A Prospective Study to Evaluate the Efficacy of Short-Term Intermittent Chemotherapy (STIC) As Per WHO Guidelines for the Treatment of Osteoarticular Tuberculosis (TB)

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I. Introduction

Tuberculosis (TB) is a worldwide problem. World Health Organization (WHO) estimates that each year approximately 8.4 million people develop tuberculosis and approximately 3 million die each year. The disease has its deep roots in developing countries with a significant number of young adults being affected by the disease. Major brunt of tuberculosis is by pulmonary tuberculosis but extrapulmonary tuberculosis accounts for 20 to 25% of total TB affected patients of which osteoarticular TB accounts for 8 – 10%. 50% of osteoarticular TB affects spine and the rest extraspinal predilection being for hip, knee, elbow and shoulder.

II. Aims Of The Study

Here we study the efficacy of short-term intermittent chemotherapy (STIC) as per WHO guidelines for the treatment of osteoarticular TB, the recurrence rate after completion of chemotherapy and the role of MRI in diagnosis and assessment of spinal TB post STIC.

III. Materials And Methods

Study group comprised of patients below 70 years of age with immunocompromised patients and patients on immunosuppressant’s, including pregnant patients being excluded from the study. The treatment regimen was followed as per WHO guidelines. It included DOTS regimen which was 2 (HREZ) + 4(HR). Patients were assessed for monthly ESR, clinically assessed for improvement in constitutional symptoms and a sense of well being along with radiological signs of healing. Once the treatment was completed patients were re-assessed once every 3 months to look out for any recurrence.

IV. Results

The study results were analyzed. 94 patients out of 104 were studied as 10 patients lost for follow up and one was diagnosed with meningioma. The maximum numbers of patients with osteoarticular TB were from 1st decade to 3rd decade. Spinal TB was more commonly seen in 2nd (34%) and 3rd (30%) decade where as extraspinal was more commonly seen in 1st decade (39%). 56 patients had spinal TB and 38 patients had extraspinal TB. Among the spinal TB patients, pain was most common symptom (95%) followed by constitutional symptoms (89%), palpable abscess (27%) and neurological deficits (36%). In extraspinal TB patients, pain (95%) again was the most common symptom followed by swelling (68%) and constitutional symptoms (53%).MRI was 100% sensitive in diagnosing spinal TB and was selectively used in extraspinal TB but had 100% sensitivity again. In spinal TB, dorsal (25%)and lumbar (37%) vertebrae were the most commonly affected vertebrae with dorso-lumbar vertebral involvement being 9%.In extraspinal TB, hip joint was commonly affected joint seen in 29 % patients followed by knee(16%). Pre treatment median ESR was 55(15-70 at the end of 1st hour) in spinal TB where as median ESR was at 50 (30 –70 mm at the end of 1st hour) in extraspinal TB. 18 % had association with pulmonary Koch’s in patients affected with spinal TB when compared to 5% in extraspinal TB patients. All patients received DOTS category –I as per WHO protocols. Patients were assessed based on ESR and well being in relation to their constitutional symptoms. 53% extraspinal TB patients received chemotherapy for 6 months and 45% for 8 months. Results showed significant drop in ESR at the end of 2 months of intensive phase of treatment with a P- value at 2 months and 6 months being < 0.001. Where as in case of spinal TB the ESR fall was not that great at 2 months, p-value being >0.005, but with continuous treatment for 6 months and more the ESR had a downward trend with a p-value<0.005 showing that drop was not by chance but indicating that patients with spinal TB required longer duration of treatment compared to extraspinal TB. 23% patients received the DOTS category 1 and the rest had an extended treatment regimen of 8 months for 57%, 9 months for 1.7% , 10 months for 12.54%, 13 months for 1.7% and 14 months chemotherapy for 2.5% of spinal TB patients. It was also found that the drop in ESR was not significant in spinal TB patients who received treatment for > 6 months indicating that these patients required a longer duration of chemotherapy in order to lower their ESR and improvement in constitutional symptoms.
A Prospective Study To Evaluate The Efficacy Of Short-Term Intermittent Chemotherapy (STIC) As).

20 patients had neurological deficits at the time of presentation with bowel and bladder involvement in 2 patients. Neurological deficits improved in 14 patients, 4 patients developed spasticity at the end of treatment. Only one case of relapse was reported during the study.

V. Conclusion

- We could say the spinal TB is more common osteoarticular TB, affection being 59.6%. Spinal TB was commonly seen in slightly older population in comparison to extraspinal TB.
- MRI is a useful diagnostic tool with a sensitivity of 100%.
- ESR was found to be elevated in (99%) of patients. It is a useful assessment tool in diagnosis and follow-up of patients. It is also a useful index of disease activity
- We found that 53% of extraspinal TB patients were treated with DOTS category I short treatment for 6 months but a treatment of 8 months was successful in 98% extraspinal TB patients. A less favoring trend was seen in spinal TB where in 23% patients received treatment only for 6 months but the results improved to 94.6% when patients with spinal TB took treatment for 10 months atleast.
- Short term intermittent chemotherapy (STIC) i.e. DOTS category-I efficacy is good but not adequate in osteoarticular tuberculosis.
- Success of pulmonary Koch’s treatment with DOTS cannot be extrapolated to osteoarticular tuberculosis due to different nature of disease.

VI. Recommendations

- All osteoarticular tuberculosis should be kept in category I group considering serious nature of the disease.
- Further studies be carried out using four months of intensive phase therapy and variable period of 4 to 6 months of continuation phase

INTRODUCTION

Tuberculosis is a worldwide problem. World Health Organization (WHO) estimates that each year approximately 8.4 million people develop tuberculosis and approximately 3 million die each year1,2. The tragedy is made more gruesome by the fact that young adults in developing countries are disproportionately affected. It produces a global burden in terms of disability adjusted life years lost as much as 35.78 million with India accounting for one-third of total cases2.

Osteoarticular tuberculosis is a paucibacillary form of disease usually secondary to a concomitant or old pulmonary Koch’s.

Although cases of osteoarticular tuberculosis have been on a downward trend in western countries, they continue to pose major public health problem in developing countries. These cases account for approximately 5% of the total number of tuberculosis cases.

Vertebral tuberculosis is the most common form of skeletal TB comprising nearly 50% of all osteoarticular tuberculosis cases. Regional distributions in order of frequency are the vertebra, hip, knee, foot, shoulder, bursal sheath etc.3

The treatment of osteoarticular tuberculosis is primarily medical. An early diagnosis in conjunction with aggressive chemotherapy is associated with excellent outcome. However, the duration for which these drugs should be administered has remained a topic of serious debate. Diagnostic criteria are primarily clinical. There is lack of specific hematological, microscopic or radiological diagnostic parameters. There are no parameters for follow-up too. There is little consensus regarding the drugs constituting the regime, the duration of regime, the role of surgery and the management of complications. All these have rendered the treatment of osteoarticular tuberculosis complicated and are still an open question.

The WHO has brought forward category based treatment regimens of various forms of tuberculosis, popularly known as short course chemotherapy (SCC)4.

According to WHO guidelines, spinal tuberculosis is a serious form of extrapulmonary TB and is therefore included in category-I. Extrapulinal osteoarticular tuberculosis is a less severe form of disease and is therefore included in category-III.
Table 1: WHO recommended treatment regimens for each diagnostic category

<table>
<thead>
<tr>
<th>Category</th>
<th>Patients</th>
<th>Treatment Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>New smear positive PTB, new smear -ve PTB with extensive parenchymal involvement, seriously ill EPTB, severe concomitant HIV disease</td>
<td>2 (HRZE)₁ + 4 (HR)₁ / 6 HE</td>
</tr>
<tr>
<td>II</td>
<td>Previously treated sputum smear +ve, PTB, relapse, treatment after interruption, treatment failure</td>
<td>2 (HRZES)₁ + 1 (HRZE)₁ + 5 (HRE)₁</td>
</tr>
<tr>
<td>III</td>
<td>New smear –ve PTB less severe form of EPTB</td>
<td>2 (HRZ)₁ + 4 (HR)₁ / 6 HE</td>
</tr>
<tr>
<td>IV</td>
<td>Chronic and MDR TB</td>
<td>Specially designed individualized required</td>
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**Intensive Phase**

This is an initial phase in which four multidrug therapy is administered. This phase is aimed at rapidly killing the bacillary load and making the patient non-infectious. Four antitubercular drugs, i.e. Isoniazide (H), Rifampicin (R), Ethambutol (E) and Pyrazinamide (Z) are administered on alternate days for 2 months.

**Continuation Phase**

This phase is aimed at killing the slowly dividing bacilli in order to prevent emergence of relapse and drug resistance. It consists of administration of Isoniazide (H), and Rifampicin (R) for a period of four months.

Though WHO protocol (SCC) is a standard recommendation for all countries, it is not being universally followed. Various workers across the world have recommended different durations of chemotherapy for an effective management osteoarticular tuberculosis⁵. However, in view of the differences in patient profile, lack of enough information on SCC in osteoarticular TB, this treatment has not received the desired acceptability in the Indian scenario. The present study is an attempt to throw further light on the efficacy of short term intermittent chemotherapy (STIC) in osteoarticular TB patient coming to Yenepoya Medical college Hospital, Deralkatte, Mangalore.

**REVIEW OF LITERATURE**

Despite great strides achieved in the treatment and cure of tuberculosis, it continues to be the foremost public health problem and a major cause of mortality in today’s world. The disease is as ancient as civilization itself with its mention in Rigveda as Yaksha and comprehensive discussion by Sushruta⁶. Archeological excavations have uncovered Neolithic Bones showing evidence of tubercular osteomyelitis⁷. Babylonian texts also describe a chronic illness which was probably TB⁸. Hippocrates has described the tubercle but considered it to be a hereditary disorder⁹.

Huge public health efforts notwithstanding, TB prevalence as well as incidence continue their up trend, with the former standing around 30 million people, India alone accounting for 20% of them. The prevalence of infection is formidable, one-third of humanity being infected by the bacillus.

Between 3.5 to 4 million new cases were reported annually to the WHO in the late 1990s. Estimates put the figure of new cases in 2004 at 8.9 million cases. The disease proves fatal for 2 million people every year⁹. Africa, South Asia and Latin America contribute 78% of global case load¹⁰.

Starting mid 1980s the falling trend of TB in the developed West, began stabilizing and even increasing. Apart from immigration the major factors held responsible were the teeming up of tubercle bacillus with HIV and emergence of Multidrug Resistant (MDR) strains CDC estimated a 14% increase in morbidity from TB in US between 1985 and 1993¹¹. Institution of stronger control programmes led to a reversal and by 1998 there was a 31% decrease in incidence from the 1992 peak.

**Osteoarticular Tuberculosis**

Infection of a joint or bone with M. tuberculosis is almost always secondary to a primary focus, in the lymphatic glands or lungs or mesentery, from where it disseminates by hematogenous route. Excavations of such bones show that the disease occurred as far back as Neolithic times from archaeological sites at Heidelberg. It is estimated that 1-6% of children with primary infection may develop bone and joint TB in 1-3 years if left untreated¹². It has been observed that extrapulmonary TB accounts for 20-25% of total cases of TB¹³. Of the extrapulmonary cases, osteoarticular TB comprises 8-10%¹⁴.

Osteoarticular TB can involve any bone or joint, but vertebral involvement is the most common and is equal to osteoarticular TB of all other regions put together¹⁵,¹⁶,¹⁷.
With rising incidence of tuberculosis in the West after 1985, osteoarticular TB has shown a concomitant ascent.

**Myobacterium Tuberculosis**

Isolated and described by Robert Koch this bacillus is the most important member of M. tuberculosis complex which includes M. tuberculosis, M. bovis and its BCG variant, M. africanum and M. microtuberculosis, differentiated by specific hypervariable regions in the gene encoding 16S-RNA. It is a slightly curved or straight bacillus, 0.2-0.6 μ by 1-10 μ in size. It is aerobic, non-encapsulated, non-sporing and non-motile. The cell wall has high lipid content which include WaxD, cord factor, mycolic acids and sulfatides. This high lipid content excludes usually aniline dyes like Gram stain but are acid fast by Zeihl Neilsen method. It grows only media rich in egg or serum.

Formerly 85% of cases of skeletal TB under age 10 years were considered due to bovine bacilli. Now most cases are caused by bacillus of human type. It is not possible to demonstrate the bacillus in all tubercular skeletal lesions. The incidence of positive cultures in these lesions in variously reported between 40 to 88%.

**Pathophysiology**

Among healthy persons, infection with M. tuberculosis is generally asymptomatic as infection is contained by the host immune system. Only a positive tuberculin test indicates the presence of latent infection. The lifetime risk of development of clinical disease is approximately 10%. The figure dramatically rises for immunocompromised individuals, which include infants and children, grade III or IV malnutrition or HIV infection.

The initial focus of lodgment and implications is the lung usually in a subpleural location and subsequently the bacilli are carried to lymph nodes. Alveolar macrophages, activated T-cells, activated NK cells and their induced cytokines and chemokines provide initial defence against infection. While macrophages are the principal effector cells that kill bacteria, T lymphocytes are the inducers of protection.

After a period of 4-8 weeks the infection is either eradicated or walled off to an asymptomatic focus by the cell mediated immunity. However, in many cases there is intermittent release of bacilli from the focus into the bloodstream with consequent seeding of various organs in the body but in particular the central nervous system, the kidney and the skeletal system.

The very fact that a patient gets skeletal tuberculosis is a reflection of his reticuloendothelial system at the time of infection. Others hypothesize that the mycobacterial infection itself brings out subtle changes to weaken the immunoregulatory system in man. Only one third of patients with bone and joint TB will give a positive tuberculin reaction. BCG vaccination activates macrophages and their induced cytokines and chemokines provide initial defence against infection. While macrophages are the principal effector cells that kill bacteria, T lymphocytes are the inducers of protection.

HIV infection not only predisposes to new tubercular infection but also reactivates dormant foci. The role of BCG as a protective measure is still to be firmly established and in various trials across the world the rate of protection offered by it varies from low to as high as 80%. BCG vaccination activates macrophages to be more effective killer cells against mycobacteria.

**Clinical Profile of the Patient**

No age is spared from the disease though it affects most frequently during the first three decades of life. In communities with low prevalence of TB, most of the cases occur after fifty years of age while in areas where prevalence is high the majority of the people are already infected by the age of twenty.

The age profile of osteoarticular TB in Indian patients shows that it is mostly a disease of first three decades. In the developed countries, however, a much older population is involved, the median age of diagnosis being 61 years.

In most series no difference in the sex composition of the disease has been recorded. Tuli in 1997 in his series reported 52 percent incidence in males and 48 percent in females.

**Clinical Presentation**

Osteoarticular TB is characteristically insidious in onset and starts as monoarticular or mono-osseous involvement. Fever and night sweats are not common. Local pain, swelling and limitation of movement are the
usual presenting features\textsuperscript{38}. The symptomatology usually presents four to eight weeks before radiological findings can be discerned. In children, it often wakes up the child at night because muscle spasm gets reduced and causes pain. It is classically called night cries\textsuperscript{41}.

Symptoms of tuberculosis of spine are commonly insidious but sometimes they may be acute. Pain is the commonest symptom and may be accompanied by local tenderness or slightly kyphosis. The spine is stiff and tender on percussion. Spasm of vertebral muscles is present. A cold abscess may be present clinically. Paraspinal abscess may develop and present as loin mass or as a psoas abscess causing hip flexion due to psoas spasm.

Articular TB usually presents with gradually worsening monoarthritis, which may often be associated with cold abscess. It needs to be underscored that articular cartilage is preserved for a long time. Cartilage is resistant to tubercular infection because it contains plasmin inhibitors and the bacilli do not possess plasminogen activators unlike pyogenic bacteria. The articular cartilage is thus not attacked by plasmin and remains intact. The potential for good functional recovery should therefore be kept in mind.

Internal gibbus formation and consequent myelomalacic cord changes may lead to poor functional outcome despite complete cessation of disease activity. In a 1997 series by SM Tuli, 20\% of the cases had neurological involvement.

The disease is more severe in children less than 10 years of age. The average vertebral involvement and vertebral destruction is more in children leading to more severe deformity and disability\textsuperscript{44,45}.

**Regional Distribution**

Any bone in the body can be involved by tuberculosis\textsuperscript{46}. Almost half the cases of osteoarticular TB will involve the spine, extraspinal predilection being most common for hip, knee, elbow, hand and shoulder\textsuperscript{47}. Spinal involvement does not spare any part but it is most commonly found in lower thoracic and thoracolumbar spine. Thoracic spine disease occurs in 42\%, lumbar spine in 26\% and cervical spine in 12\% cases. The thoracolumbar spine is commonly affected because of the excessive stresses and strains it is subjected to, due to excessive mobility in the region. Cleveland (1992)\textsuperscript{48} reported peak incidence curve falling away more or less smoothly in each direction. In the series of Paus (1964)\textsuperscript{49}, 39 cases occurred in thoracic spine, 50 in lumbar and 8 in cervicodorsal spine, while cervical spine alone was not involved in any case.

**Radiological Diagnosis**

Diagnosis can usually be established on the basis of X-ray pictures. However, MRI and CT scans will reveal more extensive disease than predicted by X-rays. They are therefore useful while planning surgical approaches and surgery\textsuperscript{50,51,52}.

Radiographs do not show any pathognomonic features in tuberculosis of bones and joints. Radiographs often reveal narrowing of the disc space as the first radiological finding in patients of TB of spine and precede the appearance of osseous destructive changes. It is later followed by rarefaction of the vertebral end plates, soft tissue abscesses, increasing loss of disc height, variable degrees of osseous destruction and new bone formation. Multiple bone involvement in the spine is not uncommon and later fusion or collapse may occur.

Findings related to extraspinal articular involvement include osteopenia, soft tissue swelling with minimum periosteal reaction, narrowing of joint space, cysts in bone adjacent to a joint and enlargement of epiphysis in the children. Lytic lesions and periosteal reaction are seen, although latter is much more prominent in pyogenic infection.

CT scan is helpful in detecting small lytic / destroyed areas in the bone. The destruction of bone due to the disease process and also the soft tissue swellings or abscess can be seen on CT scan better and much earlier\textsuperscript{50}. It also helps in evaluating difficult areas in the spine such as cervicodorsal junctions, which cannot be seen properly with plain X-rays. Similar lesions in lumbosacral, sacroiliac and posterior elements of vertebrae, ribs and sternum are better seen on CT\textsuperscript{53}. CT guided biopsies can yield adequate samples in 25-89\% of the cases\textsuperscript{54}. MRI is a far better diagnostic tool than CT scan or plain radiographs. It demonstrates the presence and extent of compression of neural elements by adjacent bone and soft tissue. The anatomical pattern of involvement, particularly of soft tissues and discs is specific for tuberculosis\textsuperscript{55}. It is useful to differentiate between pyogenic and tubercular spondylitis\textsuperscript{56}. It also helps in detection of skip and multifocal lesions. Contrast enhanced MRI is the best imaging study to differentiate abscess from fibrous tissue, evaluate intraspinal extension, cord compression, focal myelopathy, meningeal disease and paraspinal extension\textsuperscript{57}. In spinal disease,
imaging features that favour TB rather than non-TB vertebral osteomyelitis are (i) multilevel involvement, (ii) multcentric involvement, (iii) relative spacing of intervertebral disc, (iv) large paravertebral abscess, (v) bone fragment, and (vi) rim enhancement pattern on MRI.

**Haematological Tests**

Low haemoglobin, relative lymphocytosis and increased ESR are often seen in patients with active disease. Repeated estimation of ESR at 3-6 monthly intervals gives an estimation of activity of disease. According to Watts et al (1996) general markers of inflammation, such as measurement of the erythrocyte sedimentation rate, are neither specific nor completely reliable. In another study conducted in Nepal has demonstrated that an elevated value of erythrocyte sedimentation rate is non-specific and has no diagnostic value in children.

**Serological Tests**

Most of the serological tests have low turn around time, high negative predictive value and are useful as screening tests. In disease endemic countries like India, serological tests have low sensitivity. Low sensitivity is also seen in smear negative patients and HIV positive cases.

Even in children, serology has found little place in the routine diagnosis of tuberculosis, even though it is rapid and does not require sample to be taken from the site of disease. Most of the serological tests have high sensitivity but low specificity.

**Skin Test**

Purified-protein derivative or tuberculin skin test results interpretation depends on the prevalence of exposure to tuberculosis, immunosuppression, or the possibility of previous vaccination with Bacilli Calmette-Guerin. Debilitated or malnourished patients who have extensive disease too have a false negative skin test.

Patients who are co-infected with the human immunodeficiency virus and tuberculosis are prone to anergy and negative skin testing, especially in the later stage of acquired immunodeficiency syndrome.

**Microscopy and Culture**

The ultimate diagnosis of tuberculosis depends on the recognition of mycobacterium tuberculosis on either histological study or culture, or ideally both. Because of the frequency of associated tuberculosis in the lungs and kidneys, culture of specimens of sputum and urine can be useful, however, these tests are often not performed on orthopaedic patients.

Fluorochrome and the traditional Ziehl-Neelsen stain are relatively rapid and inexpensive stains for acid-fast bacilli, but may produce false-negative results. Stains to identify acid-fast bacilli reliably require the presence of at least 10^4 acid fast bacilli per milliliter of specimen, but cultures are more sensitive and reliably identify mycobacteria in a concentration of 10^5 organisms per milliliter of specimen. Drug susceptibility testing is possible with cultures.

Cold abscesses rarely demonstrate mycobacteria on microscopy. However, culture can be helpful to assess the activity of disease presenting with persistent cold abscess. A negative culture from an aspirate of cold abscess indicates high chances of loss of activity of disease.

**Biopsy**

In countries where tuberculosis is highly prevalent and where medical facilities are limited, patients who have clinical symptoms and radiographic findings suggestive of the disease may not need to have a biopsy of the lesion in order for the physician to make a diagnosis and to institute treatment. Biopsy and possible operative treatment are reserved for patients who fail to respond to adequate chemotherapy, have substantial neurological impairment, or in whom either resistant strains or other disease entities are suspected. Biopsy is mandatory in the areas with low prevalence of disease or where multidrug resistant strains are common, both to make the diagnosis and to determine the antibiotic sensitivity.

Anti-tubercular treatment should be initiated at the time of the biopsy to decrease the likelihood of dissemination of the disease during that procedure. This is most important when the infection may involve the central nervous system and when there is a high index of suspicion, either because of a high prevalence of endemic disease or because active tuberculosis has been suggested on the basis of the clinical history or the findings on frozen section.
In the spine, CT-guided needle biopsy usually yields sufficient material either from the spine itself or from an adjacent abscess. Open biopsy of the spine is usually reserved for occasions when either closed techniques have proved insufficient or other procedures, such as decompression and possibly arthrodesis, are contemplated.

If biopsy specimen is taken from a joint, tissue from adjacent cystic lesions and the synovial tissue should also be obtained and sent for both histological and culture studies. Simple aspiration of the joint is much less likely to lead to a definitive diagnosis.

**TB BACTEC System**

This technique is specific for mycobacterial growth, where presence of bacteria is detected on the basis of their metabolism rather than their visible growth. It is a highly sensitive, specific and rapid test for detection for respiratory as well as non-respiratory smear positive specimens. Time for detection of M. tuberculosis complex is half of the time period (2-8 weeks) required for growth on L-J media.

**Polymerase Chain Reaction (PCR)**

It is emerging diagnostic tool. A negative PCR never eliminates the possibility of tuberculosis, and a positive result is not always confirmatory. In extrapulmonary tuberculosis, the study by Li et al (2000) suggests that molecular diagnosis by PCR is useful for early detection of tuberculosis in histological material where morphological features are suggestive but not confirmatory because of negative staining for AFB. PCR has been found to be extremely useful in making an early and reliable diagnosis of extra-pulmonary tuberculosis especially from joint tissues, synovial fluid, bone marrow aspirate, and peripheral blood. Malhan et al (2001) too suggest role of PCR in atypical presentation of bone pains. DNA based PCR is very sensitive but it may not be able to distinguish between viable and non-viable bacilli. Messenger RNA based transcription PCR (RT-PCR) may be more specific in this regard.

**Antitubercular Drugs**

With the discovery of streptomycin by Walksman in 1944, the approach to treatment of TB was changed forever. Chemotherapy become the anchor of treatment. Streptomycin was soon followed by addition of other effective antituberculous drugs such as isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) later researchers established the usefulness of multidrug regimens. Anti-tuberculous drugs are divided into the standard or first line and reserve or second line drugs. Another classification divides these drugs according to their ability to kill the bacilli into bacteriostatic and bactericidal drugs.

Bactericidal effect refers to the ability of the drug to kill large number of actively metabolizing bacilli rapidly. Sterilizing property on the other hand is defined as the ability to kill special populations of slowly or intermittently metabolizing semi-dormant bacilli, also known as persisters.

An important property of many ATT drugs is the ability to use them intermittently i.e. twice or thrice weekly without compromising with their efficacy. This property actually is a manifestation of what is called the “Lag Phase”. The tubercle bacillus has a long generation time (20 hrs under favourable conditions). When a culture of mycobacterial tuberculosis is subjected to an antitubercular drug, it leads to reduction in the number of bacilli. When the drug is washed away after 24 hours, the organisms fail to start multiplying immediately. The numbers continue to decrease for some more time till finally new multiplication starts taking place. This time interval is called lag phase. During this lag phase, there is no need for administration of drugs. The effect takes place with most ATT drugs except thioacetazone. The lag phases after 24 hours of exposure to various drugs are as follows:

1. INH – 6 to 9 days
2. Rmp – 2 to 3 days
3. Pyrazinamide – 40 days
4. Ethambutol – 4 to 5 days
5. Streptomycin – 8 to 10 days
6. Thioacetazone – 0 days

The first line drugs include:
- Isoniazid – H
- Rifampicin – R
- Pyrazinamide – Z
- Streptomycin – S
- Ethambutol – E
- Thioacetazone
The second line or reserve drugs are the following:

- Aminoiglycosides – Amikacin, Kanamycin, Capreomycin
- Thioamides – Ethionamide, Proteionamide
- Fluoroquinolones – Ciprofloxacin, Ofloxacin, Cycloserine
- Paraaminosalicylic acid

Isoniazid (H)

It is the foremost antitubercular drug. It is bactericidal, extremely potent and inexpensive. It diffuses into the macrophages and is effective against both intracellular and extracellular bacilli. It prevents development of drug resistance to other drugs used in combination. It acts preferentially on rapidly dividing bacilli. Hence bactericidal activity is high in the early phase. Within the first two days of administration it kills 95% of tubercle bacilli. It is given in a dose of 5 mg/kg/day at maximum dose of 300 mg/day. Chief adverse effect is pyridoxine deficiency leading to peripheral neuropathy and sometimes convulsions. Hepatitis is another significant adverse effect.

Rifampicin (R)

It is an effective bactericidal. It is effective against mycobacteria resistant to other standard chemotherapy agents and also against some of the atypical mycobacteria. It acts best on slowly or intermittently dividing bacilli. It is also effective against both intra and extra-cellular bacteria and it is the only drug effective against persisters. It imparts orange red colour to body secretions. Dosage is 10 mg/kg with maximum limit of 600 mg/day. Important side effects are hepatitis and serum sickness.

Pyrazinamide (Z)

It is a synthetic analogue of nicotinamide. It is only weakly cidal. It is more effective against intracellular bacilli. It is most effective against slow multiplying bacteria at acidic pH and it possesses a strong sterilizing effect on tubercular lesions when used in combination with other drugs. It has been shown that the relapse rate in regimens not containing Z is 3 times more than those with Z. It is however ineffective against atypical mycobacteria. It is given in a dose of 35 mg/kg/day. Adverse reaction includes toxic hepatitis which is not dose dependent.

Streptomycin

It is an aminoglycoside antibiotic derived from Streptomyces griseus and major use lies against tubercle bacilli and gram-negative infection. It is bactericidal against rapidly multiplying mycobacteria in the wall of the cavity at neutral pH. It does not diffuse into macrophages and caseous material and also does not cross the blood brain barrier. Meningeal penetration increases when they are inflamed. Primary mycobacterial resistance is seen in 2-3% of cases secondary resistance can develop rapidly if used alone.

Ethambutol

It is bacteriostatic and mainly acts over the rapidly dividing bacilli and against the atypical bacteria. It possesses sterilizing property and hence prevents relapse. It is effective against mycobacteria resistant to isoniazid streptomycin, PAS and ethionamide and also against atypical mycobacteria. It has no action against intracellular bacilli. It is given in a dose of 30 µg/kg/day. Dose dependent optic neuritis and resulting poor colour discrimination and other optic side effects can be a problem in approximately 2% of patients receiving dose higher than 15 mg/kg/day.

Second Line Drugs

In general the second line drugs are less effective and more toxic than the standard / first line drugs. The need for these drugs arises in patients with resistant mycobacterial infection or in those who develop significant toxicity with one or more first line drugs.
Fluoroquinolones are synthetic compounds structurally related to nalidixic acid. They are active against mycobacteria and no cross-resistance has been reported between them and other antitubercular drugs. Apart from ciprofloxacin and ofloxacin others tried against mycobacteria are lomefloxacin, levofloxacin and temofloxacin. In case of ofloxacin spontaneous resistance occurs in about 1 in 10^6 organisms.

Amikacin is a semisynthetic derivative of kanamycin. Although it has been shown to be effective against mycobacterium avium-intercellulare complex, its activity against M. tuberculosis has been reported to be low and hence it may not be very useful in the treatment of tuberculosis. Capreomycin has the same pharmacokinetics and toxicities as other aminoglycosides. It has incomplete cross resistance against amikacin and kanamycin. In TRC study, 6% of SHR sensitive and 15% of SHR resistant strains were found to be resistant to capreomycin.

Rifabutin is a semisynthetic spiropiperidyl derivative that has been found to be active against 30% of Rifampicin resistant M. tuberculosis strains. It has greater tissue concentration and a much longer half life than rifampicin. The longer half life may possibly delay the emergence of resistance to companion drugs. It has got good in-vitro activity against both rifampicin sensitive and resistant strains. However, caseating lesions in cavity walls, containing numerous bacilli, characteristic of human cavity type of pulmonary koch’s, may contain lesser concentrations of the drug than in plasma. In such sites it may not be an effective antimycobacterial.

Rifapentine is a cyclopentyl rifamycin and has extremely long half life and has 2-4 times greater activity as compared to rifampicin. It has better tissue penetration unlike rifampicin.

Clarithromycin has been shown to be highly active against multiple drug resistant M. avium complex. It reduces bacillary load leading to clinical improvement in M. avium disease in AIDS patients. However, very little is known about its activity against mycobacterium tuberculosis.

**Treatment Regimens for Tuberculosis**

The scourge of tuberculosis has led to great global efforts to interrupt its devastating effect. Treatment methods varied from bizarre exotic methods to very simple treatments like changes in diet, residence, climate or employment. These methods might have been effective in some cases but the major breakthrough come in 1940s with the discovery of streptomycin. PAS was also discovered in the same decade and it was found that PAS prevented the emergence of drug resistance if given in combination with streptomycin, thus dawned the era of combination chemotherapy. Treatment of this dreaded disease evolved so much so that in a decade from 1942 to 1954, the prognosis of an individual with TB changed from a dismal outlook to the expectation of complete cure.

Soon after the development of the principle of multidrug therapy for active infection came the theoretical notion than an initial intensive phase of therapy with more than two drugs followed by a continuous phase during which fewer drugs could be given, would be more effective in achieving good outcome. In the 1960s several studies provided evidence for the concept of initial intensive phase using multiple drugs. In the first 20 years after the introduction of isoniazid, standard chemotherapy included 2-3 months of H, S, P followed by H and P for at least 12 months.

In the course of time it was realized that long term therapy of 18-24 months though effective was expensive and led to non-compliance on the part of the patient. Especially the British Medical Research Council took up several field trials of short course regimens. In the year 1972, Wallace Fox showed that addition of R or Z to regimens containing H made it possible to shorten the duration of treatment. The BMRC East African study showed that the relapse rate was reduced from 22% to 8% by the addition of Z and to 3% by the addition of R and that the period of study could be reduced to only 6 months by giving both R and Z.

These trials established that
a) Regimens containing rifampicin could allow for effective short course therapy of active positive, cavitary disease.

b) At least two bactericidal drugs needed to be included in SCC.

c) Relapses in the short course chemotherapy tend to occur within the first year of completion of therapy.

d) Multidrug therapy can be given with minimal toxicity.
AIMS AND OBJECTIVES

1. Evaluation of efficacy of short term intermittent chemotherapy (STIC) in osteoarticular tuberculosis, i.e. WHO category-I
2. The role of MRI in diagnosis and assessment of spinal TB and efficacy of STIC.
3. To find the local recurrence rate, if any of osteoarticular tuberculosis after completed treatment by STIC.

MATERIALS AND METHODS

Study design: Prospective study to evaluate the efficacy of short term intermittent chemotherapy (STIC) in osteoarticular tuberculosis.

Setting: Department of Orthopaedic Surgery, Yenepoya Medical College Hospital, Deralkatte, Mangalore.

Study Group: All patients below 70 years of age, who have osteoarticular tuberculosis.

Exclusion Criteria

- Cases of osteoarticular tuberculosis with immunocompromised status such as HIV, cancer, severe protein energy malnutrition, diabetes mellitus or renal failure.
- Cases of osteoarticular TB in age group of more than 70 years.
Methodology
After suitable inclusion of patient in the study, detailed clinical assessment including history, general and systemic physical examination was done for each patient in accordance with the proforma attached for the study.

Investigations
Following investigations have been done in all patients included in the study:
- Hemoglobin concentration (Hb)
- Total leucocyte count (TLC)
- Differential leucocyte count (DLC)
- Erythrocyte sedimentation rate (ESR)
- Baseline liver function test (LFT)
- Random blood sugar
- Chest X-ray PA view
- X-ray of the affected part of the body
- Ziehl-Neelsen stain of aspirate / pus or biopsy and histological examination, wherever possible
- MRI in all spinal TB cases and some extraspinal cases

Treatment Regimen
Treatment has been given according to WHO regimen for osteoarticular TB. The DOTS regimen recommended by WHO for extrapulmonary category-I has been given i.e. 2 (HRZE)3 + 4 (HR)3. Treatment duration has been increased whenever patient has complained of re-appearance of constitutional symptoms. Surgical intervention was used only as an adjunct to the chemotherapy.

All patients were called for follow-up every month and a record of ESR and clinical parameters were taken. All patients were followed till the end of study, i.e. December 2015. In some cases of spinal TB a repeat MRI was done to assess the effect of treatment.

Clinical parameters for evaluation were:
- Subjective sense of well being
- Improvement in constitutional symptoms like fever, anorexia, lassitude etc.
- Subjective decrease in pain and gain in weight
- Decrease in size of abscess
- Healing of sinus
- Erythrocyte sedimentation rate
- Radiological signs of healing

After completion of treatment, patients were called at the interval of every three month and assessed to find local recurrence of osteoarticular TB. The result has been compiled and analysed statistically.

OBSERVATIONS AND RESULTS
During the period from April 2006 to August 2007, 104 patients could qualify the inclusion criteria. During the course of study 10 patients were lost to follow-up. The following data are based on the remaining 94 patients of osteoarticular tuberculosis who came to Yenepeo Medical College Hospital, Mangalore during the above mentioned period. The patients were further divided into categories:

1) Extraspinal tuberculosis
2) Spinal tuberculosis

Regional and gender based distribution
Out of the total 94 patients, there were 38 extraspinal cases and 56 cases of spinal tuberculosis.

Table 1: Regional and gender based distribution of patients with osteoarticular tuberculosis

<table>
<thead>
<tr>
<th>Gender</th>
<th>Spinal</th>
<th>Extraspinal</th>
<th>Osteoarticular</th>
</tr>
</thead>
</table>

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<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25</td>
<td>31</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>15</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>46</td>
<td>94</td>
</tr>
</tbody>
</table>

There were 48 male and 46 female patients in the study population. The number of males was higher in extraspinal cases. i.e. 23 males as compared to the 15 female patients while the number of females was higher in spinal TB, i.e. 31 females as compared to the 25 males. However, the total number of male and female osteoarticular tuberculosis patients remain approximately equal, i.e. 48 male versus 46 female patients (Table 1 and Fig. 1).

Fig. 1: Gender distribution of patients of osteoarticular tuberculosis

There were 48 male and 46 female patients in the study population. The number of males was higher in extraspinal cases. i.e. 23 males as compared to the 15 female patients while the number of female patients is higher in spinal TB, i.e. 31 females as compared to the 25 males. However, the total number of male and female osteoarticular tuberculosis patients remain approximately equal, i.e. 48 male versus 46 female patients (Table 1 and Fig. 1).

Fig. 1: Gender distribution of patients of osteoarticular tuberculosis

Age distribution
Median age of the study population was 26 (3-70 years)

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>No. of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>7</td>
<td>8%</td>
</tr>
<tr>
<td>11-20</td>
<td>25</td>
<td>27%</td>
</tr>
<tr>
<td>21-30</td>
<td>28</td>
<td>30%</td>
</tr>
<tr>
<td>31-40</td>
<td>21</td>
<td>22%</td>
</tr>
<tr>
<td>41-50</td>
<td>5</td>
<td>5%</td>
</tr>
<tr>
<td>51-60</td>
<td>5</td>
<td>5%</td>
</tr>
<tr>
<td>61-70</td>
<td>3</td>
<td>3%</td>
</tr>
<tr>
<td>Total</td>
<td>94</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 2: Age distribution of patient with osteoarticular tuberculosis

74 (79%) patients belonged to the age group of 11-40 years. The maximum number of patients was from the age group of 21-30 years (30%) (Table 2, Fig. 2).

Table 3: Age distribution of patients with spinal TB

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>No. of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>2</td>
<td>4%</td>
</tr>
<tr>
<td>11-20</td>
<td>10</td>
<td>18%</td>
</tr>
<tr>
<td>21-30</td>
<td>19</td>
<td>34%</td>
</tr>
<tr>
<td>31-40</td>
<td>17</td>
<td>30%</td>
</tr>
</tbody>
</table>
A Prospective Study To Evaluate The Efficacy Of Short-Term Intermittent Chemotherapy (STIC) As..}

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>No. of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>5</td>
<td>13%</td>
</tr>
<tr>
<td>11-20</td>
<td>15</td>
<td>39%</td>
</tr>
<tr>
<td>21-30</td>
<td>9</td>
<td>24%</td>
</tr>
<tr>
<td>31-40</td>
<td>4</td>
<td>11%</td>
</tr>
<tr>
<td>41-50</td>
<td>3</td>
<td>8%</td>
</tr>
<tr>
<td>51-60</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td>61-70</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>38</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

Median age in spinal TB cases was 30 years. The maximum number of cases was from the age group of 21-30 years. 46 (82%) patients belonged to the age group of 11-40 years (Table 3, Fig. 3).

Median age in extraspinal cases was 18. The maximum number of patients was from the age group of 11-20, i.e. 39%, 24 (63%) belonged to the age group of 11-30 years. There was no case of extraspinal TB in the age group of 61-70 years (Table 4, Fig. 4 and 5).

**Fig. 3: Age distribution of patients with spinal TB**

**Table 4: Age distribution of patients with extraspinal TB**

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>No. of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>5</td>
<td>13%</td>
</tr>
<tr>
<td>11-20</td>
<td>15</td>
<td>39%</td>
</tr>
<tr>
<td>21-30</td>
<td>9</td>
<td>24%</td>
</tr>
<tr>
<td>31-40</td>
<td>4</td>
<td>11%</td>
</tr>
<tr>
<td>41-50</td>
<td>3</td>
<td>8%</td>
</tr>
<tr>
<td>51-60</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td>61-70</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>38</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

**Fig. 4: Age distribution of patients with extraspinal TB**

**Fig. 5: Age distribution of spinal and extraspinal tuberculosis in graphic representation**
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The most commonly affected group was of students in extraspinal tuberculosis which is 20 (53%) of the total extraspinal cases.

Most common group affected by spinal TB is housewives 25 (45%).

Factory workers are the second most common group affected in both the extraspinal and spinal TB cases (Table 5, Table 6, Fig. 6).

Clinical Evaluation

Pain is the most common presenting complaint in osteoarticular tuberculosis.

<table>
<thead>
<tr>
<th>Occupation</th>
<th>No. of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Student</td>
<td>12</td>
<td>21%</td>
</tr>
<tr>
<td>Housewife</td>
<td>25</td>
<td>45%</td>
</tr>
<tr>
<td>Factory worker</td>
<td>18</td>
<td>32%</td>
</tr>
<tr>
<td>Service</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 5: Occupation of patients with spinal TB

<table>
<thead>
<tr>
<th>Occupation</th>
<th>No. of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Student</td>
<td>20</td>
<td>53%</td>
</tr>
<tr>
<td>Housewife</td>
<td>6</td>
<td>16%</td>
</tr>
<tr>
<td>Factory worker</td>
<td>10</td>
<td>26%</td>
</tr>
<tr>
<td>Farmer</td>
<td>1</td>
<td>2.5%</td>
</tr>
<tr>
<td>Pre-school</td>
<td>1</td>
<td>2.5%</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 6: Occupation of patients with extraspinal TB

Table 7: Distribution of symptoms in patients of spinal tuberculosis

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>No. of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Student</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Housewife</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factory worker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Service</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farmer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-school</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Pain</th>
<th>53</th>
<th>95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional symptoms</td>
<td>50</td>
<td>89%</td>
</tr>
<tr>
<td>Palpable abscess</td>
<td>15</td>
<td>27%</td>
</tr>
<tr>
<td>Neurological deficit</td>
<td>20</td>
<td>36%</td>
</tr>
</tbody>
</table>

Among the spinal TB patients 53 (95%) of the patients presented with pain; 50 (89%) of the patient had the positive history of constitutional symptoms.

15 (27%) patients presented with palpable cold abscess. 20 (36%) patient presented with neurological deficit at the time of presentation. 2 of these patients had bladder and bowel involvement at the time of presentation (Table 7, Fig. 7).

Fig. 7: Comparison of symptomatology in patients of osteoarticular TB

Table 8: Distribution of symptomatology in patients of extraspinal TB

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>No. of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>36</td>
<td>95%</td>
</tr>
<tr>
<td>Swelling / abscess</td>
<td>26</td>
<td>68%</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>20</td>
<td>53%</td>
</tr>
</tbody>
</table>

Among the extraspinal tuberculosis patients, 36 (95%) patients presented with complaint of pain, 26 (68%) of patients had swelling / abscess at the time of presentation. 20 (53%) of patients gave a positive history of one or more of constitutional symptoms like loss of appetite, evening rise of temperature, loss of weight (Table 8, Fig. 7).

Hematological Parameters

Table 9: Gender based distribution of hemoglobin in patients of osteoarticular TB

<table>
<thead>
<tr>
<th>Type of TB</th>
<th>Median Hb in males</th>
<th>Median Hb in females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Extra-spinal</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Erythrocyte sedimentation rate (ESR)

All ESR studies were done from the same laboratory in each patient. An ESR value between 0-15 was considered normal in study group irrespective of gender.

93 (99%) patients had an elevated ESR at the time of presentation. Median value at the time of presentation was 52 (15-70 mm in 1st hr).

Table 10: Pattern of ESR among patients of osteoarticular tuberculosis on presentation

<table>
<thead>
<tr>
<th>ESR</th>
<th>Spinal</th>
<th>Extraspinal</th>
<th>OATB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest</td>
<td>70</td>
<td>70</td>
<td>70</td>
</tr>
</tbody>
</table>
In patients of spinal tuberculosis, 55 (98%) had an elevated ESR at the time of presentation. Median value at the time of presentation was 55 (15-70 mm in 1st hr). In patients of extraspinal tuberculosis, 38 (100%) had an elevated ESR at the time of presentation (Table 10, Fig. 8). Median value at the time of presentation was 50 (30-70 mm in 1st hr).

Table 11: Gender based ESR distribution among patients of osteoarticular tuberculosis at the time of presentation

<table>
<thead>
<tr>
<th>Type of TB</th>
<th>Median ESR in females</th>
<th>Median ESR in males</th>
<th>Median ESR in total patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra spinal</td>
<td>46</td>
<td>56</td>
<td>50</td>
</tr>
<tr>
<td>Spinal</td>
<td>55</td>
<td>55</td>
<td>55</td>
</tr>
</tbody>
</table>

Fig. 9: Gender based ESR distribution among patients of osteoarticular tuberculosis at the time of presentation

Radiology

Skiagram as well as MRI of the affected part was done in all spinal tuberculosis patients.

Table 12: Radiological and MRI findings in all spinal tuberculosis patients
Among the spinal TB cases, 24 (43%) patients had a positive picture on X-ray, 56 (100%) patients had a positive picture on MRI. 1 (1.7%) had presented with backache with neurological deficit. She had no findings on X-ray. MRI gave findings of tuberculosis which was later found to be false positive when she did not show any sign of improvement after giving one month of ATT. Repeat MRI was done which showed meningioma and was confirmed by surgery (Table 12, Fig. 10).

**EXTRASPINAL TB CASES**

**Comparison between results of skiagram and MRI in extraspinal cases**

MRI in extraspinal TB was done in selected cases. MRI was done in only 22 cases of extraspinal TB.

**Table 13: Radiological and MRI findings in extraspinal tuberculosis patients**

<table>
<thead>
<tr>
<th>Findings</th>
<th>Skiagram</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>22 (47%)</td>
<td>56 (100%)</td>
</tr>
<tr>
<td>Negative</td>
<td>32 (47%)</td>
<td>0</td>
</tr>
<tr>
<td>False positive</td>
<td>0</td>
<td>1 (1.7%)</td>
</tr>
</tbody>
</table>

MRI was done in only 22 cases and showed positive results in all cases suggestive of TB. Skiagram was done in all 38 cases.

Only 18 (47%) patients had x-ray picture suggestive of TB (Table 13, Fig. 11).

**Histopathology**

Aspiration and microscopy was done in selected patients, only when the site was accessible without causing much morbidity.

3 patients showed AFB positive on microscopy out of 18 patients, i.e. 16%.

3 patients showed FNAC positive histopathological picture.
15 patients went for diagnostic biopsy, all of them showed positive pathological picture of necrotizing granulomatous inflammation with Langhans giant cells, i.e. 100% patients showed positive histopathological picture.

Regional distribution of lesions

<table>
<thead>
<tr>
<th>Site</th>
<th>No. of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>5</td>
<td>9%</td>
</tr>
<tr>
<td>Cervico-dorsal</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Dorsal</td>
<td>14</td>
<td>25%</td>
</tr>
<tr>
<td>Dorsolumbar</td>
<td>5</td>
<td>9%</td>
</tr>
<tr>
<td>Lumbar</td>
<td>21</td>
<td>37%</td>
</tr>
<tr>
<td>Lumbosacral</td>
<td>9</td>
<td>16%</td>
</tr>
<tr>
<td>Multifocal / skip</td>
<td>1</td>
<td>2%</td>
</tr>
</tbody>
</table>

Total: 56 (100%)

Patients of spinal tuberculosis were classified into sub-groups on the basis of vertebral involvement. Those patients having contiguous involvement of two different vertebrae were categorized into that sub-group as indicated by its name.

Patients with involvement of different categories of vertebra with normal vertebra in between were designated as skip lesions.

Lumbar spine was most commonly involved 21 (37%), followed by dorsal spine 14 (25%).

An account of total number of times a particular segment of spine was involved was prepared and the male and female subsets of the population were separately observed to find any difference in pattern of involvement. One contiguous involvement of vertebra in one segment of spine irrespective of the number of vertebra involved was calculated as one lesion. In case of involvement of two different types of vertebrae, for example lumbosacral was accounted as one each in both lumbar and sacral categories (Table 14, Fig. 12).

<table>
<thead>
<tr>
<th>Level</th>
<th>Male</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>%</td>
</tr>
<tr>
<td>Cervical</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Dorsal</td>
<td>9</td>
<td>31</td>
</tr>
<tr>
<td>Lumbar</td>
<td>13</td>
<td>45</td>
</tr>
<tr>
<td>Sacral</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
<td>100</td>
</tr>
</tbody>
</table>

Fig. 13: Gender and region based distribution of lesions in spinal TB
Pattern of involvement in males:
13 (45%) lesions were seen in lumbar spine.
9 (31%) lesions were seen in dorsal spine.

Among females
23 (53%) lesions were seen in lumbar spine.
12 (28%) lesions were seen in dorsal spine (Table 15, Fig. 13).

Gender and region based distribution of lesions of spinal TB

Table 16: Gender and region based distribution of individual involved vertebra in patients of spinal TB

<table>
<thead>
<tr>
<th>Gender</th>
<th>Cervical</th>
<th>Dorsal</th>
<th>Lumbar</th>
<th>Sacral</th>
<th>Total</th>
<th>% of total vertebrae involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>7</td>
<td>22</td>
<td>25</td>
<td>6</td>
<td>60</td>
<td>39%</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>32</td>
<td>50</td>
<td>6</td>
<td>94</td>
<td>61%</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>54</td>
<td>75</td>
<td>12</td>
<td>154</td>
<td>100%</td>
</tr>
</tbody>
</table>

If an account is made of the total number of vertebra involved.
Total number of vertebra involved is 154
75 (48%) of vertebra were lumbar
54 (35%) of vertebra were dorsal
13 (9%) of vertebra were cervical
12 (8%) of vertebra were sacral (Table 16).

Table 17: Gender and region based distribution of percentage of involved vertebra in patients of spinal TB

<table>
<thead>
<tr>
<th>Level</th>
<th>No. of vertebra in males</th>
<th>% of vertebra in males</th>
<th>No. of vertebra in females</th>
<th>% of vertebra in females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>7</td>
<td>12%</td>
<td>6</td>
<td>6.5%</td>
</tr>
<tr>
<td>Dorsal</td>
<td>22</td>
<td>37%</td>
<td>32</td>
<td>34%</td>
</tr>
<tr>
<td>Lumbar</td>
<td>25</td>
<td>41%</td>
<td>50</td>
<td>53%</td>
</tr>
<tr>
<td>Sacral</td>
<td>6</td>
<td>10%</td>
<td>6</td>
<td>6.5%</td>
</tr>
<tr>
<td>Coccygeal</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Totals</td>
<td>60</td>
<td>100%</td>
<td>94</td>
<td>100%</td>
</tr>
</tbody>
</table>

Fig. 14: Gender and region based distribution of percentage of involved vertebra in patients of spinal TB
94 (61%) vertebrae were involved in females.
60 (39%) vertebra were involved in males.

Among the male patients
- 25 (41%) were lumbar vertebra
- 22 (37%) were dorsal vertebra
- 7 (12%) were cervical vertebra
- 6 (10%) were sacral vertebra
- No coccygeal involvement was seen

Among the female patients
- 50 (53%) were lumbar vertebrae
- 32 (34%) were dorsal vertebrae
- 6 (6.5%) were cervical vertebrae
- 6 (6.5%) were sacral vertebrae
- No coccygeal involvement was seen (Table 17, Fig. 14).

Association with pulmonary tuberculosis

<table>
<thead>
<tr>
<th>Type of TB</th>
<th>Positive pulmonary Koch’s</th>
<th>Negative pulmonary Koch’s</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal</td>
<td>10</td>
<td>46</td>
<td>18</td>
</tr>
<tr>
<td>Extrapsinal</td>
<td>2</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>82</td>
<td>13</td>
</tr>
</tbody>
</table>

12 (13%) patients had history of pulmonary Koch’s infection.
Of these, one patient had an active pulmonary disease.
10 (18%) patients of spinal tuberculosis had positive history of pulmonary tuberculosis.
2 (5%) patients of extraspinal TB had positive history of pulmonary tuberculosis (Table 18).

Multifocal tuberculosis

Among the patients of spinal tuberculosis, one had multifocal involvement.
The patient was 23 year old male with involvement of L3 vertebra with pre and paravertebral collection with associated left knee swelling and synovial thickening. Synovial fluid was AFB negative. He was put on DOTS category-I with extension of continuation phase for further 4 month. Total 10 month of treatment was given and patient recovered fully.

<table>
<thead>
<tr>
<th>Site</th>
<th>No. of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>11</td>
<td>29%</td>
</tr>
<tr>
<td>Knee</td>
<td>6</td>
<td>16%</td>
</tr>
<tr>
<td>Elbow</td>
<td>4</td>
<td>11%</td>
</tr>
<tr>
<td>Long bone</td>
<td>5</td>
<td>13%</td>
</tr>
<tr>
<td>Short bone</td>
<td>5</td>
<td>13%</td>
</tr>
<tr>
<td>Cold abscess</td>
<td>5</td>
<td>13%</td>
</tr>
<tr>
<td>SI joint</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>100%</td>
</tr>
</tbody>
</table>
Among the patients of extraspinal TB, regional distribution was almost uniform. Hip (29%) was the most commonly involved joint followed by knee (16%). Short bones of hand and foot were involved in 13% cases. Long bones were also involved in 13% cases. Cold abscess was found in 13% cases (Table 19, Fig. 15).

**Fig. 15: Distribution of lesions in patients of extraspinal TB**

![Pie chart showing distribution of lesions in extraspinal TB patients](image)

**Treatment**

All the patients were started on WHO DOTS category-I \([2(HRZE)]_3 + 4 (HR)]_3 + 4 (HR)]_3\) chemotherapy. Clinical evaluation and estimation of ESR was done every month. Radiographs were taken at the end 6 and 12 months. Repeat MRI was done in selected cases of spinal tuberculosis when patient showed recurrence of constitutional symptoms during the course of continuation phase of therapy to assess the nature of healing process. All repeat MRI showed healing in progress and significant reduction of lesion. But the radiological healings lagged behind the clinical healing.

Chemotherapy was stopped after there was satisfactory relief in pain, improvement of constitutional symptoms, neurological deficit and function, fall in ESR and improvement in radiological features. In patients not showing clinical improvement and satisfactory fall in ESR, treatment was extended upto 14 months on case to case basis.

Surgical intervention was done in 16 patients of extraspinal TB. 15 patients underwent diagnostic biopsy and debridement. 1 patient underwent incision and drainage of cold abscess.

**Table 20: Trend of ESR in extraspinal TB**

<table>
<thead>
<tr>
<th>ESR</th>
<th>ESR0</th>
<th>ESR1</th>
<th>ESR2</th>
<th>ESR3</th>
<th>ESR4</th>
<th>ESR5</th>
<th>ESR6</th>
<th>ESR7</th>
<th>ESR8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest</td>
<td>70</td>
<td>65</td>
<td>40</td>
<td>20</td>
<td>20</td>
<td>18</td>
<td>10</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>Mean</td>
<td>51.45</td>
<td>44.89</td>
<td>38.66</td>
<td>31.74</td>
<td>25.95</td>
<td>21.21</td>
<td>20.50</td>
<td>25.22</td>
<td>22.39</td>
</tr>
<tr>
<td>Lowest</td>
<td>30</td>
<td>22</td>
<td>5</td>
<td>5</td>
<td>10</td>
<td>10</td>
<td>15</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Out of total 38 patients of extraspinal osteoarticular TB:
- 20 (53%) were given 6 months of antitubercular treatment
- 17 cases (45%) were given 8 months of ATT
- 1 case (2%) was given 10 month of ATT i.e. 98% of extraspinal tuberculosis patients took 6 to 8 months of ATT.

A significant relief in constitutional symptoms and pain was seen at the end of 2 months when intensive phase was completed. Median ESR value was found to come to normal at the end of 2 months of intensive phase. Student 't' test was applied between the 0, 2 and 6 ESR values.

- p-value change from 0 to 2 month <0.001
- p-value change from 0 to 6 month <0.001

These p-values indicate a very significant fall of ESR with successful treatment. The fall in ESR was found to be statistically significant and not by chance alone (Table 20, Fig. 16).
Fig 16: Trend of ESR with treatment in patients of extraspinal TB who received 6 months ATT

Table 21: Trend of ESR in patients of spinal TB who received 6 months of ATT

<table>
<thead>
<tr>
<th>ESR</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>T+3</th>
<th>T+6</th>
<th>T+9</th>
<th>T+12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest</td>
<td>60</td>
<td>52</td>
<td>46</td>
<td>30</td>
<td>38</td>
<td>28</td>
<td>22</td>
<td>18</td>
<td>15</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Mean</td>
<td>46.84</td>
<td>41.69</td>
<td>33.30</td>
<td>25.46</td>
<td>20.84</td>
<td>17.46</td>
<td>15.76</td>
<td>16.38</td>
<td>12.83</td>
<td>14.16</td>
<td>13.6</td>
</tr>
<tr>
<td>Lowest</td>
<td>15</td>
<td>10</td>
<td>10</td>
<td>8</td>
<td>8</td>
<td>10</td>
<td>8</td>
<td>22</td>
<td>10</td>
<td>8</td>
<td>10</td>
</tr>
</tbody>
</table>

T=Duration of treatment (months)

Fig. 17: Trend of ESR in patients of spinal TB who received 6 months of ATT

Student *t*-test was applied between the 0, 2 and 6 ESR values
p-value change from 0 to 2 month >0.05
p-value change from 0 to 6 month <0.05
These p-values indicate a very significant fall of ESR with successful treatment. The fall in ESR was found to be statistically significant and not by chance alone (Table 21, Fig. 17).
A Prospective Study To Evaluate The Efficacy Of Short-Term Intermittent Chemotherapy (STIC) As..

Out of total 56 patients of spinal TB
- 2 patients (3.5%) were given 14 month of treatment
- 1 patient (1.7%) was given 13 month of treatment
- 7 patients (12.54%) were given 10 month of treatment
- 1 patient (1.7%) was given 9 month of treatment
- 32 patients (57%) were given 8 month of treatment
- 13 patients (23%) were given 6 month of treatment

Treatment duration was extended on subjective valuation of constitutional symptoms and ESR as these patients still have complain of constitutional symptoms and raised ESR as they approached the completion of 6 month therapy. Then they were given extension of continuation phase on monthly basis till the disappearance of constitutional symptoms and ESR normalization (Table 22, Fig. 18).

<table>
<thead>
<tr>
<th>ESR</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest</td>
<td>65</td>
<td>60</td>
<td>41</td>
<td>44</td>
<td>40</td>
<td>32</td>
<td>35</td>
<td>30</td>
<td>32</td>
<td>24</td>
<td>18</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Mean</td>
<td>54.46</td>
<td>48.37</td>
<td>39.06</td>
<td>35.13</td>
<td>29.13</td>
<td>26.09</td>
<td>29.13</td>
<td>25.79</td>
<td>24.16</td>
<td>19.79</td>
<td>19.61</td>
<td>17.31</td>
<td>16.72</td>
</tr>
<tr>
<td>Lowest</td>
<td>30</td>
<td>25</td>
<td>18</td>
<td>20</td>
<td>35</td>
<td>20</td>
<td>22</td>
<td>25</td>
<td>20</td>
<td>10</td>
<td>10</td>
<td>12</td>
<td>15</td>
</tr>
</tbody>
</table>

20 patients had neurological deficit at the time of presentation with bladder and bowel involvement in 2 cases. Neurological deficit resolved in 14 cases. 4 cases however had developed spasticity of lower limb. Repeat MRI at the end of therapy has showed healed lesion and bone marrow fatty replacement with myelomalacic changes.

ESR fall was considerably distinct as compared to other patient who had taken ATT for 6 months. The rate of fall of ESR was slow in patients who needed extension of treatment as compared to those who took 6 month of ATT and came to normal only after 10-12 months.

Student t-test was applied between the patient who took six months of ATT and >6 months of ATT and following inference was drawn:
- Both categories of patients were responding to the treatment in the same manner and their ESR was falling significantly from the baseline during the intensive phase but their fall was statistically not significant (p>0.05).
- During the continuation phase, the fall of ESR was different in both categories and their fall was statistically significant (p<0.001), which was also supported by the constitutional symptoms in the form of lassitude and loss of appetite which prompted us to extend the continuation phase till the normalization of ESR and constitutional symptoms on case to case basis.
During the follow-up and extended period of continuation phase, the fall of ESR was not significant, i.e. (p>0.05), which shows that the patient who took extended continuation phase, really needed further treatment for normalization of ESR and constitutional symptoms.

These p-values indicate that the fall of ESR was not significant during intensive phase, but with successful treatment, the fall of ESR was found to be statistically significant and not by chance alone (Table 23, Fig. 19).

### Table 23: Mean ESR value during treatment and follow-up of patients of spinal tuberculosis who received six month and >6 month of treatment

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>T+3</th>
<th>T+6</th>
<th>T+9</th>
<th>T+12</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 month</td>
<td>49.84</td>
<td>41.69</td>
<td>33.3</td>
<td>25.46</td>
<td>20.84</td>
<td>17.46</td>
<td>15.7</td>
<td>14.00</td>
<td>15.00</td>
<td>16.38</td>
<td>12.8</td>
<td>14.1</td>
<td>13.6</td>
</tr>
<tr>
<td>&gt;6 month</td>
<td>54.46</td>
<td>48.37</td>
<td>39.06</td>
<td>35.13</td>
<td>29.13</td>
<td>26.09</td>
<td>29.13</td>
<td>25.7</td>
<td>24.16</td>
<td>19.7</td>
<td>19.6</td>
<td>17.31</td>
<td>16.72</td>
</tr>
<tr>
<td>p-value</td>
<td>0.061</td>
<td>0.067</td>
<td>0.130</td>
<td>0.002</td>
<td>0.009</td>
<td>0.002</td>
<td>0.001</td>
<td></td>
<td></td>
<td>0.081</td>
<td>0.065</td>
<td>0.0318</td>
<td>0.193</td>
</tr>
</tbody>
</table>

### Fig. 19: Trend of mean ESR in patients of spinal tuberculosis who received 6 month of ATT and >6 month of ATT

**Weight gain**
Among the extraspinal tuberculosis patients 36 (95%) patients has shown increase in weight during the course of treatment. Among the spinal tuberculosis patients, 54 (96%) patients had shown increase in weight during the course of treatment.

**Complications**
Two patients had reported for nausea and vomiting after taking the drug empty stomach one each in spinal and extraspinal TB. LFT was within the normal limit. One patient required dose adjustment as she was 12 years old female.
Second patient was given symptomatic treatment or asked to take Rifampicin with breakfast.
There was no evident icterus and both patients improved without any further LFT derangement.
Not a single patient required stoppage of ATT due to side effects.

**Relapse**
During the course of study, there was no relapse. One patient has shown cervical lymphadenopathy of tubercular origin proved by FNAC after 5 month of treatment completion. He was treated for D10-D12 spinal TB for 8 month. Radiologically the vertebrae showed healed status. Now he is taking ATT category II. He has no complaint of pain or tenderness of spine. Longest follow-up is 27 months and shortest follow up is 6 months.
IV. DISCUSSION

Tuberculosis is highly prevalent in India and continues to be a leading cause of morbidity and mortality from a curable infectious disease.

The management of osteoarticular TB is primarily medical. Nussbaum et al (1997), Moon et al (1997) and Ramchandra et al (2005) have expressed inhibition to the use of SCC in osteoarticular tuberculosis especially in spinal tuberculosis. Biddulph (1990), Upadhyay (1996), Parthasarthy (1999) and Oguz et al (2005) have demonstrated that short course regimes of 6-9 months long (not necessarily, WHO protocol) have excellent results. Most of the medical community does agree to the effectiveness of short course chemotherapy for osteoarticular tuberculosis. However, many authors opined that it is not possible to extrapolate the results of treatment of pulmonary Koch’s to osteoarticular tuberculosis. Watts et al (1996) have expressed discontent with SCC and recommended 12-18 months long chemotherapy. Other authors opine 9 months to be favourable duration for treatment. It is evident that workers across the world have divided opinion regarding the duration of multidrug therapy, drug to be used, regimen to be followed and treatment of drug resistance. A proper evidence based end-point to the institution of ATT is still to be defined.

The WHO has issued standard guidelines regarding management of tuberculosis in developing countries, and has recommended SCC for treatment of osteoarticular tuberculosis.

This prospective study conducted in Yenepoya Medical College Hospital, Mangalore, Karnataka, India during the period from December 2013 to December 2015 intended to check the efficacy of WHO protocol SCC in patients of osteoarticular tuberculosis. 104 patients qualified the inclusion criteria, 9 of them were lost to follow-up. After repeat MRI one patient turned out to be a case of meningioma and was referred to higher centre for further management. The final data is based on the findings of the remaining 94 patients.

Prevalence of spinal and extraspinal tuberculosis among patients of osteoarticular tuberculosis

The patients were divided into two categories:

1) **Extraspinal tuberculosis:** Extraspinal tuberculosis included those patients of osteoarticular tuberculosis, who did not have involvement of spine. Total number of patients in this category was 38 (40.4%).

2) **Spinal tuberculosis:** Spinal tuberculosis included those patients of osteoarticular tuberculosis, who had involvement of vertebrae. Patients having other bone tuberculosis in association with vertebrae were also included in the category of spinal tuberculosis. Total number of patients in this category was 56 (59.6%). The prevalence of spinal tuberculosis seen was higher than the contemporary global prevalence of 30-50%. This higher prevalence can be attributed to more referral of spinal tuberculosis to our centre, which is a tertiary care insurance hospital.

**Gender distribution of patients with osteoarticular tuberculosis**

This study population comprised of 48 (51%) male patients and 46 (49%) female patients, thus there is no remarkable difference in sex composition. In most series no difference in the sex composition of the disease has been recorded. Tuli in 1997 in his series reported 52 percent incidence in males and 48 percent in females. The subgroup of extraspinal tuberculosis had greater predominance of male patients, there were 23 (61%) males and 15 (39%) females. In contrast, the spinal TB subgroup comprised of 31 (55%) females and 25 (45%) males. Tuli (2004) Sinan et al (2004) have shown a higher percentage of males in spinal TB. Oguz et al (2005), however have shown greater involvement of females in cases of lumbar tuberculosis. This higher incidence of spinal tuberculosis in women can probably be attributed to the relatively poorer health status of our women and the more stress their vertebral column has to bear while performing the various activities as a housewife, the activities which demand a lot of bending and lifting weights.

**Age distribution of patients with osteoarticular tuberculosis**

The median age of the study population was 26 years (3-70 years). The median age of extraspinal tuberculosis patients was 18 years (3-60), and that of the spinal tuberculosis patients was 30 years (5-70). In the study population the maximum number of patients was from the age group of 21-30 years (30%) and 74 (79%) patients belonged to the age group of 11-40 years. Watts et al have shown that age distribution of tuberculosis is based on the endemicity of disease. This skewedness towards young population signifies the endemicity of this disease in our country. However, on close observation it appears that spinal tuberculosis patients are older than the extraspinal patients. The age group 0-40 years contributes 87% patients of extraspinal tuberculosis. A similar fraction of patients (82%) were from the age group 11-50 years in spinal tuberculosis.

**Distribution of occupation among patients of osteoarticular tuberculosis**
Ninety five percent of the patients were from the class of manual workers, housewives and students in both spinal and extraspinal subgroups as well as the study population. Thus the disease hits the society where it hurts most. The young and the working class of society are affected most. However, close observation revealed that the spinal tuberculosis patients include a very large number of housewives (45%) and the extraspinal tuberculosis patients include a very large number of students (53%). This pattern can be attributed to higher stress to the spine in case of housewives and secondly to the involvement of younger population in extraspinal tuberculosis leading to large number of students getting affected.

Distribution of symptomatology among patients of osteoarticular tuberculosis

Pain is the most common symptom of osteoarticular tuberculosis. Ninety five (95%) of osteoarticular tuberculosis patients presented with the complaint of pain. Watts et al (1996)\textsuperscript{15}, Sinan et al (2004)\textsuperscript{63}, Oguz et al (2005)\textsuperscript{123} too have found pain to be the most common presenting symptoms. Among the spinal tuberculosis patients, the second most common feature was constitutional symptoms (89%), cold abscess was found in (27%) of cases. About 36% patients presented with neurological deficit.

The second common feature in extraspinal tuberculosis was a swelling / abscess (68%). 53% of patients had a positive history of constitutional symptoms. 68% of patients have swelling or abscess at the time of presentation, therefore healing of an abscess can be a useful tool to assess recovery of extraspinal tuberculosis; unfortunately this is not so in spinal tuberculosis. Constitutional symptoms (89%) can be valuable in diagnosis and evaluation during the course of treatment. Most of the patient (65%) who were given more than 6 months of treatment had shown reappearance of constitutional symptoms at the end of 6\textsuperscript{th} month of therapy. Constitutional symptoms therefore are a good clinical adjunct in addition to ESR to monitor the progress of treatment and duration of therapy, which is still an enigma to today’s orthopaedician.

Distribution of haemoglobin and ESR among patients of osteoarticular tuberculosis

Median haemoglobin in males as well as female was 10 gm%, which was below normal. This is probably a reflection of the concurrent poor nutritional status of the affected population.

An elevated ESR was seen in 99% of all patients, 98% of spinal cases and 100% of extraspinal cases. Median values of ESR at the time of presentation was 52 mm in 1\textsuperscript{st} hr among all cases, 50 mm in 1\textsuperscript{st} hr in extraspinal cases and 55 mm in 1\textsuperscript{st} hr in spinal cases. Workers around the world are not in unison regarding the usefulness of ESR as an indicator of disease activity. Vaughan (2005)\textsuperscript{136}, Vohra et al (1997) reported an elevated ESR at the time of presentation. Watts (1996)\textsuperscript{13} and Rasool (2001) found that it might remain low and is non-specific. Although the values of ESR fluctuate between a wide range, we found an elevated ESR in addition to presence of constitutional symptoms to be a useful index of disease activity and thus helpful in making an early diagnosis and treatment follow-up.

Radiographic Evaluation

Radiograph of the affected part was taken in all patients. However, findings suggestive of tuberculosis were seen in only 56% of extraspinal tuberculosis patients and 43% of spinal tuberculosis cases. Thus radiography is not a sensitive tool for early diagnosis of osteoarticular tuberculosis, which is so important for a good functional outcome. The radiological changes associated with healing also appear late and thus, if radiographic findings are the end point of treatment prolonged drug therapy is given. However, it is a cheap and very useful investigation for diagnosis especially in areas where facilities of advanced radiology are not present.

Magnetic Resonance Imaging (MRI)

MRI was done in all cases of spinal tuberculosis and selected (22 out of 38) cases of extraspinal tuberculosis. In contrast to radiography all 56 (100%) patients of spinal tuberculosis and 22 (100%) patients of extraspinal tuberculosis in whom MRI was done showed picture suggestive of tuberculosis. One case of false positive was noticed during the course of study as the patient did not responded to ATT and repeat MRI showed it to be a case of meningioma which was confirmed by surgery. This case was referred to higher centre for further management and was not included in the study. We can conclude that the changes in MRI appear earlier than the radiograph and therefore an early diagnosis is achievable with MRI. Besides as corroborated in literature, the bony involvement, soft tissue involvement, compression of neural elements are all clearly depicted in MRI\textsuperscript{13,56,63}. The findings of healing too are apparent earliest in MRI\textsuperscript{27}, however it is not possible to distinguish a resolving collection from a persisting one. Although cost is an inhibiting factor with MRI, but as quoted by Oguz et al\textsuperscript{111}, it is useful to invest time and money to make the diagnosis of spinal tuberculosis than to deal with the catastrophic consequences of delayed diagnosis. On the basis of MRI and clinical evaluation the diagnosis can be safely made. Only in case of doubt patients should be taken up for histopathological evaluation\textsuperscript{13}.
Microbiology and Histopathology

Aspiration of abscess was done in 18 cases of osteoarticular tuberculosis of which 3 cases showed AFB bacilli, i.e. 16%. FNAC was done in 3 cases and all showed positive histopathological picture. Diagnostic biopsy was done in 15 cases and a positive result in the form of necrotizing granulomatous inflammation with Langhans giant cell was seen in all cases (100%).

Demonstration of AFB in pus on direct microscopy are not common in osteoarticular tuberculosis as shown by earlier workers. The reason for this can be the paucibacillary nature of osteoarticular tuberculosis. Histopathological examination is very sensitive and specific to diagnose tuberculosis although obtaining material for evaluation is an invasive procedure. In doubtful cases it must be done to confirm the diagnosis.

Regional distribution of lesions in patients of osteoarticular tuberculosis

Regional distribution of osteoarticular tuberculosis in spinal subgroup is distinct in males and females. 53% of lesions were seen in lumbar spine of females as compared to 45% lesions in males. In contrast 31% of males have dorsal spine lesions as compared to 28% of lesions in females.

An account of total number of vertebrae involved was also made. Among the males the total number of lumbar and dorsal vertebrae was 13 (45%) and 9 (31%) respectively. Similarly cervical vertebrae was involved in 3 (10%) and sacral vertebrae 4 (14%) with no coccygeal lesions. Whereas, in females the distribution of vertebral lesions was 23 (53%) lumbar vertebrae followed by 12 (28%) dorsal vertebrae, 5 (12%), sacral vertebrae and 3 (7%) cervical vertebrae and no coccygeal involvement. Therefore the percentage of lumbar vertebrae involvement was higher in females as compared to males and the dorsal vertebrae involvement was lower than the males. In Oguz et al (2005) study of lumbar and lumbosacral tuberculosis the number of female patients was more than males.

Among the extraspinal tuberculosis cases the distribution of lesions was more or less uniform. Hip joint constituted 11 (29%) of cases and was the most common joint to be involved followed by the knee joint 6 (16%), elbow 4 (11%), long bones 5 (13%), short bones 5 (13%), cold abscess without bony involvement 5 (13%). The cold abscess patients without any bony involvement were effectively treated with short term intermittent chemotherapy (STIC) of 6 months duration without any extension of treatment duration. So, it can be safely concluded that the extrapulmonary tuberculosis without bony involvement can be treated with short term intermittent chemotherapy (STIC).

Association with pulmonary Koch’s

A history of pulmonary tuberculosis was seen in 10 (18%) spinal tuberculosis patients, 2 (5%) extraspinal tuberculosis patients and in a total of 12 (13%) osteoarticular tuberculosis patient. This is significantly lower than the 30% rate reported in literature. Of these, one patient has an active disease of pulmonary Koch’s. In our study, among the spinal tuberculosis patients, where more patients of elder age group were involved, the past history of pulmonary tuberculosis was positive in more patients (18%). This finding supports the fact that involvement of older patients is more the result of immune suppression and re-activation of disease than endemicity of tuberculosis.

Treatment (chemotherapy)

All the patients were started on WHO protocol short term intermittent chemotherapy (STIC) i.e. DOTS category-I after clinical evaluation and estimation of ESR at the time of presentation. Clinical evaluation and estimation of ESR were done every month during the course of treatment and every 3 months after completion of treatment. Though workers across the world have doubts about the reliability, sensitivity and specificity of ESR in diagnosis of tuberculosis. It has been demonstrated that the recovery of patient was associated with fall in ESR. ESR was chosen as marker of activity in these patients because of the following reasons: Consistently fall of ESR closely followed the activity of disease in majority of patients in first few months of treatment when even MRI is unable to show the healing changes and assessment of improvement is purely clinical. Besides, it is cheap, time saving and a reproducible investigation if followed from the same lab.

In patients not showing clinical improvement and a satisfactory fall in ESR, treatment was extended till the normalization of ESR and disappearance of constitutional symptoms.

20 (53%) patients of extraspinal TB received chemotherapy for 6 months and 17 (45%) patients were given 8 months of chemotherapy. Significant pain relief and a fall in ESR was found at the end of 2 months of intensive phase in all cases. On application of statistical analysis this fall at the end of 2 months (p value <0.001) and the
end of 6 months (p-value <0.001) was statistically highly significant. Chemotherapy was given to one patient for a period of 10 months as his ESR was above normal and constitutional symptoms did not subside. So, we can conclude that 98% of extraspinal TB patient can be treated with 8 months of DOTS category-I therapy.

Regarding spinal TB, all of the 56 patients who were followed up showed signs of recovery both in terms of ESR and constitutional symptoms. Of these, 13 (23%) did not show any further deterioration afterwards till the termination of the treatment at 6 months. The remaining 43 patients (77%) showed some kind of deterioration during the continuation phase. Deterioration was inferred from either ESR raised or presence of constitutional symptoms or subjective reversal of feeling of well being. On application of statistical analysis (student t-test) between patients of spinal tuberculosis who needed extension of continuation phase and those who took ATT for 6 months, the fall of ESR at the end of second month of intensive phase was not significant (p>0.05) but at the end of 6 month (p<0.05) was statistically highly significant and not by chance alone during the course of treatment.

In the absence of any fixed guidelines, the treatment duration of these patients was extended for further two months, three months or four months, the tendency throughout being to terminate the therapy as early as clinical symptoms allowed.

The fall in ESR at the end of 2 months (p-value >0.05) was statistically not significant, however at the end of 6 month (p-value <0.05) was found to be statistically significant. This implies that the fall in ESR value is not by chance in all forms of tuberculosis whether spinal or extraspinal tuberculosis. So, we can safely say that the spinal tuberculosis requires longer duration of therapy than the extraspinal tuberculosis as 94% patients required 6-10 months of chemotherapy.

After closely monitoring the patient during the treatment and follow-up in our study, we found that on the basis of clinical parameters:

- Unlike pulmonary koch's where criteria for extension of intensive phase are well defined under DOTS, it is not possible to decide whether extension intensive phase will affect the duration of treatment.
- At 6 months, i.e. at the end of DOTS therapy it is possible to decide the extension of continuation phase based on investigation and constitutional symptoms.
- In our study, we extended the duration of continuation phase at the end of 6 months if there was presence of constitutional symptoms or if the fall of ESR was not significant.

The important question that arises from the above discussion and which was always a dilemma for us was whether there was a need for prolonging the duration of intensive phase. This we think should be an important question for further research.

In pursuit of the answer to the above question, it can be suggested that future studies be carried out wherein patients are put into 3 groups A, B and C prior to start of treatment. Group A should be given 2 months of intensive phase and 4 months of continuous phase; group B should be given 3 month of intensive phase and 4 months of continuation phase, while group C should be given 4 month of intensive phase and 4 month of continuation phase. This scheme will ensure much better statistical comparison. Further it is suggested that if required therapy can be continued after the stipulated period in each group but this additional period should not be considered in the study.

20 patients had neurological deficit at the time of presentation with bladder and bowel involvement in 2 cases. Neurological deficit resolved in 16 cases. 4 cases however had developed spasticity of lower limb. Repeat MRI at the end of therapy has showed healed lesion and bone marrow fatty replacement with myelomalacic changes.

It was found that patients of TB of spine, hip and knee have to visit the DOTS Centre on alternate days during the intensive phase. This protocol goes against the principle of treatment, which requires the patient to be immobilized, instead of helping the patient to recover it causes more harm. It should therefore be brought to the notice of the authorities that there is a need to have a new look into this aspect.

**Weight Gain**

In our study weight gain was found to be a very useful indicator of clinical improvement. Among the spinal tuberculosis patients, 54 (96%) had shown increase in weight gain and in extraspinal tuberculosis 36 (95%)
patients have shown increase in weight during the course of subjective evaluation and a study to look at an objective evaluation would be worthwhile to assess early response to treatment and further follow-up.

Drug related complication
One patient of drug induced hepatitis was seen. She was a 12 year old girl and required dose adjustment and symptomatic treatment, the recovery was uneventful. Drug related complication was very low in our series but this needs to be proved statistically.

Relapse
Relapse is associated with all treatment regimens, even if the treatment has been taken religiously with 100% compliance and the standard regimen 2 HRZE / 4 HR has a relapse rate of 2 to 3%.

During the course of study there was one case of relapse among the patient after 5 months of treatment. He had taken ATT for spinal tuberculosis for 8 months. After 5 months of follow-up he came with cervical lymphadenopathy, which was proved to be tubercular in origin by FNAC report. Now he is taking ATT under DOTS category-II. Longest follow-up was 27 months and shortest follow-up is 6 months. However, a prolonged follow-up for 5-10 years is necessary for realizing the potential of short term intermittent chemotherapy in osteoarticular tuberculosis (STIC) in preventing relapse.

In this study we have found that DOTS category-I treatment is effective but the duration of treatment is not adequate as majority of patient required extension of treatment regime, especially in cases of spinal tuberculosis, where only 13 (23%) patients took ATT for 6 months.

It is thus found that 98% of extraspinal cases can be treated with 8 months of DOTS category-I treatment. In case of spinal TB 94.6% cases have been adequately treated with 10 months of therapy. With 8 and 6 months of therapy, the proportion of cured cases declines to 80% and 23% respectively. Hence, it may be concluded that for the treatment of a satisfactory proportion of patient at least 10 months of treatment will be required.

SUMMARY AND CONCLUSION
During the study period from December 2013 to December 2015 a total of 94 patients were evaluated for osteoarticular tuberculosis, started on ATT i.e. DOTS Category-I and observed for various parameters as mentioned in proforma, in the Department of Orthopaedics, ESI Hospital, Basaidarapur, Delhi.

- Osteoarticular tuberculosis has two different patterns of involvement
  - Spinal tuberculosis
  - Extrapinal tuberculosis
- Spinal tuberculosis is more common (59.6%). It is associated with a greater morbidity and has dreaded complications like paraplegia (36%) and loss of control of bladder and bowel function (3.5%).
- The population involved by spinal tuberculosis is older (86% patients from the second to fifth decade) than the extrapinal tuberculosis (87% patients from the first four decades) by a decade.
- Extrapinally hip (29%), knee (16%), and elbow (11%) are the major joints commonly involved and regional distribution in spinal tuberculosis is different in males and females.
- Majority of spinal patients are housewives most probably as a result of its preponderance in females and a decade older than extrapinal TB patients.
- Majority of extrapinal tuberculosis patients are students probably because of its preponderance in younger population.
- Constitutional symptoms like low grade fever, loss of appetite, loss of weight are common in osteoarticular tuberculosis (74%), more so in spinal tuberculosis (89%).
- Though osteoarticular tuberculosis is a secondary lesion, evidence of pulmonary disease was seen in only (13%) of patients. Patients of spinal tuberculosis have a higher rate of old pulmonary koch’s (18%), the population affected was older too.
- Radiographic changes are non-specific, appear late and suggestive of tuberculosis in (44.6%) of cases.
- MRI is a very useful diagnostic modality especially in cases where X-rays are non-contributory. Signs suggestive of tubercular involvement appear early and sensitivity in our series is 100%.
- ESR was found to be elevated in (99%) of patients. It is a useful contributory factor in diagnosis and follow-up of patients. It is also a useful index of disease activity and its fall is statistically significant during the course of treatment.
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- The fall of ESR was not steep in patient who took ATT for more than six months as compared to those who took six months of ATT.
- Diagnosis of osteoarticular tuberculosis can be made in most of the cases if three parameters are positive, i.e. presence of constitutional symptoms, raised ESR and positive MRI findings.
- Diagnosis should be reviewed if patient does not show any improvement after taking ATT for more than one month.
- The demonstration of necrotizing inflammation with granulomas and Langhan’s giant cells in a biopsy is more sensitive tool (100%) as compared to demonstration of acid fast bacilli (16.6%).
- Medical management is the mainstay in osteoarticular tuberculosis. Surgery at its best is an adjunct to chemotherapy to deal with complications and to help in diagnosis.
- WHO short term intermittent chemotherapy (STIC) in osteoarticular tuberculosis, i.e. DOTS category-I was found sufficient in (53%) in extraspinal tuberculosis and 23% in spinal TB.
- MDR TB is rare entity in osteoarticular tuberculosis, as no case was found in our study.
- There was one case of relapse during the course of study, after 5 months of treatment completion. Longest follow-up from time of stopping ATT was 27 months and shortest follow-up was six months.
- Patients are not able to take adequate rest especially in spinal, hip and knee tuberculosis as they have to go to DOTS centre on alternate days, which causes more harm. This calls for a new look on DOTS policy for this group
- Short term intermittent chemotherapy (STIC) i.e. DOTS category-I efficacy is good but not adequate in osteoarticular tuberculosis.
- Success of pulmonary koch’s treatment with DOTS cannot be extrapolated to osteoarticular tuberculosis due to different nature of disease.
- All osteoarticular tuberculosis should be kept in category I group considering serious nature of the disease.
- It is recommended that further studies be carried out using four months of intensive phase therapy and variable period of 4 to 6 months of continuation phase to find out if this might shorten the duration of treatment.

The study is not without its limitations

- Selection bias as only those patients who are ESI, beneficiary came for treatment. A multicentric study at several centres and catering to different populations would be more meaningful.
- Sample size is small. The statistical analysis will be even more relevant if a larger sample is drawn from the population.
- Intensive phase should be increased from two to four months as patient showed good improvement in intensive phase as compared to continuation phase.
- Follow-up period is short. A prolonged follow-up of 5-10 years is essential to ascertain the actual rate of relapse.

To conclude, osteoarticular tuberculosis is common orthopaedic problem in India that can be diagnosed early with judicious use of clinical evaluation and MRI. DOTS category-I treatment needs to be given for at least 8 months in extraspinal osteoarticular tuberculosis, which will treat 98% of the patients. Finally DOTS category-I treatment needs to be given for at least 10 months in spinal osteoarticular tuberculosis if at least 95% of the patients are to be treated.
Case No. 1 (extraspinal TB)
- A 21 year old female
- Presented with complaints of pain and swelling left elbow
- Severe restriction of movement of left elbow

Range of movement at the time of presentation

X-ray showing soft tissue swelling, no bony changes

MRI clearly demonstrated bony as well as soft tissue changes

Range of movement after the end of treatment
Case No. 02 (Spinal TB)
A 38 year old male presented with complaints of pain in back, associated with neurological deficits.
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Case No. 03 (Spinal TB)
A 11 year old male Presented with complain of pain in cervical spine for 1 month

X-ray film at the time of presentation showing paraspinal muscle spasm

MRI film clearly demonstrate the lesion
A Prospective Study To Evaluate The Efficacy Of Short-Term Intermittent Chemotherapy (STIC As).

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