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Role of Extended Anti-Tubercular Therapy Course Duration in Slowly Responsive or Non-Responsive Tubercular Cervical Lymphadenopathy

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Abstract **Original Research Article**

Introduction: Tubercular cervical lymphadenopathy (TCL) remains a significant health concern, particularly in developing countries. The effectiveness of extended anti-tubercular therapy in slowly responsive or non-responsive TCL cases is a subject of ongoing debate. This study aimed to assess the role of extended anti-tubercular therapy course duration in such cases and to explore the need for alternative treatment strategies. ***Methods:*** This retrospective study was conducted over a period of 4 years, from January 2019 to January 2023, at the Department of ENT & Head Neck Surgery, Dhaka Medical College Hospital, Dhaka, Bangladesh. The initial sample size of 189 TCL patients was narrowed down to 125 slow or non-responsive patients after 6 months of standard treatment. Various characteristics such as swelling type, swelling size, and swollen node were analyzed, and the response rate to standard medication was assessed. ***Result:*** The study revealed that 90.40% had swelling sizes of 3 cm or less, with limited changes in nodal size over time, and only 16.80% reaching a nodal size of less than 10 mm after a year. The response rate to medication was 33.86% after 6 months and 46.56% after a year, with 19.58% still showing a slow response. The swelling size shifted from 51.32% being less than or equal to 3 cm initially to 70.27% being greater than 3 cm after a year, suggesting that continuing medication might not be effective for a significant number of non/slow-responsive TCL cases. ***Conclusion:*** The findings of this study highlight the limitations of extended standard treatment for TCL and emphasize the need for personalized approaches, possibly including surgical intervention. The evidence presented calls for further research to explore alternative strategies and a reevaluation of current treatment guidelines, prioritizing patient outcomes and responsiveness to therapy.

Keywords: Tuberculosis, Tubercular cervical Lymphadenopathy, Re-treatment, Relapse.

INTRODUCTION

Tuberculosis, a persistent global health challenge, continues to be a prevalent cause of cervical lymphadenopathy, particularly in developing nations. This condition predominantly affects children and young adults, although it is not confined to any specific age group [1]. Lymph nodes, with their essential role in dealing with various forms of antigens, whether organisms, particulate material, or soluble antigens, are central to understanding this disease [2]. The world is witnessing a marked increase in mycobacterial infections, with tuberculosis emerging as a significant contributor to morbidity and mortality [3]. As one of humanity's oldest diseases, tuberculosis inflicts profound suffering and loss of life, with nearly 9 million new cases and 2 million deaths reported globally each year. Lymph node tuberculosis accounts for approximately 35 percent of extrapulmonary tuberculosis, constituting about 15 to 20 percent of all tuberculosis cases [4]. In the context of the head and neck region, tuberculosis can manifest in various areas, including the lymph nodes, larynx, middle ear, oral cavity, and pharynx. This multifaceted presentation makes the head and neck region a compelling field of research, as tuberculosis may often resemble malignancy, leading to misdiagnosis and subsequent delays in treatment [5]. While the mortality rate of Tubercular Cervical Lymphadenopathy (TCL) remains underdocumented, it is recognized that delayed diagnosis and treatment can result in grave

complications such as airway obstruction and TB dissemination to other body parts [6]. The current treatment regimen endorsed by the World Health Organization (WHO) for new TB cases (Regimen I) consists of a combination of isoniazid (H), rifampicin (R), pyrazinamide, and ethambutol for the initial 2 months, followed by H and R for an additional 4 months (WHO, 2009). However, the rise of Multidrug-resistant TB (MDR-TB) and Extensively Drug-resistant TB (XDR-TB) poses new challenges (WHO, 2009), and the WHO emphasizes the importance of drug susceptibility testing at the onset of therapy, particularly for previously treated patients [7]. Anti-Tubercular Therapy (ATT) under DOTS remains the primary treatment, with surgery being considered for enlarged lymph nodes or TCL unresponsive to medication [8]. Yet, the issue of drug resistance, stemming from both inherent and acquired mechanisms, leads to slowly responsive or non-responsive outcomes. The prolonged treatment duration (often exceeding 6 months for drug-sensitive TB) with multiple agents further complicates matters, potentially leading to the selection of resistant subpopulations during treatment. The resistance in TB is mainly mediated by chromosomal mutations, and there are no known instances of horizontal gene transfer. However, the bacilli can become resistant through various means, not all of which involve mutation of the drug target [9]. Surgery combined with drug therapy or drug therapy alone has been explored with mixed results. This study is designed to assess the role of extended anti-tubercular therapy course duration in slowly responsive or non-responsive tubercular cervical lymphadenopathy, shedding light on an area that requires further exploration and understanding.

OBJECTIVE

General Objective

- To see the role of extended anti-tubercular therapy course duration in slowly responsive or non-responsive tubercular cervical lymphadenopathy.

Specific Objectives

- To see the socio-demographic status of the participants.
- To know the duration of extended treatment.
- To see the duration of relapse.

METHODS

This retrospective study unfolded over a span of 4 years, from January 2019 to January 2023, within the Department of ENT (Ear, Nose, Throat) & Head Neck Surgery, Dhaka Medical College Hospital, Dhaka, Bangladesh. Initially, the study encompassed 189 TCL (Tubercular Cervical Lymphadenopathy) patients from the study hospital, all of whom had received standard TB medication as an initial treatment. Upon applying the predetermined inclusion and exclusion criteria, the sample size was refined to 125 TCL patients. These patients had been undergoing TB medication for a duration of 6 months without achieving a complete response. A complete response was defined by specific criteria, including a lymph node size of less than 15 mm, and the absence of symptoms such as fever, abscess, etc. Data collection was meticulously carried out through a review of hospital record files, ensuring a comprehensive and accurate representation of the patient information. A simple random sampling technique was employed to maintain the integrity of the study, and the data were processed using SPSS version 20.0. The processed data were subsequently presented in the study through various illustrative means, including tables and pie charts. The Ethical Review Committee of Dhaka Medical College Hospital granted approval for this study, reinforcing its adherence to ethical standards. In line with this commitment, all data collected were anonymized, safeguarding the confidentiality of the participants and upholding the ethical principles that guided the research.

Inclusion Criteria

- Patients of both gender over the age of 15 years.
- Diagnosed patients with TCL.
- Patients with record of 6 months of TB medication without complete response
- Patients who had given consent to participate in the study.

Exclusion Criteria

- Patients who were diagnosed with other forms of tuberculosis.
- Patients who showed resistant TB strains.
- Patients who did not give consent to participate in the study.
- Patients with other chronic or infectious diseases.

RESULTS

Table 1 provides an insightful overview of the baseline characteristics of the initial 189 participants in the study. The age distribution reveals that the majority of participants (71.43%) were in the 15-30 age group, followed by 21.16% in the 31-45 age group, and a smaller proportion (7.41%) above 45 years of age. Gender-wise, the study included a higher percentage of females (68.25%) compared to males (31.75%). The swelling type among participants was categorized into three groups: bilateral swelling was observed in 23.28%, unilateral swelling on the right side in 41.27%, and unilateral swelling on the left side in 35.45%. When examining the swelling size, the participants were almost evenly distributed, with 51.32% having a swelling size of 3 cm or less, and 48.68% with a swelling size greater than 3 cm. Lastly, the swollen nodes were classified into two categories: single-level

nodes, which comprised 37.57% of the cases, and multiple-level nodes, accounting for the remaining 62.43%.

Table 1: Distribution of initial participants by baseline characteristics, (N=189)

Characteristics	Frequency	Percentage
Age		
15-30	135	71.43%
31-45	40	21.16%
>45	14	7.41%
Gender		
Male	60	31.75%
Female	129	68.25%
Swelling Type		
Bilateral	44	23.28%
Unilateral (Right side)	78	41.27%
Unilateral (Left side)	67	35.45%
Swelling Size		
≤3 cm	97	51.32%
>3 cm	92	48.68%
Swollen Node		
Single Level Node	71	37.57%
Multiple Level Nodes	118	62.43%

Table 2: Distribution of baseline characteristics of slow/non-responsive patients after 6 months of standard treatment, (N=125)

Characteristics	Frequency	Percentage
Age		
15-30	95	55.55%
31-45	23	22.22%
>45	7	22.22%
Gender		
Male	35	33.33%
Female	99	66.67%

Table 2 delineates the baseline characteristics of the 125 patients who exhibited slow or non-responsive reactions to standard treatment after a 6-month period. The age distribution within this subset of patients is segmented into three groups. The 15-30 age group constitutes the majority, with 55.55% of the patients, while both the 31-45 and the >45 age groups each comprise 22.22% of the patients. The gender distribution further illuminates the characteristics of this specific patient population. Males represent 33.33% of the slow/non-responsive patients, while females account for a larger proportion, making up 66.67% of this group.

Table 3: Distribution of slow/non-responsive patients by neck swelling related characteristics, (n=125)

Characteristics	Frequency	Percentage
Swelling Type		
Bilateral	30	23.28%
Unilateral	95	41.27%
Swelling Size		
≤3 cm	113	90.40%
>3 cm	12	9.60%
Swollen Node		
Single Level Node Involvement	44	37.57%
Multiple Level Nodes Involvement	81	62.43%

Table 3 provides a detailed breakdown of the neck swelling-related characteristics among the 125 patients who were slow or non-responsive to treatment. The swelling type is categorized into two main groups: bilateral and unilateral. Bilateral swelling was observed in 30 patients, accounting for 23.28% of the cases, while unilateral swelling was more common, found in 95 patients or 41.27% of the cases. The swelling size

further differentiates these patients, with a significant majority (90.40%) having a swelling size of 3 cm or less, and a smaller proportion (12 patients or 9.60%) with a swelling size greater than 3 cm. Lastly, the swollen nodes were analyzed based on the level of involvement. Single-level node involvement was identified in 44 patients, making up 37.57% of the cases, while multiple-level nodes involvement was more prevalent, found in 81 patients or 62.43% of the cases.

Table 4: Nodal Size among slow/non-responsive cases after continuous treatment, (n=125)

Nodal Size	After 10 Months of medication		After 1 year of medication	
	Frequency	Percentage	Frequency	Percentage
<10 mm	18	14.40%	21	16.80%
10-15 mm	48	38.40%	57	45.60%
16-19 mm	15	12.00%	10	8.00%
≥20 mm	44	35.20%	37	29.60%

Table 4 presents a longitudinal analysis of the nodal size among 125 slow or non-responsive patients, comparing the outcomes after 10 months of medication with those after 1 year of medication. Nodal size was defined as the indicator of treatment response among the participants, with patients showing <15 mm nodal size was declared cured, while those who had nodal size within 16-19 mm were also declared treated, but follow up was advised. In the category of less than 10 mm, there was a slight increase in the percentage of patients, from 14.40% after 10 months to 16.80% after 1 year. The 10-15 mm category witnessed a more substantial growth, from 38.40% to 45.60%. Conversely, the 16-19 mm category experienced a decrease, from 12.00% to 8.00%, and the category of 20 mm or greater also saw a reduction, from 35.20% to 29.60%. The table further clarifies the criteria for evaluating treatment response: patients with a nodal size of less than 15 mm were declared cured, while those within the 16-19 mm range were considered treated, with follow-up advised.

Table 5: Distribution of patients by response to standard medication at different follow-ups, (N=189)

Response rate	Frequency	Percentage
After 6 months treatment	64	33.86%
After 1 year treatment	88	46.56%
Slow/no response after 1 year	37	19.58%

Table 5 delineates the distribution of the 189 patients based on their response to standard medication at various follow-up intervals. Response to medication was identified via decrease in nodal size within <15 mm. After 6 months of treatment, 64 patients (33.86%) showed a response, while the response rate increased to 88 patients (46.56%) after 1 year of treatment. Additionally, there was a category of slow/no response even after 1 year of standard treatment, encompassing 37 patients or 19.58% of the cases.

Table 6: Neck node related characteristics after different follow-ups among non/slow-responsive cases

Variable	Initial record (n=189)		After 6-months treatment (n=125)		After 1-year treatment (n=37)	
	n	%	n	%	n	%
Swelling Size						
≤3 cm	97	51.32%	53	42.40%	11	29.73%
>3 cm	92	48.68%	72	57.60%	26	70.27%
Swollen Node						
Single Level Node	71	37.57%	44	35.20%	13	35.14%
Multiple Level Nodes	118	62.43%	81	64.80%	24	64.86%

Table 6 provides a comprehensive view of the neck node-related characteristics among non/slow-responsive cases, tracking the changes from the initial record (n=189) through 6 months of treatment (n=125) to 1 year of treatment (n=37). In terms of swelling size, the initial record showed a nearly even distribution between ≤3 cm (51.32%) and >3 cm (48.68%). However, after 6 months of treatment, the proportion shifted to 42.40% for ≤3 cm and 57.60% for >3 cm. This trend continued after 1 year of treatment, with 29.73% at ≤3 cm and 70.27% at >3 cm. Regarding swollen nodes, the initial record showed 37.57% with single-level node involvement and 62.43% with multiple-level nodes. After 6 months, the distribution was 35.20% for single-level nodes and 64.80% for multiple-level nodes, and after 1 year, it was 35.14% for single-level nodes and 64.86% for multiple-level nodes.

DISCUSSION

The present study commenced with an examination of 189 patients diagnosed with tubercular cervical lymphadenopathy (TCL), a condition that continues to challenge healthcare systems in many developing regions. Observationally, the demographic distribution revealed a concentration within the 15-30 age group (71.43%) and a higher prevalence among females (68.25%). This is similar to other findings where TCL was more commonly observed among females [10, 11]. After 6 months of standard treatment, a subset of 125 patients (66.14%) exhibited slow or no response to the medication, and the present study focused on these cases. This observation is significant, as it underscores the limitations of standard treatment within a substantial proportion of the patient population. A significant majority, 90.40%, had swelling sizes of 3 cm or less, which suggested that standard medication had some response among these cases, and had very limited effect on the remaining 9.60% of the participants. This observation aligns with a study conducted in Dhaka, which evaluated the role of surgical dissection in tuberculous cervical lymphadenopathy [12]. Furthermore, over time, it was observed that changes in nodal size were limited, with only 16.80% reaching a nodal size of less than 10 mm after a year of treatment. This finding emphasizes the complexity of TCL management and resonates with the challenges highlighted in the aforementioned study, where surgical intervention was explored as an alternative approach [12]. The response rate to the medication was also telling. After 6 months, only 33.86% showed a response, and this number increased only slightly to 46.56% after a full year. Even more concerning, 19.58% were still showing a slow response after that year. These numbers raise serious questions about how effective prolonged medication is for treating TCL. A study evaluating the treatment efficacy of surgical interventions for tubercular cervical lymphadenopathy found that while anti-tubercular therapy is effective, surgical intervention may be necessary, further emphasizing the limitations of prolonged medication alone in treating TCL [13]. We also looked at how TCL evolved over time by examining the neck node-related characteristics. We found that the swelling size shifted from 51.32% being less than or equal to 3 cm initially to 70.27% being greater than 3 cm after a year of treatment. This trend, along with the consistent distribution in single and multiple-level node involvement, suggests that continuing medication might not be effective for a significant number of non/slow-responsive TCL cases. A study conducted in Dhaka also emphasized the need for surgical treatment in the management of tubercular cervical lymphadenopathy, further supporting our observation that medication alone may not be sufficient for a substantial portion of TCL cases [14]. The remaining 37 patients who still did not show the appropriate response after 1 year of medication were treated with standard medication for another 6 months. But only 3 out of those 37 had seen a decrease of nodule size <2 cm. As the remaining 34 still didn't show the appropriate response, they were advised for neck dissection surgery. This suggests that extending the course of standard medication for over 1 year is not an effective approach, and such slow/non-responsive cases should be suggested for neck dissection. These findings paint a clear picture of the challenges and limitations of using extended standard treatment for TCL. The specific percentages and trends we observed provide solid evidence that supports looking at alternative treatment strategies, such as surgery, especially when standard medication doesn't work within the first 6-10 months. Overall, our observational approach and detailed examination of various factors provide valuable insights into managing TCL. It highlights the need for more personalized approaches that consider the unique and complex nature of TCL and calls for more research to explore different strategies.

Limitations of The Study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

CONCLUSION

The present study contributes valuable insights into the management of TCL and highlights the need for a more personalized and possibly surgical approach, particularly when standard medication fails to yield the desired response within the first 6-10 months. It calls for further research to explore alternative strategies and a more nuanced understanding of TCL, to ensure that patients receive the most effective treatment tailored to their specific condition. The evidence presented here may serve as a foundation for reevaluating current treatment guidelines and developing new protocols that prioritize patient outcomes and responsiveness to therapy.

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REFERENCES

1. Biswas, P. K., & Begum, S. N. (2007). Tubercular Cervical lymphadenopathy clinicopathological study of thirty cases. *TAJ: Journal of Teachers Association*, *20*(1), 36-38.
2. Shah, J. P. (2003). Cervical lymph nodes. In: Head and neck: surgery and oncology, 3rd edn Edinburgh: Mosby, 353–394.

3. Das, D. K. (2000). Fine-needle aspiration cytology in the diagnosis of tuberculous lesions. *Laboratory Medicine*, *31*(11), 625-632.
4. Sharma, S. K., & Mohan, A. (2004). Extrapulmonary tuberculosis. *Indian Journal of Medical Research*, *120*(4), 316-353.
5. Aisenberg, G. M., Jacobson, K., Chemaly, R. F., Rolston, K. V., Raad, I. I., & Safdar, A. (2005). Extrapulmonary tuberculosis active infection misdiagnosed as cancer: Mycobacterium tuberculosis disease in patients at a Comprehensive Cancer Center (2001–2005). *Cancer: Interdisciplinary International Journal of the American Cancer Society*, *104*(12), 2882-2887.
6. Seok, H., Jeon, J. H., Oh, K. H., Choi, H. K., Choi, W. S., Lee, Y. H., ... & Park, D. W. (2019). Characteristics of residual lymph nodes after six months of antituberculous therapy in HIV-negative individuals with cervical tuberculous lymphadenitis. *BMC infectious diseases*, *19*(1), 1-7. Available from: https://doi.org/10.1186/s12879-019-4507-0
7. World Health Organization (WHO). Treatment of tuberculosis guidelines. 4th ed. Geneva: WHO, 2009. [Cited 2010 Nov 23]. Available from: URL: http://www.who.int/tb/ publications/cds_tb_2003_313
8. Castro, D. J., Hoover, L., Castro, D. J., & Zuckerbraun, L. (1985). Cervical mycobacterial lymphadenitis: medical vs surgical management. *Archives of Otolaryngology*, *111*(12), 816-819.
9. Bhagwat, A., Deshpande, A., & Parish, T. (2022). How Mycobacterium tuberculosis drug resistance has shaped anti-tubercular drug discovery. *Frontiers in Cellular and Infection Microbiology*, *12*, 974101.
10. Purohit, M. R., Mustafa, T., Mørkve, O., & Sviland, L. (2009). Gender differences in the clinical diagnosis of tuberculous lymphadenitis—a hospital-based study from Central India. *International Journal of Infectious Diseases*, *13*(5), 600-605.
11. Kamal, M. S., Hoque, M. H. E., Chowdhury, F. R., & Farzana, R. (2016). Cervical tuberculous lymphadenitis: clinico-demographic profiles of patients in a secondary level hospital of Bangladesh. *Pakistan journal of medical sciences*, *32*(3), 608.
12. Asaduzzaman, A. K. M., Uddin, M. K., Azad, M. A., Safi, A., & Haque, W. S. (2017). Evaluation of Tubercular Cervical Lymphadenopathy: Diagnostic and Therapeutic Utility. *Bangladesh Journal of Otorhinolaryngology*, *23*(2), 127-132.
13. Zada, B., Durrani, S. N., Billah, M., Iqbal, J., Khan, A., & Nadeem, M. (2022). Evaluation of Treatment Efficacy of Surgical Interventions for Tubercular Cervical Lymphadenopathy. *Pakistan Journal of Medical & Health Sciences*, *16*(10), 752.
14. Mahfuz, M. S. I., Islam, M. Z., Akram, M. S., Hossain, T., & Hossain, M. N. (2022). Outcome of Surgical Treatment in the Management of Tubercular Cervical Lymphadenopathy: An Experience in NIENT, Dhaka. *Bangladesh Journal of Otorhinolaryngology*, *28*(1), 84-90.