Indian J Lepr 2025, 97 : 375-382

http://www.ijl.org.in

Original Article

Colchicine has a Minimal Role as an Adjuvant to Prednisolone in the Treatment of Severe Erythema Nodosum Leprosum in Multibacillary Leprosy

N Chhabra[1], PSM Reddy[2], R Choudhary[3], AK Mishra[4], S Ganguly[5], N Prabha[6]

Received: 16.01.2025 Revised: 15.05.2025 Accepted: 15.06.2025

This study aimed to determine the efficacy and safety of colchicine as an adjuvant to prednisolone in the management of severe ENL. The study included adult multibacillary leprosy cases with severe ENL (ENLIST ENL severity score ≥9) from December 2021 to December 2023. The patients were randomized into two treatment groups; Group I patients received prednisolone, and group II patients received colchicine as an adjuvant along with prednisolone. A total of 41 patients were recruited out of which 20 patients completed the study with 12 patients in group I (control group) and 8 in group II (intervention group). The mean duration to achieve ENLIST score 0 was 3.5 weeks in the intervention group and 4 weeks in the control group (p value= 0.181). The mean duration of prednisolone treatment was 25.5 weeks in the control group, and 32 weeks in the intervention group (p value=0.020). The mean cumulative prednisolone dose was 4513.08 ± 2013.89 in the control group and higher in the intervention group (5105.63 ± 1710.75) (p value> 0.05). The mean number of ENL flare-ups was higher in the control group (2) compared to the intervention group (1) during the study period (p value= 0.792). Few patients had steroid related adverse effect while colchicine was well tolerated in the intervention group.The conclusions from this study have limitation as a large number of patients (n=21/41) were withdrawn from the study due to inadequate control with the treatment regimen in both the groups resulting in smaller sample size. It is concluded that **c**olchicine is not an effective adjuvant to prednisolone in the management of severe ENL. It might have a role in preventing the recurrent episodes in ENL, however, this needs further evaluation.

Keywords: Colchicine, Erythema Nodosum Leprosum, ENL, Prednisolone, Leprosy

Introduction

Erythema Nodosum Leprosum (ENL) is a multisystem, relapsing and remitting disorder occurring in lepromatous and borderline lepromatous leprosy patients with high bacillary load (Ridley & Jopling 1966). Despite the advent of multiple adjuvant drugs, steroids remain indomitable in the management of ENL. The requirement of prolonged use of steroids in chronic, recurrent, steroid-dependent and

[1] Dr Namrata Chhabra, Additional Professor, Department of Dermatology
[2] Dr. P. S. Meghana Reddy, Senior Resident, Department of Dermatology (*Presently: JIPMER, Puducherry*)
[3] Dr Ritul Choudhary, Assistant Professor, Department of Dermatology (*Presently: Government Medical College, Sri Ganganagar, Rajasthan*)
[4] Dr Amit Kumar Mishra, Associate Professor (*Current designation*), Department of Community and Family Medicine
[5] Dr Satyaki Ganguly, Additional Professor, Department of Dermatology
[6] Dr Neel Prabha, Associate Professor, Department of Dermatology
All India Institute of Medical Sciences, Raipur, Chhattisgarh, 492099, India
Corresponding Author: Dr Namrata Chhabra, **Email**: namrata81@aiimsraipur.edu.in

steroid-non-responding ENL has well-known deleterious adverse effects, including a mortality risk. Multiple adjuvant drugs like thalidomide, immunosuppressive drugs, vaccines and biologics have been recommended in various studies; however, many of these drugs are unaffordable by leprosy patients (Singal 2020). The evidence for the efficacy of adjuvant drugs is still insufficient owing to the limited number of trials. Colchicine is a cheap, widely used medication reported to be effective in mild to moderate ENL (Sarojini & Mshana 1983). However, there are no randomized controlled trials conducted so far to see the efficacy of colchicine as a steroid-sparing drug in the treatment of severe ENL. This trial studies the efficacy of colchicine as adjuvant to prednisolone against prednisolone alone in treating severe ENL.

Materials and Methods

We conducted a randomized controlled trial to determine the efficacy and safety of colchicine as an adjuvant to prednisolone in the management of ENL over two years from December 2021 to December 2023 after obtaining approval from the institutional ethical committee [ECR/714/Inst/CT/2015/RR-21]. We included all adult multibacillary leprosy cases with severe ENL (ENLIST ENL severity score ≥9) presenting to the department of Dermatology, All India Institute of Medical Sciences, Raipur. Patients with contraindications for steroids (glaucoma, active tuberculosis, uncontrolled diabetes), or colchicine (leukopenia, thrombocytopenia, haemoglobin< 8 gm/dl, severe renal or hepatic dysfunction), pregnant, lactating women orthose who are unable to follow up regularly were excluded from the study.

Detailed history and clinical examination findings were noted in the case record proforma. The diagnosis of leprosy was made based on clinical examination supported by a slit skin smear (SSS) examination. The diagnosis of ENL was mainly clinical, and a biopsy from the suggestive lesion was done only in the case of clinical suspicion. Periodic assessments from enrolment were carried out at week 2, 4, 8, 12, 16, 20, 24, 28, and 32. The ENLIST ENL severity scale to assess the severity of ENL was calculated at inclusion and every 4 weeks thereafter for a total of 32 weeks (Walker et al 2017). Nerve -function tests were also performed at baseline and subsequent follow-up visits. During the study period, ENL flare ups was diagnosed if ENL symptoms and/or signs occur resulting in an increased ENLIST score to 8 or more, while on treatment.

Participants with severe ENL were randomized into two treatment groups. Group I patients received prednisolone alone, and group II patients received colchicine as an adjuvant with prednisolone. If there was no improvement with treatment in either of the groups, the cases were taken out of the trial and treated with other adjuvants like thalidomide, etanercept, methotrexate. Oral prednisolone was given at a dose of 0.75-1mg/kg body weight, depending upon the clinical assessment of the severity of ENL. The dose was tapered by 10 mg every 2 weeks till a dose of 20 mg, which was tapered by 5 mg every 2 weeks. In group II, in addition to prednisolone, oral colchicine was given at a dose of 0.5 mg thrice daily till complete tapering of prednisolone. The cumulative dose of prednisolone was calculated in both the groups.

The data was analyzed using SPSS version 21. Data was presented as mean± SD, frequency/proportion and graphs. The per-protocol analysis was used to calculate treatment effects on individuals in each group. Fisher exact test, independent t-test or Mann-Whitney U tests were used for data comparisons between groups. P value <0.05 was considered to be statistically significant.

Results

A total of 41 patients were recruited out of which 20 patients completed the study with 12 patients in group I (control group) and 8 in group II (intervention group) (Fig. 1). The mean age of the study participants was 36 ± 12.37 years, ranging from 27-42.5 years. The gender ratio of the participants was 1.9:1 (M:F). 85%(n=17) patients belonged to Lepromatous leprosy (LL) spectrum and, 15%(n=3) to Borderline lepromatous (BL) leprosy type. On SSS examination, all patients were smear positive with 15 (75%) patients having high bacteriological index (≥4+) and 5 (25%) patients had BI <4+. Most of the patients (40%, n=8) had recurrent ENL followed by acute ENL (35%, n=7) and, chronic ENL (25%, n=5). Neuritis was present in only 30%(n=6) of the patients. There was no statistically significant difference between the age, gender, type of leprosy, type of ENL and presence of neuritis between the control and intervention groups (Table 1).

The mean duration to achieve clinical remission (drop in ENLIST score to 0) was 3.5 weeks in the intervention group and 4 weeks in the control group (p value=0.181) (Table 2). The mean duration of prednisolone treatment was 25.5weeks in the control group, while it was significantly longer in the intervention group (32 weeks) (p value=0.020). The mean cumulative prednisolone dose was 4513.08 ± 2013.89 in the control group and higher in the intervention group (5105.63 ± 1710.75) (p value> 0.05). The

Table 1 : Demographic and clinical characteristics of study groups.

Variable	Control Group (n=12)	Intervention Group (n=8)	p value
Mean age (years)	37.5	30	0.571[#]
Mean Baseline ENLIST score (Mean ± SD)	13±4.88	13±5.53	1.000[@]
Duration of ENL (months) Median (IQR)	2.5 (0.31-3.75)	12 (2.5-21)	0.057[#]
Gender			
Male	9	4	0.356*
Female	3	4	
Type of Leprosy			
BL Hansens	3	0	0.242*
LL Hansens	9	8	
Type of ENL			
Acute	5	2	0.844*
Chronic	3	2	
Recurrent	4	4	
Neuritis			
No	8	6	1.000*
Yes	4	2	

*[#]Mann-Whitney U Test, [@]Independent sample t test, *Fisher's Exact Test*

Table 2 : Comparison of outcome parameters between the control and intervention groups.

Outcome parameter	Control Group (n=12) Median (IQR)/ Mean (SD)	Intervention Group (n=8) Median (IQR)/ Mean (SD)	p-value
Mean duration of ENLIST score becoming 0 (weeks)	4 (2.25-6)	3.5 (2-4)	0.181*
Mean number of ENL flare ups	1 (1-3.5)	2 (1-2)	0.792*
Mean duration of prednisolone treatment (weeks)	25.5 (16.5-31)	32 (32-32)	**0.020***
Cumulative prednisolone dose (mg)	4513.08 (2013.891)	5105.63 (1710.753)	0.504#

**Mann-Whitney U Test, #Independent T Test*

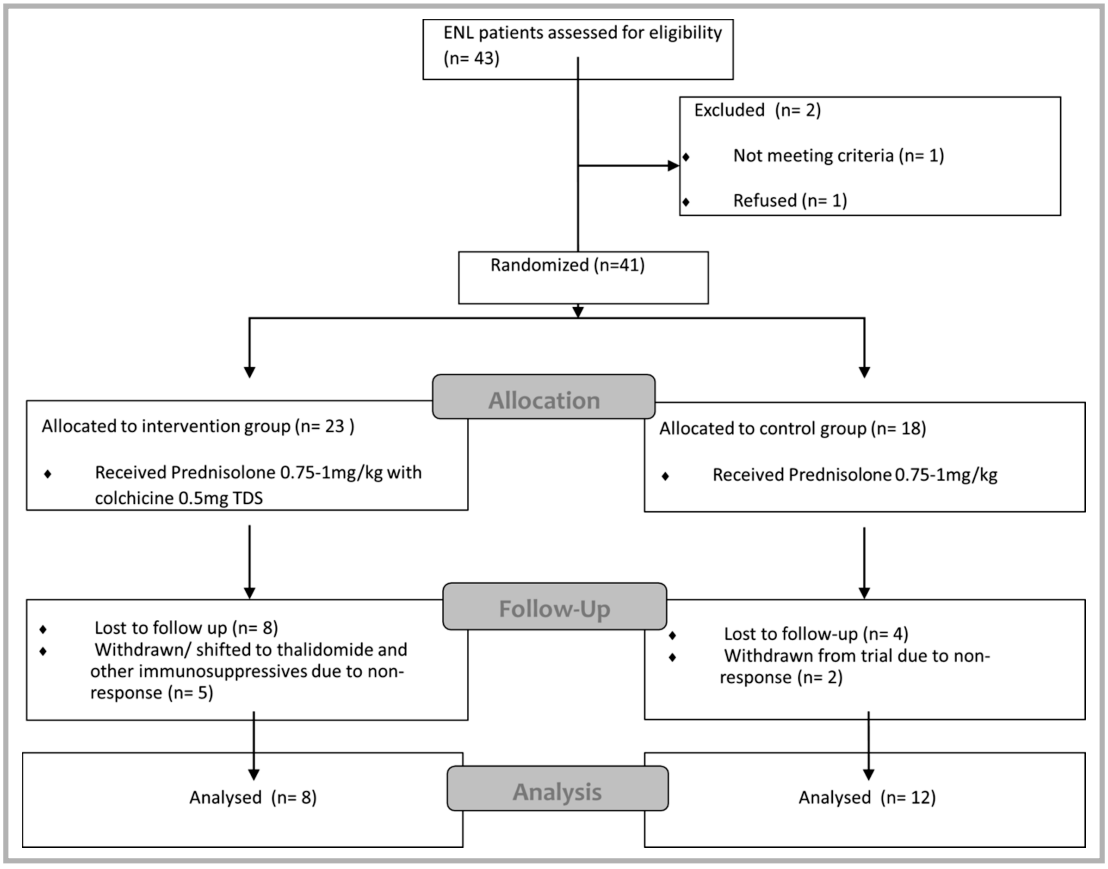

Fig. 1 : CONSORT Flow Diagram.

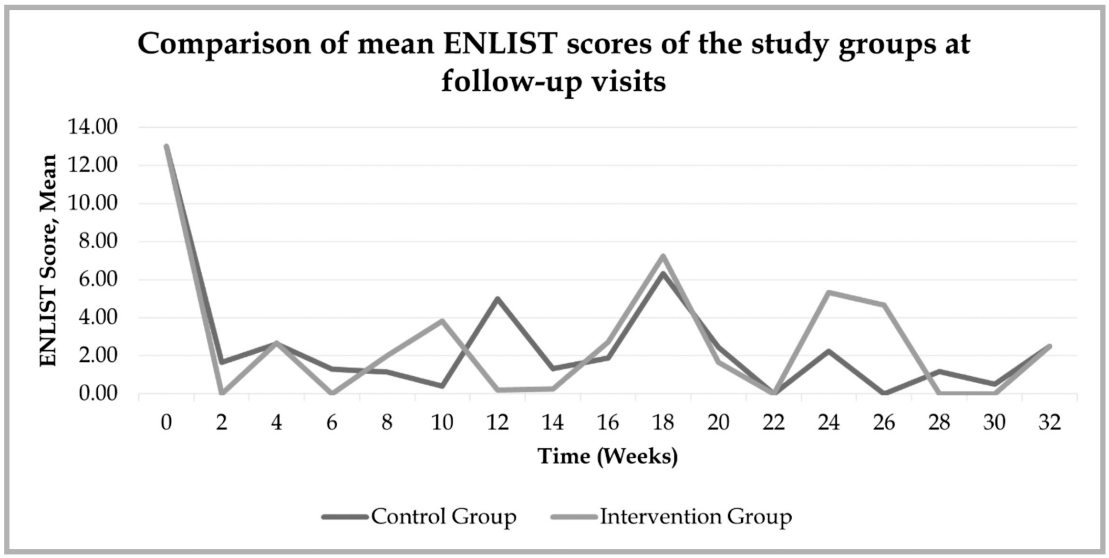

Fig. 2 : Comparison of mean ENLIST score in both the study groups during the follow-up visits.

mean number of ENL flare-ups was higher in the control group (2) compared to the intervention group (1) during the study period (p value= 0.792). The mean ENLIST scores of the study groups at baseline and follow-up visits have been depicted in Fig. 2. Among the 20 analysed patients, dermatophytosis and pityriasis versicolor were seen in three patients, cataracts in two, and steroid withdrawal symptoms like weakness and fatigue was seen in one patient. None of the eight patients in the intervention group had colchicine related side effects.

Discussion

Leprosy is a chronic infectious granulomatous disease caused by obligate intracellular bacilli *Mycobacterium leprae*, predominantly affecting the peripheral nerves and skin. The recent NLEP data shows the highest prevalence of leprosy (2.3 cases per 10,000 population) in Chhattisgarh, where the study was conducted (Ministry of Health & Family Welfare 2023).

It is also known that leprosy has a chronic course interrupted by hypersensitivity reactions such as type 1 reaction or type 2 reaction (ENL). ENL is an immune complex-mediated hypersensitivity reaction seen in 5–10% of BL and 50% of LL patients, especially those with a bacterial index >4, either during, before, or after the institution of leprosy treatment (Walker et al 2015). The broad spectrum of symptoms from mild constitutional symptoms such as fever, myalgia malaise, arthralgia and eruption of evanescent tender subcutaneous nodules to severe neuritis and or other systemic organ involvement characterizes ENL. Serious consequent permanent nerve damage and deformities can be alarming if ENL is left untreated.

The overall prevalence of ENL is variable, ranging from 25% in Brazil and Thailand to 49.4% in India among lepromatous leprosy patients. In a large cohort study in India, less than 10% patients only had a single episode of ENL, while 62.5% patients had chronic ENL (Pocaterra et al 2006).

Voorend & Post (2013) observed that multiple episodes of ENL were reported in 39-77% of cases, with an average of 2.6 episodes per patient.

Most of the patients in our study had recurrent ENL (40%, n=8) followed by acute ENL (35%, n=7) and, chronic ENL (25%, n=5). The ENLIST severity scale for ENL was used in our study to assess the clinical features of ENL objectively and to determine the treatment response accurately. All the patients in our study had ENLIST scores more than 8. Prednisolone is the anti-inflammatory drug of choice in severe ENL. WHO recommends managing severe ENL with Prednisolone at the dose of 1mg/kg/day (WHO 1998). Recurrent and chronic ENL require prolonged and higher doses of steroids to control the inflammation and symptoms (Sardana et al 2020). Both control and intervention arms received 0.75-1mg/kg/day prednisolone in our study as they all belonged to the severe ENL category as per WHO guidelines. Despite the rapid and remarkable symptomatic response of steroids in ENL, chronic ENL patients are at great risk of becoming steroid dependent. The indications for using additional or second-line drugs are steroid non-response, steroid dependence and contraindications to steroids (Sardana & Khurana 2020). Between the rebound effects of prednisolone and a possible build-up of tolerance, it may be challenging to stop prednisolone in patients with chronic ENL. The numerous harmful adverse effects of steroids, along with their seeming role in decreasing the antimicrobial effects of antibiotic drugs and inducing drug resistance to anti-leprosy drugs, collectively question the prolonged use of steroids (Sardana et al 2020, Prabha 2023). Walker et al (2014) found 9% mortality in Ethiopian patients taking steroid treatment for ENL due to steroid-related complications, which occurred mostly in young people. Among the 20 patients analyzed in our study, three had developed superficial cutaneous fungal infections, two had developed cataracts, and one patient had steroid withdrawal symptoms.

The search for steroid-sparing alternate effective drugs in ENL has been round-the-clock over several years. The alternate steroid-sparing agents include immunosuppressive agents such as thalidomide, cyclosporine, pentoxifylline, methotrexate, and azathioprine and anti-inflammatory agents such as aspirin, chloroquine, colchicine, indomethacin and apremilast. Various other agents like zinc and immunotherapy have also been tried (Sardana et al 2020). The Cochrane review in 2009 regarding the management of ENL assessed the clinical trials using betamethasone, pentoxifylline, thalidomide, clofazimine, levamisole, and indomethacin. It concluded that most trials had poor quality and no results could be pooled due to the heterogeneous treatments (Van Veen et al 2009).

WHO advises the use of thalidomide or clofazimine in severe ENL as an adjuvant drug with steroids. Thalidomide is effective in treating severe ENL, although it is ineffective in neuritis and iritis. Its use is limited, especially in developing countries, due to non-availability, cost, strict monitoring, teratogenicity, and possible neurotoxicity (Van Veen et al 2009). Clofazimine is effective at higher doses (300mg/day), ineffective at lower dosages, and takes four to six weeks to become effective with no effects on acute episodes (Pai 2015, Maghanoy et al 2017). The unavailability and the unwanted stigmatizing skin dyspigmentation also preclude clofazimine use.

There is minimal literature regarding the use of colchicine in type 2 lepra reactions. Although the exact mechanism of action of colchicine in ENL is unknown, its main action on neutrophils and its effective response in neutrophilic dermatoses makes it a very cheap and effective option to consider in ENL management (Sardana et al 2020). Most of the studies on colchicine in ENL were conducted three decades ago. An open, unblinded study by Sarojini & Mshana (1983) in

Ethiopia on ten male adult patients for acute ENL showed a dramatic response with colchicine. The mean duration of ENLIST score becoming 0 was around 3.5(2-4) weeks in the intervention group, a few days faster response than 4(2.25-6) weeks in the control group, although not statistically significant. A double-blind controlled trial in India in 1987 compared aspirin and colchicine in both mild and moderate ENLs, which revealed equal effects with both drugs in mild reactions and superior effects of colchicine in moderate pain relief (Kar & Roy 1988). Neither of the drugs was found helpful in severe ENL reaction. Sharma et al (1986) found colchicine effective in all mild, 85% of moderate and 33% of severe ENL reactions. Although these studies emphasize colchicine's minimal role in managing severe ENL, the data could not be compared because of different severity grading. Sachdeva et al (2021) reported a case of successful treatment of recurrent steroid-dependent ENL with colchicine.

Ironically, in our study, the intervention group required prednisolone for a longer mean duration of 32 weeks than the control group (25.5 weeks), which was statistically significant. The mean total cumulative dose of prednisolone required was higher in the intervention group (5105.63mg) when compared with 4513.08 mg in the control group. This depicts that colchicine neither has an adjuvant effect with prednisolone nor it decreases the prednisolone requirement when used concomitantly in severe ENL. Stanley et al (1984) also showed similar findings as they did not notice any effect on the steroid dose requirement when given colchicine in 5 adult male patients with severe type 2 reaction.

The ENL flare-ups in our study were managed by increasing the dose of steroids. The mean number of ENL flare-up episodes was less in the colchicine intervention group when compared with the control group showing that colchicine might not decrease the chronicity of the reaction but may have a role in controlling the recurrence of ENL episodes, however this need further evaluation as the difference was not statistically significant.

The limitation of this study was the small sample size. We could not complete our calculated sample size within the study period due to the COVID pandemic leading to fall in outpatient load. Also, a significant number of patients had to be withdrawn due to the inadequate control of ENL with steroids with/ without colchicine in these patients.

Conclusion

Colchicine does not have a significant role as an adjuvant to prednisolone in the management of severe ENL. It does not have the steroid sparing effect, nor does it potentiate the efficacy of prednisolone when used concomitantly in severe ENL. It might have a role in preventing the recurrent episodes in ENL, however, this needs further evaluation.

Acknowledgements

We would like to acknowledge the Indian Association of Dermatologists, Venereologists and Leprologists for the funding support ((IADVL Research Grant 2021)

References

1. Kar HK, Roy RG (1988). Comparison of colchicine and aspirin in the treatment of type 2 lepra reaction. *Lepr Rev.* **59**: 201-203.
2. Maghanoy A, Balagon M, Saunderson P et al (2017). A prospective randomized, double-blind, placebo- controlled trial on the effect of extended clofazimine on erythema nodosum leprosum (ENL) in multibacillary (MB) leprosy. *Lepr Rev.* **88**: 208-216.
3. Ministry of Health & Family Welfare (HFW), Govt of India (2023). Update on leprosy cases in the country /21 March 2023/5(https://www.pib.gov.in).

4. Pai VV (2015). Role of clofazimine in management of reactions in leprosy: A brief overview. *Indian J Drugs Dermatol.* **1:** 12-15.
5. Pocaterra L, Jain S, Reddy R et al (2006). Clinical course of erythema nodosum leprosum: An 11-year cohort study in Hyderabad, India. *Am J Trop Med Hyg.* **74**: 868-879.
6. Prabha N(2023). Do steroids cause drug resistance in leprosy? *Lepr Rev.* **94**: 253-254.
7. Ridley DS, Jopling WH (1966). Classification of leprosy according to immunity. A five-group system. *Int J Lepr Other Mycobact Dis.* **34**: 255-273.
8. Sachdeva S, Sinha S, Sardana K (2021). A case of recurrent steroid-dependent severe type 2 lepra reaction treated successfully with colchicine. *Int J Mycobacteriol.* **10**: 472-474.
9. Sardana K, Khurana A (2020). Reactions in leprosy. In: Jopling's Handbook of Leprosy, Sixth Edition, CBS Publishers and Distributors Pvt Ltd. New Delhi, India, pp. 192–227.
10. Sardana K, Sinha S, Sachdeva S (2020). Colchicine in Dermatology: Rediscovering an old drug with novel uses. *Indian Dermatol Online J.* **11**: 693-700.
11. Sarojini PA, Mshana RN (1983). Use of colchicine in the management of erythema nodosum leprosum (ENL). *Lepr Rev.* **54**: 151-153.
12. Sharma VK, Kumar B, Kaur I et al (1986). Colchicine in the treatment of type 2 lepra reaction. *Indian J Lepr.* **58**: 43-47.
13. Singal A (2020). Current concepts and challenges in the management of erythema nodosum leprosum. *Indian Dermatol Online J.* **11(4)**: 479-481.
14. Stanley JNA, Kiran KU, Pearson J M H (1984). The use of colchicine in the management of type 2 lepra reaction (erythema nodosum leprosum). *Lepr Rev.* **55**: 317-318.
15. Van Veen NH, Lockwood DN, Van Brakel WH et al (2009). Interventions for erythema nodosum leprosum. A Cochrane review. *Lepr Rev.* **80**: 355-372.
16. Voorend CG, Post EB (2013). A systematic review on the epidemiological data of erythema nodosum leprosum, a type 2 leprosy reaction. *PLoS Negl Trop Dis.* **7:** e2440.
17. Walker SL, Lebas E, Doni SN et al (2014). The mortality associated with erythema nodosum leprosum in Ethiopia: a retrospective hospital-based study. *PLoS Negl Trop Dis.* **8**: e2690.
18. Walker SL, Balagon M, Darlong J et al (2015). ENLIST1: an international multi-centre cross-sectional study of the clinical features of erythema nodosum leprosum. *PLoS Negl Trop Dis.* **9:** e0004065.
19. Walker S, Sales A, Butlin C et al (2017). A leprosy clinical severity scale for erythema nodosum leprosum: An international, multicentre validation study of the ENLIST ENL Severity Scale. *PLoS Negl Trop Dis.* **11**: e0005716.
20. WHO Expert Committee on Leprosy (1998). Techn Rep Ser 874, WHO, Geneva, Switzerland.

How to cite this article : Chhabra N, Reddy PSM, Choudhary R et al (2025). Colchicine has a Minimal Role as an Adjuvant to Prednisolone in the Treatment of Severe Erythema Nodosum Leprosum in Multibacillary Leprosy. *Indian J Lepr.* **97**: 375-382.