



### Original Research Article

## Efficacy of Four drug regimen vs. Three drug regimen in Patients of Tuberculous Lymphadenitis, Registered at S.N Medical College, Agra

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### Abstract

**Background:** Tuberculosis can involve any system in the body. About 15% of people may develop tuberculosis in any organ other than lung. Lymph nodes are most common extra pulmonary site of get involved. Disease may affect a single lymph node or a number of lymph nodes in a particular chain sometimes bilaterally

**Aims:** To compare the efficacy of 4 drug Regimen (HRZE) vs.3 drug Regimen (HRE) in patients of tuberculous lymphadenitis

**Materials and Methods:** Patients of proved cases of tuberculous lymphadenitis by FNAC (Fine Needle Aspiration Cytology) have been selected for this study, irrespective of age, sex, case and religion. No discrimination has been made regarding site size or number of lymph nodes. These patients are those who attended OPD of the department of Tuberculous and Chest Diseases. The results of both regimens were compared in relation to decrease in the size of lymph node(s) clinical, hematological and other investigation relevant in the diagnosis.

**Result:** In HRZE group (56) lymph nodes were completely resolved in 42 (75%) cases. Residual lymph nodes (>2 cm) were present in 14 (25%) which on further FNAC 8(14.3%) were positive. Favorable response were seen in 48 (85.7%) cases. 7 (12.5%) cases were treated on retreatment. One case 1 (1.7%) was resistant to rifampicin and isoniazid which was treated with multi drug resistant treatment. In HRZ group (50) lymph nodes were completely resolved in 32 (64%) cases. Residual lymph nodes (> 2 cm) were present in 18 (36%) cases. Further FNAC was positive in 12 (24%) cases. Thus favorable response were seen in 38 (76%) cases. 10 (20%) cases responded on retreatment while 2 (4%) cases presented with drug resistant.

**Conclusion:** The study shows that 6 months, thrice weekly HRZ regimen in initial intensive phase for tuberculous lymphadenitis showed response rate 76% while HRZE regimen in initial intensive phase showed 85.7% response rate. So HRZE seem to have more efficacy than HRZ in treatment of tuberculous lymphadenitis.

**Keywords:** Tubercular Lymphadenitis, HRZE, HRZ, FNAC.

## Introduction

Tuberculosis is responsible for up to 43% of all peripheral lymphadenopathy in the developing world.<sup>(1)</sup> It affect cervical lymph nodes (63.3%) followed by mediastinal lymph nodes (26.7%) and axillary lymph nodes (8.3%)<sup>(2)</sup>. The prevalence of tuberculous lymphadenitis in children upto 14 year of age in rural India is approximately 4.4 cases per 1000<sup>(3)</sup>. In United State 5.4% of all tuberculosis is extra-pulmonary and 31% of these cases are lymphatic<sup>(4)</sup>. Tuberculous lymphadenitis is more common in women than men<sup>(5)</sup>.

Mycobacterium tuberculosis accounts 95% of all Mycobacterial lymphadenitis in adult where as in children 92% of all Mycobacterial lymphadenitis was due to NTM<sup>(6)</sup>. It is so widely prevalent in India as to constitute a major health problem. Therefore its early and correct diagnosis is essential for prompt treatment and containment of disease. Clinically tuberculous lymphadenitis has insidious onset<sup>(7)</sup> characteristics of multiplicity, matting and caseation<sup>(8)</sup>. Tuberculin skin test has less importance in diagnosis especially in adults.

FNAC Fine Needle Aspiration Cytology (FNAC) is most conventional way of diagnosis. It is easy to perform as nodes are easily assessable and no high level of training is required<sup>(9)</sup>. FNAC has high sensitivity and specificity for diagnosis of tuberculous lymphadenitis<sup>(10)</sup>. Diagnostic finding on cytology are epitheloid cells, granuloma, giant cell granuloma, necrotic cells, langhan's cells and acid fast bacilli<sup>(11)</sup>. According to Lioe and Coworkers<sup>(12)</sup>, 1990 sensitivity and specificity of FNAC of tubercular lymph nodes was 77% and 93% respectively. Evaluation of AFB smear result revealed a high positive rate (47%) when necrosis was present and 15% when necrosis was absent.

In present study FNAC proved cases of tuberculous lymphadenitis HRZE regimen and HRZ regimen were compared. Outcome of both the regimen were compared to see the efficacy of the in treatment of tuberculous lymphadenitis.

## Material & Methods

**Selection of Patients:** Patients of confirmed cases of tuberculous lymphadenitis by FNAC (Fine Needle Aspiration Cytology) have been selected for this study, irrespective of age, sex, case and religion. No discrimination has been made regarding site size or number of lymph nodes. These patients are those who attended OPD of the department of Tuberculous and Chest Disease. Only those patients have been selected who fulfilled the Inclusion Criteria

### Inclusion Criteria

- Having one or more soft rubbery or cystic lymph node.
- X-ray chest showed no tuberculous lesion of any type.
- No history of previous tuberculosis infection or antituberculous therapy.
- No concomitant disease like leprosy, diabetes, mellitus, renal disease or liver disease that might alter the immune response of individual.
- Not on steroid or immunosuppressive drugs
- Sputum negative cases.

### Exclusion Criteria

- Unwilling to participate in the study.
- Patients who are registered outside the study period.

### Patient Selection

After taking informed consent, all the patients were arranged in serial number i.e. (n = 1, 2, 3 .....). Treatment were given 2 (HRZ)<sub>3</sub> + 4 (HR)<sub>3</sub> odd serial number i.e. (n = 1, 3, 5....) and 2(HRZE)<sub>3</sub> + 4 (HR)<sub>3</sub> even serial number i.e. (n = 2, 4, 6) and outcome was measured. Patients having no response or persistent lymphadenitis underwent lymph nodes aspirate or lymph node tissue homogenate for mycobacterial culture regimen i.e. 2 (SHERZ)<sub>3</sub> / 1(HER)<sub>3</sub> / 5 (HR)<sub>3</sub>.

### Definitions

**Four Drug (HRZE) Regimen:** New cases who are sputum positive or seriously ill patient with

smear negative or extra pulmonary disease. Treatment is given in two phases. The intensive phase consists of isoniazid, rifampicin pyrazinamide and ethambutol given under direct observation thrice a week on alternate days and last for 2 months. In continuation phase isoniazid and rifampicin were given thrice a week on alternate day for four months.

**Three Drug (HRZ) Regimen:** Patients who are smear negative and who have extra pulmonary tuberculosis and are not seriously ill treatment is given in two phases. The intensive phase consist of isoniazid, rifampicin and pyrazinamide thrice a week on alternate day and last for two months. In continuation phase isoniazid and rifampicin were given thrice a week an alternate day.

### Analysis of Results

The results of both regimens were compared in relation to decrease in the size of lymph node(s) clinical, hematological and other investigation relevant in the diagnosis. All cases were interrogated and investigated i.e. detailed clinical history, duration of illness, present, occupational history, personal history, and past illness especially pertaining to respiratory system, family history and history of previous chemotherapy.

**Study Period:** The study was conducted from June 2008 to June 2009.

### Fine Needle Aspiration Cytology (FNAC)

#### Method of Aspiration

Patient with suspected tuberculosis of cervical lymphadenitis were selected. The skin was cleaned with antiseptic lotion with spirit.

### Observation

**Table 1** Outcome of patients after treatment

| Patients                             | HRZE Regimen |      | HRZ Regimen |    | Total |      |
|--------------------------------------|--------------|------|-------------|----|-------|------|
|                                      | No.          | %    | No.         | %  | No.   | %    |
| Completely resolve                   | 42           | 75   | 32          | 64 | 74    | 69.8 |
| Residual Lymph node (> 2 cm)         | 14           | 25   | 18          | 36 | 32    | 30.2 |
| FNAC of Residual Lymph Node Positive | 8            | 14.3 | 12          | 24 | 20    | 18.9 |
| Favorable Response                   | 48           | 85.7 | 38          | 76 | 86    | 81.1 |

Table 1 shows Comparison of outcome of patients in HRZE Regimen and HRZ Regimen and the difference was found to be statistically significant (p=0.03698)

The lymph node was fixed with the help of an assistant in the position favorable for needle aspiration.

The steps of the aspiration were as follows:

- The needle (standard disposable 22 - 23 gauge 1' to 1.5' in length) were inserted into the lymph node and positioned.
- The plunger was pulled to create negative pressure inside the syringe (20 ml disposable syringe).
- The needle was then moved to and fro within the lymph node in two/three different directions.
- The negative pressure was then released gently, while the needle was still within the lymph node.
- The needle was then withdrawn from the lymph node and detached from the syringe.
- Air was drawn into the syringe and aspirate was blown onto the slide
- Smear was prepared over the slides, fixed and stained for microscopic examination.

### Preparation of the Smear

Smear was prepared on the clean glass slide with the help of loop smear as the area of 2 - 3 cm. Air dried smear is fixed by gently heating over the flame.

### Statistical Analysis

The data was analyzed using SPSS (Ver22) software. Chi Square test was used wherever applicable. P < 0.05 is statistically significant.

**Table 2** AFB (Acid Fast Bacilli) Positive from FNAC smears.

| AFB      | HRZE |      | HRZ |    | Total |      |
|----------|------|------|-----|----|-------|------|
|          | No.  | %    | No. | %  | No.   | %    |
| Positive | 24   | 42.8 | 24  | 48 | 48    | 48.3 |
| Negative | 32   | 57.2 | 26  | 52 | 58    | 54.7 |

Table 3 shows comparison of AFB positive in HRZE Regimen and HRZ Regimen patients and it was not statistically significant ( $p=0.595$ )

### Results

- We found that there was favorable response was seen in 85.7% of HRZE patients and 76% of HRZ patients and statistically it was significant ( $p=0.03698$ ).
- We found that AFB Positive from FNAC smears was seen in 42.8% of HRZE patients and 48% of HRZ patients and it was not statistically significant ( $p=0.595$ )

### Discussion

The present study included 121 cases of FNAC proven tuberculous lymphadenitis 106 are available for analysis after completion of 6 month chemotherapy. All were allocated DOTS HRZE (56) and HRZ (50) alternatively. All were made to undergo test and smear for AFB from Fine Needle Aspirate.

In HRZE group (56) lymph nodes were completely resolved in 42 (75%) cases. Residual lymph nodes ( $> 2$  cm) were present in 14 (25%) which on further FNAC 8(14.3%) were positive. Favorable response were seen in 48 (85.7%) cases. 7 (12.5%) cases were treated on retreatment. One case 1 (1.7%) was resistant to rifampicin and isoniazid which was treated with multi drug resistant treatment. While Arora<sup>(13)</sup> analyzed two hundred cases on 2HERZ/4HR on domiciliary basis. 91% showed favorable response and 4 showed relapsed.

In HRZ group (50) lymph nodes were completely resolved in 32 (64%) cases. Residual lymph nodes ( $> 2$  cm) were present in 18 (36%) cases. Further FNAC was positive in 12 (24%) cases. Thus favorable response were seen in 38 (76%) cases. 10 (20%) cases responded on retreatment while 2 (4%) cases presented with drug resistant. One was resistant to rifampicin only other was resistant to

both rifampicin and isoniazid. Both were successfully treated on drug resistant treatment.

All aspirates were also subjected to Ziehl – Neelson staining for AFB detection. AFB was detected in 48 (48.3%) cases. which was corresponds to different worker 53% (Lou et al<sup>(12)</sup> 52% Radhika<sup>(14)</sup> 49.2% Jayalakshmi<sup>(15)</sup> 46.4%) 56.7% Getachew (16).

Ziehl Neelson staining for AFB may be negative due to

- Aspirate material may be not adequate
- The number of bacilli would be less (paucibacillary stage).

Six months, thrice weekly HRZ Regimen in initial intensive phase for tuberculous lymphadenitis showed response rate 76% while HRZE Regimen in initial intensive phase showed 85.7% response rate. So HRZE Regimen seem to have more efficacy than HRZ in treatment of tuberculous lymphadenitis.

### Conclusion

The study shows improved efficacy of HRZE in Tubercular Lymphadenitis which was found to be statistically significant ( $p= 0.03698$ ) Based on these studies and clinical results, Category III (2HRZ/4HR) was subsequently removed from the RNTCP- DOTS programme in 2012.

### Acknowledgements

We are thankful to entire staff of Department of Pathology for their valuable co-operation.

**Funding:** No funding sources

**Conflict of interest:** None declared

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