YEAR OF SUBMISSION : **NOVEMBER 1998**


SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY TRIVANDRUM 695 011


| | |
|---|---|
| Name | |
| Page | of |
| Date | |
| | |

# CERTIFICATE

I, Dr. ATRI CHAKRABORTTY .....hereby declare that I have actually performed all the procedures listed/carried out the project under report.

Signature.....

Place : **Trivandrum**

Date : 12th Nov '98

Name in capital letters

ATRI CHAKRABORTTY

Forwarded. He has carried out the project under report.

Signature
Head of the Department

| | | |
|---|---|---|
| SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY TRIVANDRUM 695 011 | Name | |
| | Page | of |
| | Date | |
| | | |

# PROJECT REPORT DONE

**TITLE**

## SHORT COURSE CHEMOTHERAPY IN TUBERCULAR MENINGITIS


NAME : **DR. ATRI CHAKRABORTTY**

PROGRAMME : **D.M. NEUROLOGY**


MONTH & YEAR OF SUBMISSION : **NOVEMBER 1998**


SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY TRIVANDRUM 695 011


| | |
|---|---|
| Name | |
| Page | of |
| Date | |
| | |

# ACKNOWLEDGEMENT

*I take this opprtunity to sincerely thank* ***Dr. Asha Kishore****, Associate Professor, Dept. of Neurology who has helped and guided me at every step of this endeavour always goading me on to do my best. Her strife for perfection is unmatched.*

*I thank the Director of the Institute* ***Prof. K. Mohandas,*** *for giving me the opportunity to do this work.*

*I thank* ***Prof. K. Radhakrishnan,*** *HOD, Dept. of Neurology without whose unfailing support this project would not be possible.*

*I thank* ***Dr. Sankara Sarma****, Assistant Professor, Achutha Menon Centre for Health Sciences studies for helping me with the statistical analysis the backbone of any comparitive study.*

*I sincerely acknowledge the help extended to me by* ***Mr. Rajesh,*** *Neurotechnician, Dept. of Neurology for typing out large sections of the manuscript.*

*Finally I thank my wife Topoti for aiding me throughout this project and without whose help this would never have been completed in time.*

*ATRI CHAKRABORTTY*

# CONTENTS

# *Introduction*

Meningitis is a dreaded complication of TB. It is a devastating illness in terms of mortality and morbidity and can produce a wide range of permanent neurological sequelae. Inorder to minimize both mortality and morbidity, treatment should be timely, vigorous and complete.

With the introduction of streptomycin in the 1940's and INH in the 1950's and the recent addition of other drugs, we have sufficient mean to eradicate the TB bacillus. Although many specific anti TB drugs are now available, the main drawback to adequate and effective therapy is the length of treatment that is required. RFN and INH have been used successfully against pulmonary TB in short course chemotherapy. Although various combination of drugs have been effective in short course chemotherapy for pulmonary TB (6 months) sufficient definite data is not available with regard to its efficacy in TBM.[1]

The advantages of short course chemotherapy are the better compliance to $R_x$ and the reduction to drug induced side effect much a shorter duration.

Nevertheless there is no consensus regarding the number of drugs to be administered, the type of drugs and the duration for which the drugs have to be administered. The short course $R_x$ the drug duration has ranged from 6 months to 1 year. There are advocates for each subgroup.[2,3,4] Furthermore direct comparison with the time tested conventional chemotherapy regimens is also difficult as most studies of short course chemotherapy have small patient populations. This underscores the need for prospective studies employing large patient population and comparing short course chemotherapy with conventional chemotherapy.

# *Aims and Objectives*

1. To test the efficacy of short course anti tuberculosis treatment in TBM.

2. To compare the outcome of short course $R_x$ with the data of matched group of controls ($R_x$ with 4 drugs, INH, RFN, PZA x 2 mth 2 drugs INH, RFN x 16 mth).

# *Materials and Methods*

The study period extended from June 1994 to May 1995.

All consecutive cases both pediatric and adult suspected to have TBM on the basis of symptoms and signs of meningitis > 2 weeks, CSF pleocytosis, CSF glychachia and exclusion of other causes such as fungal, bacterial, carcinomalous and spirochaetal, who were admitted in the Dept. of Neurology at Sree Chitra Thirunal Institute for Medical Sciences and Technology were selected for the short course chemotherapy study.

All patients at admission were graded according to the BMRC grading after detailed neurological examination.[5,6]

**Stage I** : No definite neurological symptoms on admission or in the history before admission with or without meningismus.

**Stage II** : Signs of meningeal irritation with or without slight clouding of consciousness, with focal neurological signs such as cranial nerve palsies and or hemiparesis.

**State III** : Severe clouding of consciousness or delirium, or convulsions and serious neurological signs such as hemiplegia, paraplegia or involuntary movements.

**Diagnosis was established by**

1. History and clinical examination.
2. Analysis of CSF - cell count / differential count.
   - biochemical analysis

- staining for AFB
- culture for AFB in LJ medium
- immunological study by ELISA technique

3. Bacteriological analysis of sputum and gastric aspirate
4. Chest X-ray
5. Mantoux test : Test was rated as positive if necrotic or > 15 mm is size.
6. CT scan brain : Plain and contrast.

CSF study was repeated at 10 days, 30 days, 60 days, 90 days and 270 days after initiation of anti TB drugs. CSF was planed to be repeated if abnormal at 9 months.

2 categories of diagnosis were established for TBM.

a. Definite : CSF smear / culture +ve for AEB
b. Probable
   i. AFB smear / culture from extraneural tissue (+) OR
   ii. ELISA (+) for TB antibody OR
   iii. i or ii and one of the following : Chest X-ray positive for TB, Mx positive, history of contact with TB, CT scan showing basal exudates, hydrocephalus or arteritis.

As soon as a diagnosis of TBM was made all patients were treated with

1. INH (5mg/kg)
2. PZA (20-30mg/kg)
3. RFM (600mg if > 45kg, 450mg if < 45mg)
4. SM (750-1000mg)

For 2 months, followed by INH and RFM for 7 months in the same doses Pyridoxine 40 mg daily was given throughout the course of chemotherapy.

Prednisolone (1mg/kg) was given for 3 weeks and then tampered and stopped by 3 months, for patients with hydrocephalus, arteritis, spinal and optochiasmatic meningitis and impairment of consciousness.

Hepatic enzymes (SGOT, SGPT), serum bilirubin, alkaline phosphatase and uric acid along with ESR and serum electrolytes were monitored weekly for the first one month and thereafter once a month. Drugs were not discontinued for mild and transient rise in hepatic enzymes which is known to occur during treatment.

All patients were followed up at monthly interval till 9 months course was completed and thereafter every 3 months for 1 year.

Patient were discharged 2 weeks after staring Rx or after a 2nd e.sf, study, unless complications warranted more prolonged hospitalisation.

At the time discharge category of outcome was determined. This was reappeared during follow-up at 6 months, 9 months, 1 year and 24 months after starting treatment.

Category of outcome[7]

| | Category | Description |
|---|---|---|
| 1. | Normal | |
| 2. | Slight sequelae, slight mental impairment, well established physical deformity, capable of leading relative autonomous life with assistance? | |
| 3. | | |
| 4. | Severe sequelac, severe mental impairment or having severe physical deformity, who are totally dependent. | |
| 5. | Died | |

Patients who for some reasons did not have a follow up according to the protocol were contracted by post at the end of their 9 months course or thereafter and the category outcome was assessed after clinical examination.

Controls were an equal number of patients selected randomly from the hospital records, of SCTIMST who underwent the conventional 18 months course of chemotherapy.

Their outcome category was evaluated on the same scale and at the same periodic intervals as the cohort group from the files of the patient which contained their follow-up data.

# *Review of Literature*

Tuberculosis continues to be a major health problem in all the developing countries. In industrialized nations there has been a recent resurgence of tuberculosis due to the human immune deficiency (HIV) epidemic, immigration from developing countries, poverty and homelessness.[8,9] The incidence of tuberculosis varies from 9 cases per 100,000 per year in the United States to 110 to 165 cases per 100,000 population in the developing regions of Asia and Africa.[10] According to World Bank report there are more than 7 million newly diagnosed cases of tuberculosis and more than 2.5 million deaths due to tuberculosis annually in developing countries.[11] Tuberculosis accounts for 26% of preventable deaths among persons in the 15-59 years age group in developing nations.[12]

Indian investigators have contributed a great deal in understanding the pathogenesis, pathology, diagnosis and treatment of neurological tuberculosis. The last two decades have witnessed major changes in several aspects of neurological tuberculosis. These include re-emergence of tuberculosis as a significant health problem even in industrialized nations largely due to the HIV epidemic; change in the clinical picture of neurological tuberculosis with an increasing number of atypical cases; more widespread availability and utilization of modern neuroimaging techniques facilitating diagnosis, early detection of complications and follow up; introduction of more sensitive and specific diagnosis methods such as polymerase chain reaction (PCR); trial of short courses of chemotherapy; and an alarming increase in the number of patients with multidrug-resistant tuberculosis.

Tuberculous meningitis (TBM), which accounts for 70-80% of cases of neurological tuberculosis, is still an important health problem in developing countries. In spite of its common occurrence, extensive research and widespread public awareness, there is often a delay in the diagnosis and appropriate therapy of TBM. This is unfortunate as the promptness with which antituberculous treatment (ATT) is initiated is the most important physician-controlled factor influencing prospects for recovery without serious neurological sequelae.

The majority of cases of TBM are due to the human type of tubercle bacilli (Mycobacterium tuberculosis var hominis). Isolated cases of TBM caused by bovine, avian and atypical mycobacteria have been documented.

Central nervous system (CNS) tuberculosis is invariably secondary to tuberculosis elsewhere in the body. It is generally believed that the critical event in the development of meningitis is rupture of a subependymally located tubercle (the so called Rich focus) resulting in delivery of infectious material into the subarachnoid space. In the preallergic bacillemic phase of primary lung infection, metastatic foci can get established in any organ, which can become active after a variable period of clinical latency. Whether the critical subependymal tubercle develops during primary hematogenous dissemination or due to secondary shematogenous spread from an area of extranervous system chronic organ tuberculosis is a matter of dispute.

Conditions such as intercurrent viral infections, advanced age, malnutrition, alcoholism, use of corticosteroids and HIV infection may compromise cellular immunity of the host leading to reactivation of a latent infection. However, a majority of cased of TBM occur in the absence of any clinically demonstrable extracranial infection or overt disturbance in host immune function.

## CLINICAL FEATURES

In developing countries, TBM is still a disease of childhood with the highest occurrence in the first three years of life.[13] A lowering of general resistance due to intercurrent bacterial or viral infection may be elicited. The disease usually evolves gradually over 2 - 6 weeks. However, acute onset of illness can occur in 50% of children, but only in 14% of adults. In the prodromal phase, usually lasting 2 - 3 weeks there may be a history of vague ill health, apathy, irritability, anorexia and behavioural changes. With the onset of meningitis, headache and vomiting becomes troublesome and the fever rises. Focal neurological deficit and features of raised intracranial pressure may precede signs of meningeal irritation. Convulsions, focal or generalized, are encountered in 20 - 30% of patients sometime during the course of illness. Cranial nerve palsies can occur in 20 - 30% of patients, the 6th nerve involvement being the commonest.[13,14]

Complete or partial loss of vision is a major complication of the disease. Exudates around the optic chiasma, arteritis, compression of the anterior visual pathways due to hydrocephalus or tuberculoma, and ethambutol toxicity may contribute to the visual impairment. The frequency of optic nerve involvement in clinical reports vary from 4 to 35%. Visual evoked potential testing have shown disturbance in over 50% of patients examined in the acute stage of the disease.[13,14]

In untreated cases, progressive deterioration in consciousness, pupillary abnormalities and pyramidal signs may be seen due to increasing hydrocephalus and tentorial herniation. The terminal illness is characterised by deep coma and decerebrate or decorticate posturing. Without treatment, death usually occurs in 5 to 8 weeks.

According to the severity of the illness, patients with TBM can be categories into 3 or 4 clinical stages. The Medical Research Council,[15] and Kennedy and Fallon[16] systems stage the patients into 3 categories : stage 1, patients are conscious and oriented with or without signs of meningeal irritation, but no focal neurological deficit; stage 2, patients with altered sensorium or focal deficits; stage 3, comatose and dense deficits. The clinical staging helps to optimize therapy (eg. to add dexamethasone to ATT or not) and to predict the prognosis. The prognosis of TBM is determined by the clinical stage at the time of therapy is initiated.

During the last 2 decades, the picture of TBM has changed in developed countries with an increasing number of atypical cases. A typical presentations of TBM include acute meningitic syndrome simulating pyogenic meningitis, progressive dementia, status epilepticus, psychosis, stroke syndrome, locked-in-state, trigeminal neuralgia, infantile spasm and movement disorders. The factors responsible for this changing pattern include delay in the age of onset of primary infection, immunization, problems related to immigrant populations and HIV infection.[17,18]

## DIAGNOSIS OF TUBERCULOUS MENINGITIS

TBM has to be differentiated from other causes of subacute and chronic meningitis. Early and accurate diagnosis of TBM can substantially reduce the morbidity and mortality, especially in children. However, the diagnosis of TBM is fraught with difficulties because demonstration of bacteria in CSF has a poor yield and is time consuming. TBM is diagnosed based on neurological symptoms, signs and CSF findings. Supporting features include radiological evidence from CT or MRI such as basal exudates, hydrocephalus, infarcts, tuberculomas and gyral enhancement; evidence of tuberculosis outside the CNS, with appropriate microbiological, radiological of histopathologic proof; a positive Mantoux test, if

previous subclinical or BCG vaccination have been excluded; significant contact with infectious tuberculosis; and response to ATT with resolution of symptoms and signs of TBM.

## INVESTIGATIONS

Routine laboratory studies provide very little clues to the diagnosis of TBM. Elevated ESR, anaemia and lymphocytosis are not seen in the majority.

## RADIOLOGICAL STUDIES

The chest radiographs in adult patients reveals abnormalities consistent with pulmonary tuberculosis in 25 to 50% of patients with TBM, while they occur in 50 to 90% of children seen in western countries.[19]

CT or MRI of brain may reveal thickening and enhancement of basal meninges, hydrocephalus, infraction, edema (often periventricular) and mass lesions due to associated tuberculoma or tuberculous abscess.[20] Hydrocephalus is the single most common abnormality and is reported in 50 to 80% of cases. The degree of hydrocephalus generally correlates with the duration of disease. The next common findings is enhancement of the basal meninges (60%) followed by cerebral infarction (28%), most frequently in the middle cerebral artery territory. Bhargava et al. demonstrated hydrocephalus on CT in 83%, cerebral infarct in 28% and tuberculoma in 10% of patients with TBM. Serial CT scan are very helpful in assessing the course of tuberculomas and hydrocephalus. Gadolinium enhanced MRI is superior to CT scan in the detection of basal meningeal enhancement and small tuberculomas.[20]

## MANTOUX TEST

Skin testing for delayed hypersensitivity to M.tuberculosis with purified protein derivative (PPD) has been reported to be positive in 40 - 65% of adults with TBM

and in 85 - 90% of children in western studies.[21] PPD lacks specificity in developing countries because of the possibility of previous sensitization of the individual to environmental mycobacteria and BCG vaccination.

## CSF STUDY

### Cytology and biochemistry

The typical CSF picture TBM is a clear fluid with moderately raised cells and protein and low glucose. However, these characteristics are shared by other forms of chronic meningitis and partially treated pyogenic meningitis. In TBM, the leucocyte count is usually between 100 - 500 cells/dl, but rarely can exceed 1000 cells/dl. Median leucocyte counts in various reports range from 63 to 283 cells/dl. The predominant cell type is lymphocytes, although in the acute stages a polymorphnuclear response is not unusual. This response is transient and is replaced by lymphocytic response in the course of days to weeks. Occasionally the cell count may be normal. Rarely the CSF may be hemorrhagic because of fibrinoid necrosis of vessels. A negative cytology for malignant cells is an essential CSF criterion for diagnosing TBM.

CSF protein is generally between 100 - 200 mg/dl. In the presence of coexisting spinal meningitis and spinal block, the values can exceed 1 gm/dl and the fluid may be xanthochromic. If allowed to stand, a pellicle or cobweb may form, indicating the presence of fibrinogen. The pellicle is highly suggestive but not pathognomonic of TBM. CSF protein has been reported to be normal in some patients with AIDS and tuberculous meningitis. CSF glucose levels are abnormal in the majority of cases, being less than 40% of the corresponding blood sugar. Median CSF glucose values are reported to be between 18 - 45 mg%. Glucose levels are never undetectable as can occur in pyogenic meningitis. Low CSF chloride level was previously considered a nonspecific marker of TBM. It is actually a reflection of

co-existent serum hypochloremia and is unhelpful in discriminating between bacterial, viral and TBM. In an anlysis of the CSF findings in 214 patients with TBM, Thomas et al. observed the classical tuberculous pattern in 66.8% of cases; pseudopyogenic response was seen in 31 patients and in 11 cases, the CSF was normal.[14]

**Microbiologial tests**

A negative gram stain, negative India ink stain and a sterile routine culture for bacteria and fungi are prerequisites to diagnose TBM. Domonstration of AFB in the CSF by smear or culture confirms the diagnosis of TBM. The yield of CSF smear by Zeihl-Neelsen staining (also auramine staining) is low and ranges from 4 - 40% in various reports. Large numbers of bacteria (>10-4 per ml) must be present to reliably detect AFB in CSF smears or culture. Centrifuging the CSF (10 - 20 ml) for 30 minutes and thick smear examination from the pellicle enhance the detection rate. The chances of pick up rises with repeated CSF examinations.

CSF culture for AFB takes 4 - 8 weeks to isolate the organism because of the growth of mycobacteria. The reported positivity of CSF culture ranges from 25% to 70% of cases, but is less than 50% in most reports. In many Indian reports the yield has been much lower, around 19%.[13] The yield can be increased by using liquid cultre media such as Septi - Chek AFB system, and Middlebrook 7H9, instead of the conventional Lowenstein - Jensen medium. The isolation rate of M. tuberculosis is higher cisternal and ventricular CSF, but in routine practice, CSF is seldom collected from the ventricles. In cases with miliary dissemination, cultures from extraneural sites such as the sputum and bone marrow may be positive.

**Treatment of tuberculosis meningitis**

The decision regarding the initiation of ATT is the most important step in the

management of TBM. Though delay in commencement of therapy should be minimized, adequate evidence favouring the presence of TBM should be gathered before starting therapy, as ATT is both, potentially toxic and required for aprolonged duration. Confirmation of the diagnosis, either by PCR or by immunological methods is seldom possible in every case, with the available facilities in the developing countries. Apart from the investigations discussed earlier, a history of pulmonary tuberculosis, especially if inadequately medicated, an exposure to patients with pulmonary tuberculosis, evidence in chest radiograph of old tubercular lesion, a clinical history favouring a chronic meningitis, a persistently elevated ESR, a positive Mantoux skin reaction and CT or MRI evidence of basal meningitis and/or its sequelae, are all indiret evidence of the disease being TBM, especially in countries with a hgh prevalence of tuberculosis infection. Though noneof the above information in isolation is a good evidence in itself, a combination of these factors should raise the suspicion of TBM. Following this, a CSF study is mandatory if there is no contraindication for a lumbar puncture.

If suspicion of TBM is high then ATT should be initiated at the earliest. The pros and cons of initiating ATT before the confirmation of the diagnosis should be carefully weighed in each patient. However, "the most important principle of therapy is that it should be initiated when the disease is suspected, nor delayed until proof has been obtained".

The following situations can be considered as separate management issues in TBM : Uncomplicated TBM; Drug resistant TBM; TBM in HIV infected / immunocopromised patients and complications of TBM requiring surgical management.

**Uncomplicated TBM**

It is important to stage TBM patients according to one of the clinical stages described earlier, before the initiation of treatment. Primary management of this condition is through first-line anti-tubercular agents.[15,16,22]

**Major / first and second-line drugs:**

Experimental studies indicate that meningeal permeability is enhanced by non-ionisation of a drug, small molecular weight, low protein-binding and high lipid solubility of the unionised moiety. Ioniazid (INH) is non-protein bound any rapidly penetrates into CSF, whether or not the meninges is inflammed, to give concentrations more than 30 times the minimum inhibitory concentration (MIC) for M.tuberculosis.

Rifampicin is highly protein bound and only upto 20% is available to penetrate into the CSF. Though peak plasma levels are achieved at around 4 hours, the maximum CSF concentration which is only 10% of the plasma concentration, is achieved only at 8 hours. This concentration too is only marginally above the MIC. However, in spite of these facts, clinical experience suggests that possibly rifampicin is almost as active as TBM as in pulmonary tuberculosis.

Pyrazinamide has excellent penetration into CSF which is uninfluenced by the state of the meninges. In view of this unique sterilizing activity and the significant reduction in relapse rates which it can achieve, it is highly recommended in treatment of TBM.

Ethambutol penetrates into the CSF only when the meninges are inflammed. Accurate estimates of its concentration in CSF are unavailable. In contrast, ethionamide at a dose of 250 mg crosses both the healthy any inflammed meninges and attains a CSF concentration that is comparable to that of serum and is well

above the MIC for M.tuberculosis.

Streptomycin concentration in CSF varies with severity of the disease. As the meningeal inflammation reduces, its penetration declines. With a daily dose of 750 mg, its concentration in CSF is only slightly above the MIC for M.tuberculosis. In trathecal routes of injection, which can provide better concentration of this agent, have now been abandoned as this has not improved the outcome.

**Role of corticosteroids**

The role of corticosteroids in the treatment of TBM has been a subject for intense and interesting debates for many years with both proponents and opponents for its use. A comprehensive review in 1966 and a large Chinese study in 1984[23] provided some evidence to recommend use of steroids to reduce mortality in patients with clinical stages 2 and 3 but found no benefit in those with clinical stage 1 of the disease. In addition to confirming these findings, Girgis et al. from Egypt[24] found that steroids also reduced the morbidity and complications if initiated early in the course of treatment. However, they reported no benefit with steroids in patients with very advanced disease (late stage 3 or stage 4).

Kumarvelu et al[25] concluded a trial of 47 patients with TBM who were stratified into mild, moderate and severe groups and randomly allocated to dexamethasone and non-dexamethasone groups. At the end of 3 months, the dexamethasone fared better, especially in patients who had severe disease.

Complications of TBM for which steroids are found to be most beneficial are raised intracranial pressure, cerebral edema, stupor, focal neurological signs, spinal-block, hydrocephalus and basilar optochiasmatic pachymeningitis. The role of steroid therapy in majority of these situations remains to be established. The recommended

daily dose of prednisolone is 60 mg in adults and 1 to 2.5 mg/kg in children. Any possible contraindication for the use of steroids, especially if a fungal meningitis has not been clearly ruled out, should alert the treating physician against using steroids prompt the use of adequate precautions.

**Treatment regimen**

There are no convincing randomised controlled clinical trials to suggest any particular regimen for treatment of TBM. However, vast amount of clinical experience has accumulated over the last many years to suggest some treatment regimens. Since the prevalence of drug-resistant Mycobacterium strain amonst patients from developing countries is relatively high, it is advisable to commence a four-drug regimen for these patients.[13,17,1] The recommended drugs are INH, Rifampicin, Pyrazinamide and Streptomycin or Ethambutol. Ethambutol is preferable over streptomycin because of its better transfer to CSF. Though a drug susceptibilty result is preferred prior to or soon after starting therapy, it is seldom practically possible, especially in developing countries. Unless there is a very high suspicion of drug-resistant organism in a particular patient, the proposed four-drug regimen is generally effective. After two months of treatment, pyrazinamide and ethambutol (or streptomycin) are withdrawn and only INH and rifampicin need to be continued. For patients hailing from communities with low prevalence (<4%) of drug-resistant. Mycobacterium strain, triple drug-regimen consisting of INH, rifampicin and pyrazinamide may be adequate, as per the recommendation of Centers for Disease Control, Atlanta, USA. Pyridoxine is routinely given with ATT to reduce the risk of INH related neuropathy.

**Duration of treatment**

The optimum duration of treatment of TBM is unknown. Longer duration of treatment possibly have lower relapse rates, though the cost, risk of toxicity and

chances of poor compliance is greater. Although 18 - 24 months duration was recommended in the past, there is evidence accumulating to suggest that a duration ranging between six to twelve months may be adequate. According to Humphrics, whose experience in the management of central nervous system tuberculosis in Asian communities is widely recognised, patients in clinical stages 1 or 2 can be treated for 9 or 12 months, while those in clinical stages 3 or 4 shuld be prefierably treated for at least 12 months and often for 18 months.[1] In a prospective study by Phuapradit et al,[26] 28 adults with TBM were treated with pyrazinamide (PZA), isoniazid (INH), Rifampicin and streptomycin daily for 2 months, followed by INH and Rifampicin daily for 7 months with intensive management of the complications during the acute stage of TBM. 22 patients completed the course with minimal morbidity in 3 patients. Two patients died from other causes and four patients dropped out early in the course of treatment. No recurrence of meningitis was observed on 21 patients who were observed for 12 - 29 months after completing therapy. Thus, intensive chemotherapy of TBM with this regimen before the development of serious neurological damage can shorten the duration of treatment to 9 months with a favourable outcome.

V.N. Acharya et al, studied 102 cases of adult TBM over a period of 5 years. According to treatment regimens, they were divided into 4 groups - Groups A and B were treated with streptomycin, isoniazid and PAS/Ethambutol initially for 3 months followed by mainteance with INH + PAS/Ethambutol for 15 months (total 18 months). Group C and D were treated with streptomycin, isoniazid + Rifampicin or Rifampicin + Pyrazinamide for 2 months followed by INH + Rifampician for 7 months (total 9 months). The response to therapy, which was quantitated by means of a scoring system on a computer, was poor for Group A, fair for Group B and good for Group C and D.

Ramachandran P et al[28] studied 180 patients with TBM who were treated for 12 months withone of 3 regimens : first consisted of streptomycin, INH and rifampicin daily for 2 months followed by ethambutol (ETB) + INH for 10 months; in the second, PZA was added for the first 2 months and in the third rifampicin was reduced to twice weekly in the first 2 months. M. tuberculosis was isolated from the CSF of 59 (33%) of 180 patients. CSF smear for AFB was available in only 103 patients and of these in 60 (58%) the CSF was positive by either smear or culture. In all the studies, 27% of patients died of TBM, 39% had neurological sequelae and 34% recovery completely. There was a strong association between the stage on admission and the mortality rate, the deaths being highest in stage III.

51 children of TBM were prospectively studied by Visudhiphan P et al.[4] They were treated with INH and Rifampicin for 12 months. 5, 25 and 21 patients were respectively in stages I, II and III. Raised intracranial pressure of more than 200 mm of H2O was observed in 42 patients. 3 required ventriculostomy and one of them needed ventriculoperitoneal shunting, 3 patients died within the first week of admission and 4 were lost of follow up. Of the 44 patients who were followed for 1½ - 7 years - 31 recovered completely; 13 recovered with neurological sequelae like mental retardation, motor weakness, seizures and hydrocephalus. No serious side-effects were observed except for transient elevation of liver enzymes in 4 patients.

Doganay M et al,[29] in a prospective study, studied 2 groups of patients with TBM: 15 patients were treated with INH, Streptomycin and Rifampicin and 14 patients with INH, Streptomycin and ETB for 12 months. Both groups received prednisolone at the beginning of treatment. No difference in recovery rate between the two groups was observed. 6 patients (21%) died (5 in group I and 1 in group II). Residual sequelae developed in 9 cases (5 in group I and 4 in group II; 31%). The difference

between the groups was not significant. The regimen including Rifampicin for TBM did not result in any superiority compared to standard therapy.

Markova EF et al,[30] studied the course and outcome of TB of the CNS in adults within 2 consecutive 10 years periods. It was seen that within the last 10 year period the number of adults with TBM had lowered while the proportion of adults with TB of the CNS with active pulmonary TB became more frequent. Higher levels of neutrophilic - lymphocytic pleocytosis as compared to the previous ones, marked hypoglycorrhachia and more frequent isolation of mycobacteria from the liquor were noted. There was no change in the efficacy of treatment or death rate. The situation should be explained by the incidence of common forms of pulmonary TB including fibrocavernous and disseminated TB, insufficient prophylaxis, the incidence of concomitant diseases, sometimes acute onset of the disease, asymptomatic process of the disease inattention of the physicians as to possible incidence of TBM.

On the other hand, Goel A et al,[31] observed in a series of 35 patients in which chemotherapy for TBM was given for lessthan 2 years. This was associated with recrudescence of TBM and, in some cases, with the development of deep cerebral infarcts and permanent neurological deficits. It was concluded that though short course chemotherapy was well established for the treatment of pulmonary TB, it was inadequate for TB of the CNS.

In March 1986, Alarc et al,[32] began a six month short course trial of therapy for TBM, in which 28 patients were analysed. In 53.5% of these cases, M. tuberculosis was identified on smear; in 57% culture was positive; in 83.3% the detection of anti-bacille Calmette Guerin (BCG) antibodies by ELISA was positive and in 74% of dosification of adenosine deaminase activity was positive. In 21.4% of cases, the diagnosis was established by autopsy findings. 32.4% of patients died despite

treatment - all of these were in the last stage of the disease at the onset of therapy. 16% had neurological sequelae at the end of 18 months of follow up. With the 6 month therapeutic regimen, the morbidity/mortality was similar to that found in the longer course therapies.

In a prospective study by Biddulph et al,[33] 639 children with TB treated with short course chemotherapy were followed for 24 months. 165 (26%) of these were younger than 2 years old. 227 (35%) had extrapulmonary TB (peripheral lymph nodes - 110; CNS - 43; abnormal - 27; miliary - 16; bone and joint - 11; pleural - 11; polyserositis - 9). Clinical response to short course chemotherapy was rapid. 12 (2%) died, 38 (6%) daily rifampicin. INH, PZA and Streptomycin followed by a 4 month course of twice weekly rifampicin and isoniazid; though 71 (11%) had their treatment modified. 7 of 373 patients relapsed, mostly within 3 months; 5 had been irregular with their treatment. (Only 70 i.e. 19% of these 373 children were available for post treatment follow up. Jacobs RF et al,[2] evaluated 53 children of TBM with 8, 29 and 16 patients patients respectively in stages I, II and III. The overall mortality was 20.8% (11 out of 53) with a rate of sequelae of 35.7% (5 of 42) in survivors reflecting the advanced stage at diagnosis. Various combinations of the standard ATT were given and various time periods were evaluated - 12, 9 and 6 months with only the 6 months regimen receiving PZA. Severe disease at presentation was associated with early mortality ($p<0.05$) regardless of drug regimen. Intensive short course chemotherapy (6 months) with PZA, regardless of the stage at presentation was more efficacious than 9 or 12 months without PZA.

Anastasatu C et al,[34] studied the effect of short course chemotherapy (9 months) in severe forms of TBM in children. They applied the following regimens : 3HRZ2 6HRZ (in the experimental group) and 3HR / 3HRZ / 6HZ (in the control group).

In the granular and caseous forms - at 5 years after end of treatment - the results were very good in 100% of cases in both groups. In meningitis clinically very good results (without sequelae) presented a proportion of 70.1% in the experiemental group and 68.2% in the control group (difference was statistically non significant).

Bazin C observed that favourable host factors associated with non specific neurological abnormalities must lead to the hypothesis of a meningeal tuberculosis. The diagnosis is established when tubercle bacilli are identified in the CSF. New methods of diagnosis are not routinely available. Treatment must be started before identification of the bacilli. Usually for immunocompetent patients, short course treatment is chosen - Rifampicin, INH and PZA for 2 months followed by a 4 month therapy of INH and Rifampicin; ETB should be included systematically during the first 16 weeks in prevention of isoniazid resistance.

Nikoli et al,[35] studied the pathogenetic mechanisms of occurrence of TEM and modern recommendations for therapy. According to them, meningitis was never a primary localization of TB infection, but occurs by dissemination from some primary focus; or by rupture of subependymal tubercles into the subarachnoid are and discharge of their caseous content. These tubercles occured by previous hematogenous dissemination in the preallergic phase of pulmonary primary infection or re-infection, prior to meningeal infection. Treatment for 9 months - daily 3 or 4 ATT drugs for 2 months and then INH and Rifampicin for 7 months was given. The results of this short course intermittent therapy was the same, or better, than the results of "standard" therapy for 18-24 months.

Prior to the initiation of treatment of individual patients, additional factors that need to be considered include age, renal or hepatic disease and pregnancy. One of the most common drug induced side-effect during the treatment of tuberculosis,

encountered in practice, is developmetn of jaundice. It is practically impossible to differentiate drug induced hepatotoxicity from coincidental viral hepatitis that is highly prevalent in developing regions. In patients wo develop derangement of hepatic functions, the regien is stopped and a combination of streptomycin and ethambutol is started. When the liver function improves INH is added and liver function tests are repeated every fourth day. If liver fuctions improve or remain stable, other drugs are gradually added. In most cases of drug induced hepatitis, it is possible to re-introduced all the agents one after another. However, it is prudent to avoid pyrazinamide and use rifampicin with caution in patients with pre-existing or recently acquired hepatic dysfunction.

# *Results*

The study group comprised of 26 patients received short course chemotherapy and were followed up for 1-2 years after stoppage of treatment. Study group was compared with 27 control patients from the medical records who were matched for capacity age, gender and grade of disease and had received the conventional chemotherapy regime with 4 drugs and duration of 18m. The result are summarised as follows. Group I are cases and II are controls.

Patient characteristics

**TABLE 1**

| | | Group I | Group II | P value |
|---|---|---|---|---|
| Income | High | 4 | 4 | 0.41 |
| | Middle | 11 | 17 | -- |
| | Low | 11 | 6 | -- |
| Gender | M/F | 15/11 | 17/10 | 0.69 |

| | Group I/II | Mean Group I/II | SD Group I/II | SE of mean Group I/II |
|---|---|---|---|---|
| Age | 26/27 | 32.03/38.74 | 14.40/12.64 | 2.82/2.433 |
| Duration | 26/27 | 67.96/55.37 | 62.01/49.47 | 12.16/9.52 |

No statistically significant difference was found between the two groups, who received short course and conventiona chemotherapy for the patient characteristics of Income, gender, age and duration of symptoms.

**Symptoms**

The different symptoms in the clinical presentation in the two groups are summarised in the table II.

**TABLE 2**

| Symptom | Group 1 No./% | Group II No./% | P value |
|---|---|---|---|
| Headache | 25(96.2) | 27(100) | 0.3 |
| Vomiting | 20(76.9) | 25(92.6) | 0.11 |
| Fever | 24(92.3) | 26(96.3) | 0.52 |
| Diplopia | 8(30.8) | 7(25.9) | 0.69 |
| Impared vision | 1(3.8) | 5(18.5) | 0.09 |
| Bulbar symptoms | 5(19.2) | 0(0) | 0.01* |
| Altered sensorium | 14(53.8) | 12(44.4) | 0.49 |
| Seizures | 4(15.4) | 4(14.8) | 0.95 |
| Hemiparesis | 3(11.5) | 1(3.7) | 0.28 |
| Quadriparcsis | 1(3.8) | 3(11.1) | 0.31 |
| Paraparesis | 3(11.5) | 5(18.5) | 0.47 |
| Ataxia | 6(23.1) | 2(7.4) | 0.11 |

The commonest symptoms in the clinical presentation was headache (96.2%) followed by fever (92.3%). Altered sensorium was observed 53.8%. Motor deficits included hemiparesis (11.5%), quadriparesis 3.8% and paraparesis (11.5%). No statistically significant difference was observed in symptoms of presentation between the two groups. An exception was bulbar symptoms found more in the Group 1 than in the control.

**Signs at presentation**

The different signs in the clinical presentation of the two groups are summarized in the Table 3.

**TABLE 3**

| Signs | Group I No./% | Group II No./% | Group III No./% |
|---|---|---|---|
| Alteration of sensorium | 15(57.5) | 22(81.5) | 0.06 |
| Cranial neuropathy | 15(57.7) | 12(44.4) | 0.33 |
| Optic atrophy | | | |
| Primary | 4(15.4) | 4(14.8) | -- |
| Secondary | 2(7.7) | 0(0) | 0.33 |
| Papilloedema mild | 6(23.1) | 2(7.4) | -- |
| Moderate to severe | 2(7.7) | 0(0) | 0.07 |
| Motor deficits | paraplegia | 9(34.6) | 3(11.1) |
| Monplegia | 1(3.8) | 0(0) | -- |
| Hemiplegia | 0(0) | 1(3.7) | -- |
| Quadriplegia | 1(3.8) | 0(0) | 0.22 |
| Sensory deficits | 3(11.5) | 1(3.7) | 0.28 |
| Cerebellar signs | 6(23.1) | 1(3.7) | 0.03* |
| Meningial signs | 21(97.2) | 27(100) | 0.25 |
| Cognitive dysfunction | 7(26.9) | 6(22.2) | 0.69 |

There was no statistical difference between two groups except for cerebellar signs which was more in the study population. 57.7% of patients presented the altered of sensorium. The 6th nerve was the commonest to be involved followed by the 3rd and the 2nd nerve. Primary optic atrophy was seen in 4 patients of the study population and secondary optic atrophy subsequent to papilloedema was seen in 2 patients.

The commonest motor deficit was paraplegia seen in 9 patients. 3 patients of the study population showed sensory deficits, mainly involving large fibre pathways. Meningal signs was present in 21 patients of the study group. 5 patients in the study group who did not have meningal signs were comatose. Cognitive dysfunction was seen in 7 patients and the commonest abnormalities observed were in the field of memory and orientation.

**MRC grading of TBM**

As per the medical research council grading of TBM patients in both the group were bracketed in grade 1, 2 and 3. The break-up is depicted in Table 4.

**TABLE 4**

| MRC grading | Group I No./% | Group II No./% | p-value |
|---|---|---|---|
| 1 | 4(15.4) | 7(25.9) | |
| 2 | 15(57.7) | 12(44.4) | |
| 3 | 7(26.9) | 8(29.6) | 0.55 |

Maximum number of patients were in grade II (57.7%) followed by grade III and then in grade I (26.9%). This number of patients in different grades in both groups were similar with no statistical significant difference between the two. This was because the two groups of patients were matched for grade of illness during the selection of the control population.

Category of TBM

Patients in both the groups were catagorised as definite, and probable tuberculo meningitis, on the basis of CSF picture, ELISA test, AFB staining, AFB culture and evidence of extrapulmonary tuberculosis. The details of which are summarized in table 5.

**TABLE 5**

| TBM category | Group I No./% | Group II No./% | p-value |
|---|---|---|---|
| 1. Definite | 0(0) | 0(0) | |
| 2. Probable | 26(100) | 26(100) | 0.17 |
| 3. Possible | | | |

Most patients were in the category of possible TBM on the basic of -ve AFB smear and AFB culture but with +ve evidence extra CNS tuberculosis.

No statistically significant difference was found between the two groups the groups for the three categories of TBM.

## INVESTIGATIONS

### CSF studies

CSF studies were performed at time of admission (1st CSF) 10 days after the institution of ATT (2nd CSF) and at the end of the eessation of short course chemotherapy in the study population (3rd CSF). Details of CSF studies are summarised in Table 6.

**TABLE 6**

| CSF parameter | Group I/II (No. of pts) | Mean (Group I/II) | SD (Group I/II) | SE of mean (Group I/II) |
|---|---|---|---|---|
| 1st CSF total (cell cnt) | 26/27 | 254/281 | 303/197 | 59/38 |
| Polymorphs | 26/27 | 25.6/13.8 | 33.5/12.17 | 6.6/2.3 |
| Lymphocyts | 26/25 | 70.96/83.3 | 35.33/19.008 | |
| CSF sugar | 26/27 | 42.7/39.51 | 27.7/15.8 | 5.5/3.0 |
| Blood sugar | 26/27 | 126.38/109.96 | 63.18/30.53 | 12.4/5.88 |

| | | | | |
|---|---|---|---|---|
| Proteins | 26/27 | 157.3/202 | 112/196.6 | 22/37.8 |
| 2nd CSF total cell cnt | 26/25 | 185.54/122 | 257.67/111.24 | 50.53/22.25 |
| Sugar | 26/25 | 50.31/47.56 | 25.67/18 | 5.034/3.59 |
| Proteins | 26/25 | 97/140 | 57.20/120.7 | 11.217/24.14 |
| 3rd CSF total cell cnt | 26 | 3/5 | -- | -- |
| Surgar | 25 | 41 | -- | -- |
| Proteins | 25 | 14 | -- | -- |

**Other diagnostic tests for tuberculosis meningitis**

Other diagnosis tests to establish the diagnosis (definite, possible and probable) were done in the study population and the control group. These are summarised as follows in Table 7.

**TABLE 7**

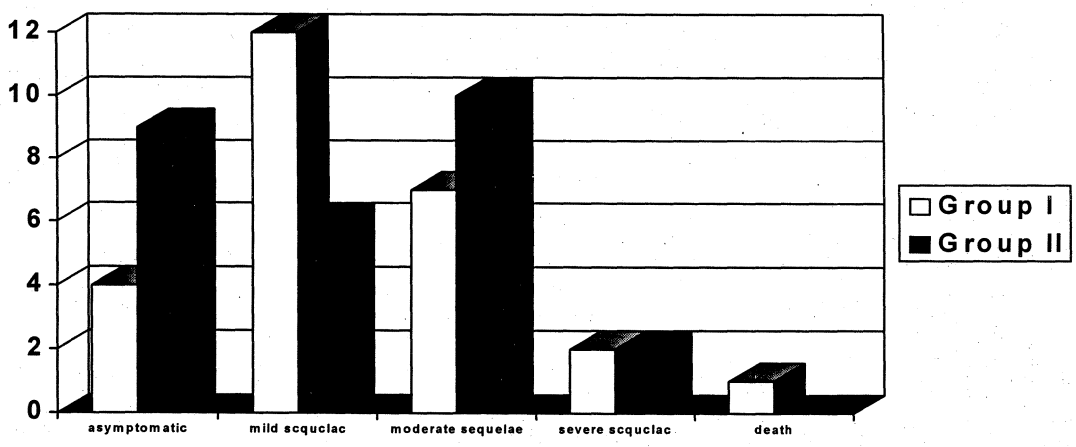
| Investigation | Group I No./% | Group II No./% | p-value |
|---|---|---|---|
| CSF Elisa +ve | 15(57.7) | 16(59.3) | 0.0978 |
| AFB staining | 0(0) | 0(0) | 0 |
| AFB culture | 0(0) | 0(0) | 0 |
| Chest X-ray normal | 13(50) | 20(74.12) | -- |
| Non specific | 12(46.20 | 7(25.9) | -- |
| Specific | 1(3.8) | 0(0) | 0.15 |
| CT scan normal | 13(50) | 14(51.9) | -- |
| Abnormal | 13(50) | 13(48.1) | 0.89 |
| Exudate | 10(38.5) | 7(25.9) | 3.33 |
| Hydrocephalus Mild | 3(11.5) | 3(11.1) | -- |
| Moderate | 1(3.8) | 2(7.4) | -- |
| Severe | 1(3.8) | 2(7.4) | 0.44 |
| Tuberculoma | 2(7.7) | 1(3.7) | 0.52 |

These findings was similar to those in the control population and no statistical significance was detected between the investigative parameters between the two groups. Exudates seen in the CT-scan were the commonest abnormality seen in the investigative parameters in tuberculomeningitis besides abnormal CSF picture. Outcome categories at different time points between the study group and the control group:

The outcomecategories in patients who were given short course chemotherapy were compared with the control group. The details of the same for the different time points are summarized in Table 8 to 13. The outcome categories quantitatively assessed on a scale of 1 to 5, 1 being asymptomatic and 5 being death.

**GRAPH 1**

OUTCOME CATEGORY AT DISCHARGE




At discharge most patients were in group II (Mild sequelae) followed by group 3 (moderate sequelae). Only 1 death was seen in the study population. No significant difference statistically was observed between the 2 groups in the outcome category at 1 month p-value 0.25.

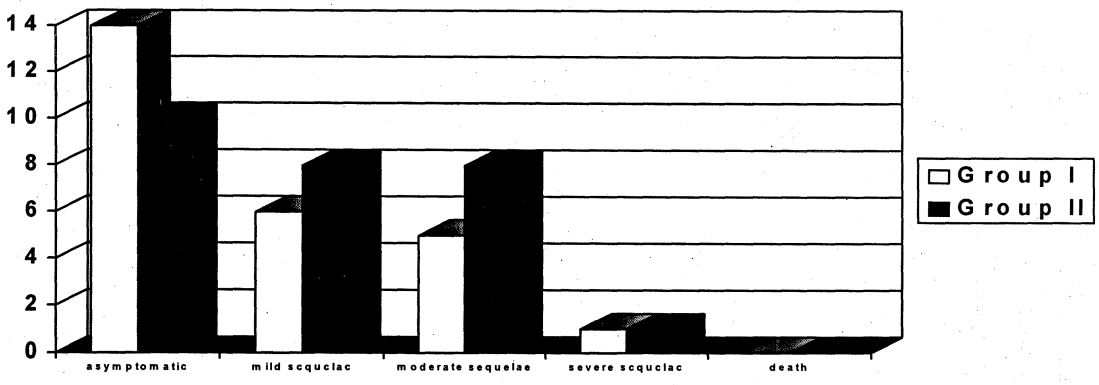
## GRAPH 2

OUTCOME CATEGORY 1 MONTH


At 1 month after discharge most patients (38.5%) were in grade 1 (asymptomatic) followed by group 2 (mild sequelae). No death were seen at 1 month of follow-up. Again no statistically significant difference was observed between the two groups. p -value 0.75.

## GRAPH 3

OUTCOME CATEGORY AT 6 MONTHS

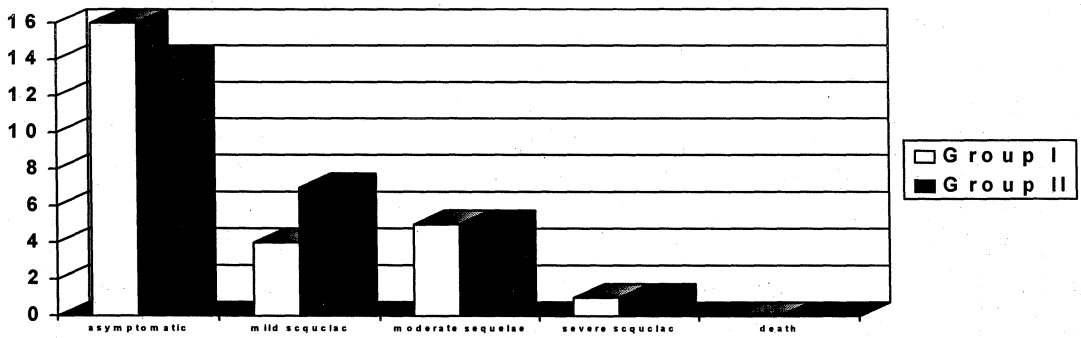



At 6 months after discharge, most patients were in the asymptomatic category with mild sequelae seen in 6 patients and moderate sequelae in 1 patient. No death

were observed either in the case or in the control population. There were no statistically significant difference in the outcome category between the two groups.

**GRAPH 4**

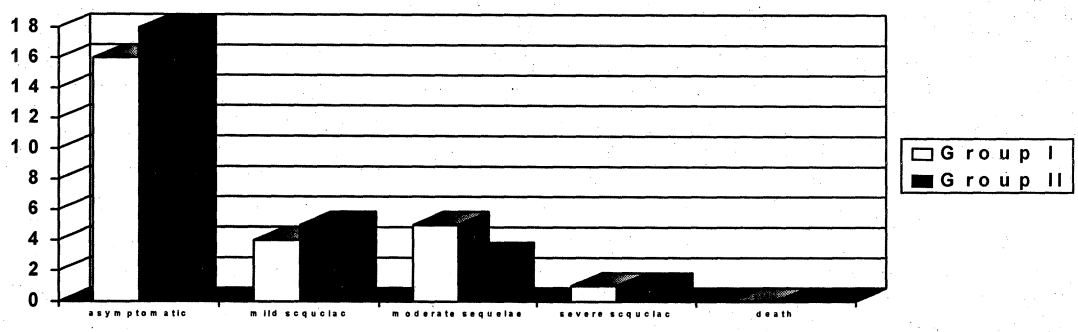
OUTCOME CATEGORY AT 9 MONTHS




At 9 months after discharge, most of the patients reached asymptomatic stage (61.5% in the case population and 51.9% in the control population). There were no statistically significant difference in the outcome category between the two groups.

**GRAPH 5**

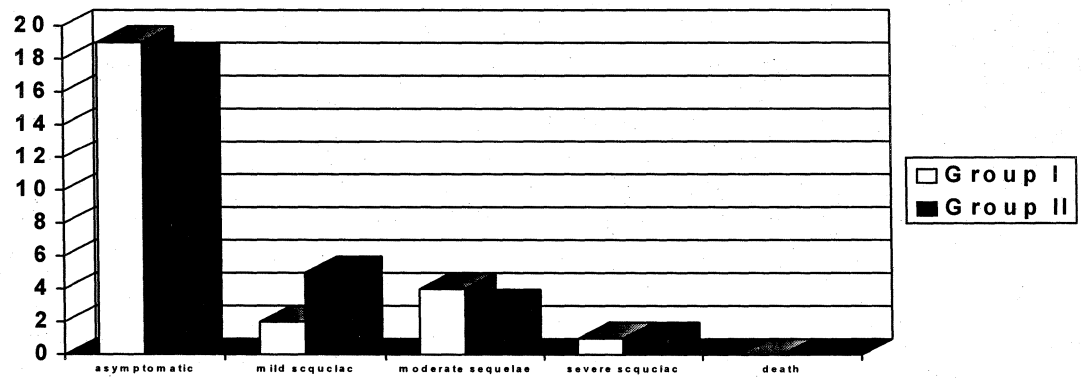
OUTCOME CATEGORY AT 1 YEAR




Outcome category at 1 year, was characterised by most patients in the case and control population reaching in the asymptomatic stage (61.5% vs 66.7%). Again the statistically significant difference in the outcome category between the two groups.

## GRAPH 6

OUTCOME CATEGORY AT LAST FOLLOW-UP




At last follow-up most patients were in grade 1 in both the group 1 and group 2 populations. However again the difference in the follow-up clinical state was not significant between the 2 groups.

To assess the final outcome and response to short course chemotherapy and conventional chemotherapy were also compared with regard to outcome category at discharge and at last follow-up and details of the same are summarised in table 8.

## TABLE 8

| Group 1 Outcome category at discharge | Outcome category at least follow-up | | | | Row Total |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | |
| 1 | 4(100) | -- | -- | -- | 4(15.4) |
| 2 | 11(91.7) | 1(8.3) | -- | -- | 12(46.2) |
| 3 | 2(28.6) | 1(14.3) | 4(57.1) | -- | 7(7.7) |
| 4 | 1(50) | -- | -- | 1(50) | 2(7.7) |
| 5 | 1(100) | -- | -- | -- | 1(3.8) |

4 patients who presented in grade 1 was discharged as grade 1 TB. Out of 12 patients who presented in grade 2, 11 becomes asymptomatic and 1 had mil sequelae. Out of 7 patients who presented as grade 3 TBM 2 become asymptomatic, 1 had mild sequelae and 4 had moderate sequelae. Out of 2 patients who presented as grade 4 TBM, 1 become asymptomatic and 1 had severe sequalae. 1 patient expired during the 1st month after discharge.

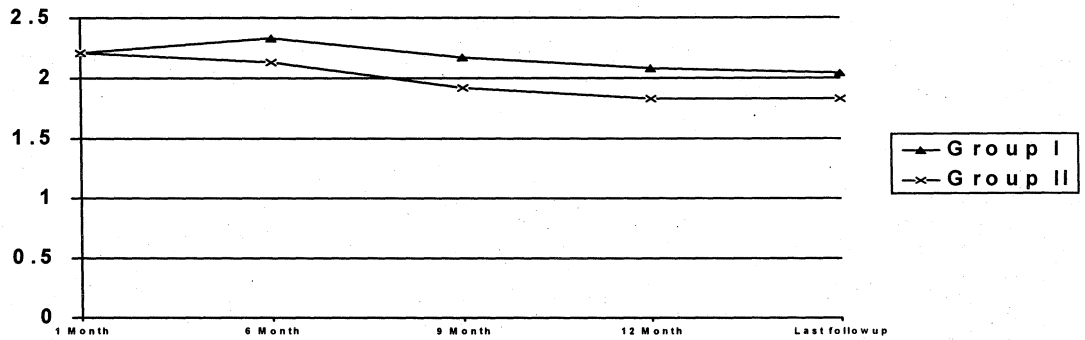
**TABLE 9**

| Group 2 Outcome category at discharge | Outcome category at least follow-up | | | | Row Total |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | |
| 1 | 9(100) | -- | -- | -- | 9(33.3) |
| 2 | 6(100) | -- | -- | -- | 6(22.2) |
| 3 | 3(30) | 4(40) | 3(30) | -- | 10(37) |
| 4 | -- | 1(50) | -- | 1(50) | 2(7.4) |

Similar findings were obtained in a control population with maximum improvement seen in patients presenting in grade 1 were all the patients who presented in this grade did not show further worsening, while patients presenting in grade 4 did not show significant improvement and markedly residual disability.

## GRAPH 7

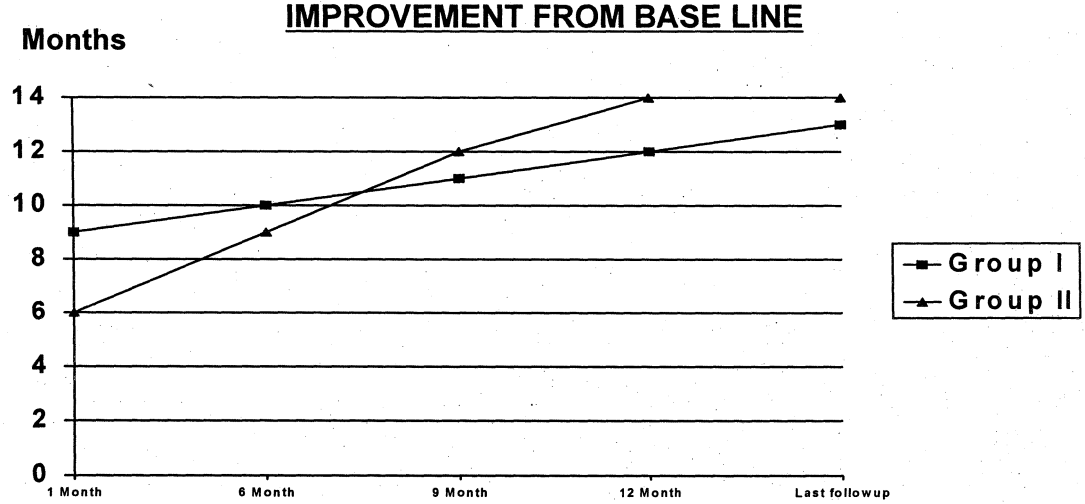
## M E A N  G R A D E




This shows the mean grade of patients for both the groups at different time points.

## GRAPH 8

## IMPROVEMENT FROM BASE LINE

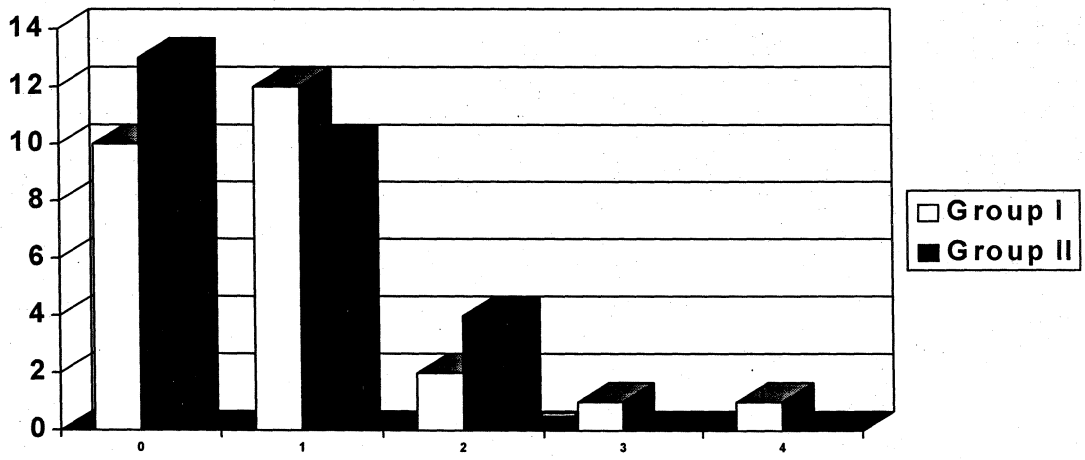



The above shows the percentage improvement of patients in both the groups from the base line.

To compare the degree of improvement on the basis of gradingof TBM. Comparative analysis has been done between the case population and control population.

## GRAPH 9

### IMPROVEMENT GRADING OF TBM




The ten patients in group 1 did not show any improvement in grading of TBM. However most of these patients were already in grade 1 TBM (asymptomatic). 12 patients showed improvement by 1 grade followed by 2, 1 and 1 patients showing improvement by 2, 3 and 4 respectively. These data are not significantly difference from that of grade 2 patients. No statistically significant difference between the two groups.

Overall 10 patients in group 1 did not show any improvement as per the grading of TBM. 12 patients showed improvement of grade 1 and 2, 1 and 1 patient showed improvement 2, 3 and 4 grade respectively. 1 patient died. This data is not significantly different from the control group. The p-value is only 0.52.

The single most parameter determining the prognosis of tuberculomeningitis is the MRC grade in which the patient clinically presents.

# Discussion and Conclusion

Ours was a prospective study in which we tested the efficacy of short course chemotherapy in tuberculous meningitis and compared the out come of short course chemotherapy with conventional chemotherapy.

We found short course chemotherapy efficacious in all stages of TBM. Patients steadily improved even after discontinuation of ATT at 9 months when they were examined periodically during fellow up. There were no relapses during the course of follow up in any of the patients. The final out come and degree of improvement was influenced only by the grade of TBM at the time of diagnosis and delay in starting treatment. Patients in grade disease fared better than patients in grade 3 as expected.

There were also no side effects of the drugs like hepatotoxicity or neuropathy and we did not have to discontinue or change ATT in any patient because of drug toxicity. Earlier studies quieted the complication rate of about 5-6%[36] especially[ecially for hepatotoxicity and most of the complications were within the first nine months of starting therapy.

Our study was quite similar to that of phua pradit et al.[26] They studied 28 patients who received short course chemotherapy who were followed for 21-29 months. They did not find any recurrences of meningitis. They concluded that intensive chemotherapy of TBM with their regimen before the development of serious neurological damage can short on the duration of treatment to 9 months. Al arc et al[32] also found that with a 6 month course of chemotherapy the reduction of morbidity

and mortality was similar to that found in longer course therapies. Biddulph[33] who studied 639 children on short course chemotherapy followed for 24 months found so very favourable. Who ever relapsed did so in the first three months.

Jacobs[2] found that severe disease at presentation was associated with earlier mortality and a 6 months course of chemotherapy with PZA was more efficacious than a 9 or 12 month course of chemotherapy without PZA. Nikoli et al 35 also found that results of short course chemotherapy was the same or better than standard course of chemotherapy. On the other hand others had advocated short course chemotherapy was insufficient to treat TBM especially in grade 2 and grade 3.[1,37]

One comparing the study population who received short course chemotherapy with the control population we oliserved interesting results. Both the groups were well matched for age, sex and income group. Clinical features observed in both the groups were also sinilar. Headache was the commonest symptom and ataxia was least common. Most patients had altered sensiorium and it was followed by cranial neuropathy of which involvement of 6th nerve was the commonest. Signs of raised intracranial pressure was found in about 30% in both the groups. These results were quite similar to that of a large study from north west India.[14]

Both groups had maximum number of patients in grade 2 category. This could have had an influence on the final outcome, as the number of patients in grade 3 were less in this already small population. However the two could be well compared the number in each grade was similar.

In the diagnostic category all the patients in both the study and control groups were possible TBM. No case of definite TBM was there in this study as defined by a positive smear or culture. This is possibly due to the low yield of CSF smear and low positurity of CSF culture[13] thence the absence of definite cases was not surprising.

The timing of cytological cure could not be compared between the groups. Only group had a CSF study at the end of treatment. Cytological cure was observed in the entire study population at the end of 9 months of ATT. When the outcome categories were compared between groups, no statisti cally significant difference was found at any point of time. There was a trend for the long course to fare slightly better. But this was not statistically significant. Besides, more side effects (? drug induced) were observed in then. MRC grading at time of starting treatment appeared to be the single most important factor which decided the fuial out come.

A comprehensive liter ature survey tic last year did not identify any previous Indian studies comparing short carwash chemotherapy and cenventneias chemotherapy. To the best our knowledge ours is the first study in the country comparing the out come of short course chemotherapy with conventional chemotherapy. However the study has a few flaws. Most importantly the study sample was small sufficient number of patients were not available in grade III category to comment on their outcome a short course chemotherapy. Study group was studied prospectively and the control group data was collected remospectvely from the case records.

We conclude that short course chemotherapy proved efficacious in our study as eri danced by CSF cure at end of treatment and comparable outcome with long course treatment all grades of TBM. Short course ATT would be very useful for a developing country like India as it would cut costs, improve patient compliance and reduce drug induced side effects. We recommend a large prospective study including larger number of patients in grade 3 to compare their outcome with short course chemotherapy and conventional chemotherapy. This study should also determine exactly at what point of tine cytological cure is established in the course of conventional long duration ATT.

# Bibliography


1. Humphries MJ, Teoh R, Ian J, Gabriel M. Factors of progrostic significance in Chinese children with tuberculous meningitis. Tubercle 1990;71; 161-168.

2. Jacobs RF, Sunakorn P, Chotpita yasunonah T, pope S, Kelleher K, Intensive short course chemotherapy for tuberculous meningitis. Pediatric Infect Dis J 1992 Mar; 11 (3) : 194 - 8.

3. Alarc on F, E scal ante L, perez Y, Banda H, chacon G, Duenas G. Tuber culous meningitis short course of chemotherapy. Arch neurol 1990 Dec; 47 (12) : 1313 - 7

4. Visudhiphan P, Chiemchanya S. Tuberculous meningitis in children : treatment with is niazid and rifampicin for twelve months. J Pediatr 1989 May; 114 (5) : 875 - 9 875 - 9

5. Medical Research Council :

   Streptomycin treatment of tuberculous meningitis : report of the committee on strepto mucin in tuberculosis trials. Lancet 1948; 1 : 582 - 597.

6. Kennedy DH, Fallon RJ. Juberculous meningitis. JAMA 1979; 241 : 264 - 268.

7. Gourie - Devi M, Satish P. Hyaluronidase as an adjuvant in the treatment of cranial arach noiditis (hydrocephalus and optochiasmatic orachnoiditis) complicating tuberculous meningitis. Acta Neurol Scandinav 1980; 62 : 368 -381.

8. Ellner JJ, Hinman AR, Dooley SW et al. Tuber culosis symposium : emerging problem and promise. J Inject Dis 1993; 168 : 535-537.

9. Berenguer J, Moreno S, Languna F et al. Tuber culous meningitis in patients infected human immunodeficiency virus. N Eng J Med 1992; 326 : 668 -672.

10. Gracey DR., Tuberculosis in the world today. Mayo clin proc 1988; 63 : 1251 - 1257

11. Murray CJL, Feachem RG. Adult mortality in the developing world. Trans R Soc Trop Med 1990; 84 : 21 - 22

12. Murray CJL, Styblo K, Rouillon A. Tuberculosis in developing countries : burden, intervention and cost. Bull Int Union Tuberc Lung Dis 1990; 65 : 6 - 25.

13. Tandon P.N, Bhatia R, Bhargava S. Tuberculous meningitis, In : Handbook of Clinical Neurology (Revised series), Vol 8 (52), Harris A A (ed). Amsterdam : Elsevier Science, 1988 : 195 - 226.

14. Thomas MD, Chopra JS, Walia BNS. Tuberculous meningitis. A clinical study of 232 cases. J Assoc Phy India 1977; 25 : 633 - 639.

17. Sheller JR, Des Prez RM. CNS tub erculosis. Neurol clin 1986 ; 4 : 143 - 158.

18. Kent SJ, Crowe SM, Yung A, Lucas CR, Mijdi AM. Tuberculous meningitis : a 30 year review. Clin Infect Dis 1993; 17 : 987 - 994.

19. Berger JR. Tuberculous Meningitis. Curr opin Neurol 1994; 7 : 191 - 200.

20. Bhargava S, Gupta AK, Tandon PN. Tuberculous meningitis : a CT study. J Radiol 1982; 55 : 189 - 196.

21. Udani PM, Parekh UC, Dastur DK. Neurological and related syndromes in CNS tuberculosis : clinical features and pathogenesis. J Neurol Sci 1971; 14 : 341 - 349.

22. Palur R, Raja shekar V, Chandy MJ, Joseph T, Abraham J. Shunt surgery for hiydrocephalus in tuberculous meningitis : a long-term follow-up study. J Neurosurg 1991; 74 : 64 - 69.

23. Shaw PP, Wang SM, Tung SG et al. Clinical analysis 445 adult cases of tuberculous meningitis. Chinese J Tuberc Respir Dis 1984; 3; 131 - 132.

24. Girgis NI, Farid Z, Kilpatriclc ME et al. Dexamethasone adjunctive treatment for tuberculous meningitis. Pediatr Inject Dis J 1991; 10 : 179.

25. Kumarvelu S, Prasad K, Khosla A, Behari M, Ahcja G.K. Randomized controlled trial of dexa meth asone in tuberculous meningitis. Tuberc Lung Dis 1994;75 : 203 - 207.

26. Phuapradit P, Vejjajiva A. Treatment of tub erculous meningitis : role of short course chemotherapy. Q J Med 1987; 249 - 258.

27. Acharya VN, Kudva BT, Retnam VJ, Mehta PJ. Adult tuberculous meningitis : comparative study of different chemotherapeutic regimens. J Assoc Phy India 1985; 33 : 583 - 585.

28. Ramachandran P, Duraipandian M, Nagarajan R, Prabhakar R, Ramakrishnan CV, Tripathy SP. Three chemotherapy studies of tuberculous meningitis in children. Tubercle 1986; 67 : 17 - 29.

29. Do ganay M, Bakir M, Dokmetas I. Treatment of tuberculous meningitis in adults with a combination of is niazid, rifampicin and streptomycin : a perspective study. Scand j Inject Dis 1989; 21 (1) : 81 - 5.

30. Markova EF, Gasparian AA. The course and outcome of tuberculous meningitis in adults. Probl Tuberk 1989; (12) : 35 - 8.

31. Goel A, Pandya SK, Satoskar AR. Whither short course chemotherapy for tuberculous meningitis ?

Neurosurgery 1990 Sep; 27 (3) : 418 - 21.

33. Biddulph J. short course chemotherapy for childhood tuberculosis. Pediatr Inject Dis J 1990 Nov; 9 (11) : 794 - 801.

34. Anastasatu C, Anastasatu O, Murgoci G, Dobre M. The late results of intensive chemotherapy (9 months) in sever forms of tuber culosis in children. Pneumojtiziologia 1993 Oct - Dee; 42 (4) : 9 - 12.

35. Nikoli CS. Modern concepts on the pathogenesis and therapy of tuberculous meningitis. Srp Arh Celok Lek 1996 Jan - Feb ; 124 (1 - 2) : 24 - 8.

36. Parthasarthy R, Sarma GR, Janardhanan B. Hepatic toxicity in South Indian Patients during treatment of tuberculosis with short course regains containing isoniazid, rifampicin and pyrazinamide. Tubercle 1986; 67 : 99 - 101.

37. Pandya SK, Goel A, Satoskar AR. Whither short course chemotherapy for tub erculous meningitis ?

Neurosurgery 1990. Sep ; 27 (3) : 418 - 21.