

Steroid prophylaxis for prevention of nerve function impairment in leprosy: randomised placebo controlled trial (TRIPOD 1)

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Abstract

Objective To determine whether addition of low dose prednisolone to multidrug treatment can prevent reaction and nerve function impairment in leprosy.

Design Multicentre, double blind, randomised, placebo controlled, parallel group trial.

Setting Six centres in Bangladesh and Nepal.

Participants 636 people with newly diagnosed multibacillary leprosy.

Intervention Prednisolone 20 mg/day for three months, with tapering dose in month 4, plus multidrug treatment, compared with multidrug treatment alone.

Main outcome measures Signs of reaction, impairment of sensory and motor nerve function, and nerve tenderness needing full dose prednisolone at four months and one year.

Results Prednisolone had a significant effect in the prevention of reaction and nerve function impairment at four months (relative risk 3.9, 95% confidence interval 2.1 to 7.3), but this was not maintained at one year (relative risk 1.3, 0.9 to 1.8). Fewer events occurred in the prednisolone group at all time points up to 12 months, but the difference at 12 months was small. Subgroup analysis showed a difference in response between people with and without impairment of nerve function at diagnosis.

Conclusions The use of low dose prophylactic prednisolone during the first four months of multidrug treatment for leprosy reduces the incidence of new reactions and nerve function impairment in the short term, but the effect is not sustained at one year. The presence of nerve function impairment at diagnosis may influence the response to low dose prednisolone.

Introduction

Irreversible, progressive damage to peripheral nerves and the tissue damage secondary to motor and sensory impairments are the most important consequences of leprosy. These result in the physical impairments and the limitation of physical activities and social participation that are associated with leprosy.¹ Any intervention that prevents this damage to peripheral nerves in leprosy is highly desirable. Current multidrug treatment for leprosy is primarily aimed at killing *Mycobacterium leprae* and not at preventing nerve damage.

Steroids are the accepted method of medically treating nerve function impairment and reactions in leprosy,² but recovery of nerve function is limited. Reactions in leprosy are acute clinical states related to rapid changes in the host immune response, during which nerve function is lost. Few studies have investigated

whether prophylactic steroids, combined with multidrug treatment, would prevent nerve function impairment and reactions.^{3,4} The results of two trials of steroid prophylaxis indicate that such an intervention may be effective. A small (150 participants) randomised trial, conducted in India, suggested that 10 mg of a steroid administered daily along with chemotherapy for one month prevented nerve damage in paucibacillary patients.⁵ An open controlled trial conducted in Bangladesh showed a beneficial effect of 20 mg prednisolone daily for three months.⁴

Prospective studies have indicated that multibacillary patients and those with existing impairment of nerve function are at greatest risk of new nerve function impairment and reactions.⁶ We tested the hypothesis that low dose prednisolone given in the first four months of multidrug treatment would reduce the incidence of reaction and nerve function impairment in multibacillary patients. Our primary objective was to compare the proportion of people given low dose (20 mg) prednisolone or placebo for four months who had an acute episode of reaction or nerve function impairment such that intervention with full dose prednisolone was indicated.

Methods

Study design

We conducted a multicentre, randomised, double blind, parallel group trial, with a treatment phase of four months and follow up to 12 months. The trial formed one part of the TRIPOD trials; the other parts examined the use of prednisolone in the treatment of mild sensory impairment and longstanding impairment of nerve function. Six centres participated in the trial—three in Bangladesh (Chittagong, Dhaka, and Nilphamari) and three in Nepal (Biratnagar, Lalghadh, and Western Region).

We determined the size of the study by assuming that a reduction by 50% in the number of people having an acute episode of reaction or nerve function impairment would be the minimal clinically important difference and that the expected event rate was 10% in the first six months of multidrug treatment.⁷ Based on a power of 0.8 to detect a significant difference ($P=0.05$), we needed 343 people for each study group, which we increased to 385 to compensate for an expected loss to follow up of 10%.

Participants

All patients diagnosed as having multibacillary leprosy at the participating clinics, between 15 and 50 years of age, and being prescribed a standard adult dose, 12 month course of multidrug treatment⁸ were eligible for the trial. We excluded patients if they

already had indications for full dose prednisolone or had contraindications to oral corticosteroid (signs of peptic ulcer, psychosis or endogenous depression, acute or chronic bacterial infection, corneal ulcer, history of diabetes mellitus or a measured urine sugar by reagent strip >2+ (equivalent to 500 mg/dl), history of hypertension or a measured diastolic blood pressure of > 100 mm Hg, history of glaucoma, mature cataract). We excluded patients weighing less than 35 kg, those taking long term medication unrelated to leprosy, women who knew that they were pregnant, and people whose home was so remote that follow up would be impossible. Participants gave written informed consent.

Assignment and masking

A statistician produced the randomisation schedules centrally by using computer generated random numbers and a permuted block design of size 12. The randomisation was stratified for each centre to minimise the risk of inequality of the groups in the event of curtailment of the trial in one or more centres. Participants were allocated equally to each group. Central teams pre-packed active and placebo prednisolone (5 mg tablets) in monthly doses and stored all four packs for the prophylaxis for each patient in a sealed, numbered envelope. We packed the envelopes into numerical order for each centre; staff in each centre issued them sequentially. The placebo tablets were manufactured to be the same size, shape, and colour as the prednisolone tablets. The treatment allocation was concealed from all study personnel and participants for the duration of the study. We withheld coding and the method of randomisation from the trial centres. We informed centres of allocation after a patient had been withdrawn from the trial, if knowledge of the previous treatment was important in the clinical decision making.

Protocol

Staff clinically examined patients for signs of reaction or neuritis and tested sensory and motor nerve function. They recorded all data on standardised integrated, colour coded forms by using the same data entry system for the whole of the TRIPOD trial.

Using the numbered treatment packs, staff allocated eligible patients to multidrug treatment plus prednisolone or multidrug treatment plus placebo, at 20 mg/day prednisolone for the first three months, with a tapering dose in the fourth month. Prednisolone was administered orally in 5 mg tablets. Multidrug treatment was continued for the recommended full 12 months.

Trial follow up points were at 1, 2, 3, 4, 6, 9, and 12 months from the start of multidrug treatment. Staff assessed patients monthly for the duration of multidrug treatment and at any time if they developed complications. Follow up examination included assessment of adverse events as well as testing of sensory and motor nerve function and assessment of skin lesions. Signs of acute reaction or new impairment of nerve function needing full dose prednisolone were considered as the primary outcome event. Patients then stopped the trial medication and were treated according to standard clinical procedures.

Test methods

We diagnosed multibacillary leprosy by field methods. Patients had to have multibacillary leprosy according to the criteria set in both Bangladesh and Nepal—that is, skin smear positive or having three or more body areas with lesions and six or more skin lesions.

We assessed nerve function and nerve tenderness by standardised methods. Sensory testing used coloured graded

Table 1 Reasons for primary outcome events

Code	Name	Definition	Field test
1	Type 1 reaction	Skin signs of severe type 1 reaction needing prednisolone, but without nerve function impairment	Skin examination; <2 levels of change in voluntary muscle test and <3 levels of change in sensory test; no severe nerve tenderness
2	Type 2 reaction	Skin signs of severe type 2 reaction needing prednisolone, but without nerve function impairment	Skin examination; <2 levels of change in voluntary muscle test and <3 levels of change in sensory test; no severe nerve tenderness
3	Facial lesion	Reactional lesion over a facial nerve, without nerve function impairment	Skin examination; <2 levels of change in voluntary muscle test and <3 levels of change in sensory test; no severe nerve tenderness
4	Nerve tenderness	Severe nerve tenderness in any tested nerve	Gentle nerve palpation; patient shows signs of distress
5	Motor function impairment	New motor function impairment in any tested muscle	Reduction in MRC score of 2 points from baseline at trial entry
6	Neuritis	New partial motor or sensory loss and partial tenderness in the same nerve	Reduction in MRC score of 1 point or change in monofilament test of 1 or 2 levels, plus mild tenderness in the same nerve
7	Median sensory nerve function impairment	New sensory loss in the median nerve by monofilament	Change in sensory function as measured by monofilament of 3 levels from baseline at trial entry
8	Ulnar or posterior tibial sensory impairment	New sensory loss by monofilament in the ulnar or posterior tibial nerve	Change in sensory function as measured by monofilament of 3 levels from baseline at trial entry

MRC=Medical Research Council.

monofilaments at three sites for the median nerve and ulnar nerve and four sites for the posterior tibial nerve.⁹ Normal thresholds had previously been established for the population.¹⁰ We gave one point for every level that the monofilament threshold was increased from normal at each test site, and we used the sum of the points as the score for each nerve. We scored motor testing by using a modified Medical Research Council system.¹¹ All study centre staff received training in all test methods and participated in reliability testing.¹²

Primary outcome measure

We defined the primary outcome as signs of acute reaction, new nerve function impairment, or both, such that full dose prednisolone was indicated. We defined eight possible reasons for this primary outcome (table 1).

Analysis

Recruitment to the study began in April 1997 and was completed in December 1999. We collected data and analysed them by using EPI INFO software, version 6.04.¹³ We did a preplanned interim analysis of the six month follow up data at three years after the start of recruitment. The full analysis was at four years after the start of recruitment; it was based on the intention to treat principle and used a comparison of proportions at 4, 6, and 12 months and Kaplan-Meier analysis for all data. We did only one retrospective subgroup analysis, which was based on the presence or absence of impairment of nerve function at diagnosis.

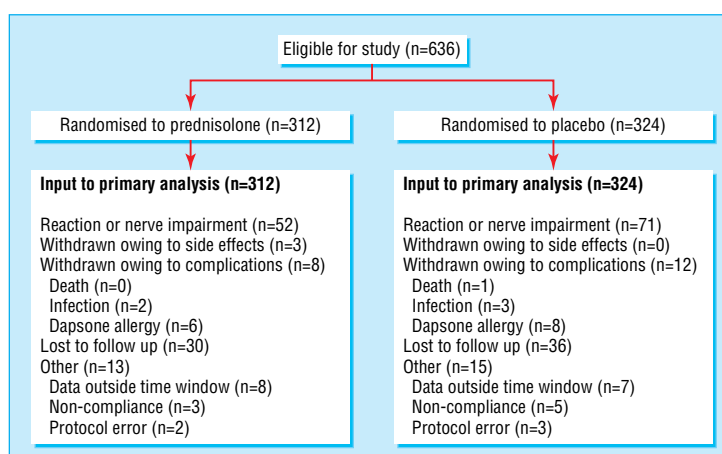


Fig 1 Flow of participants through trial

Results

Figure 1 shows the flow of participants through the trial. We recruited 636 patients (83% of our intended number) with previously undiagnosed multibacillary leprosy. Of these, 324 people received placebo and 312 received low dose prednisolone. We followed patients to one year (December 2000) and checked for symptoms of tuberculosis in trial participants in December 2001. The randomisation successfully produced groups that were similar with respect to baseline characteristics (table 2). Pre-existing impairment of nerve function was present in 153 (24%) of patients. Sixty six (10%) patients were lost to follow up. All patients were included in the analysis.

Reactions and nerve function impairment

At four months, the end of the prophylactic treatment phase, 61 people (9.6%) had experienced a primary event. Twelve of these people had been taking prophylaxis (4% of prednisolone group),

and 49 had been taking placebo (15% of placebo group). The results indicate a significant protective effect, with a relative risk of 3.9 (95% confidence interval 2.1 to 7.3) of developing a primary event if taking placebo compared with prophylaxis with prednisolone. By 12 months, eight months after the completion of prophylaxis, 71 (22%) people in the placebo group had a primary outcome event compared with 52 (17%) people in the prednisolone group. The relative risk of having a primary event if taking placebo, compared with the prednisolone treated group, was 1.3 (0.9 to 1.8). Kaplan-Meier curves using data from all 636 people show the time to event at all time points up to 12 months (fig 2).

Pre-existing nerve function impairment

We found evidence of an interaction with the presence or absence of impairment of nerve function at diagnosis at the four month follow up but not at later time points (table 3). As pre-existing nerve function impairment could be a clinically important factor in determining response to prophylactic prednisolone, we plotted the time to event for those two groups (figs 3 and 4).

Table 2 Baseline characteristics. Values are numbers (percentages)

Characteristic	Prednisolone (n=312)	Placebo (n=324)
Age (years):		
15-20	67 (21.5)	71 (21.9)
21-30	90 (28.9)	98 (30.3)
31-40	102 (32.7)	92 (28.4)
41-50	53 (17.0)	63 (19.4)
Sex:		
Male	209 (67.0)	238 (73.5)
Sensory impairment by monofilament:		
Normal	250 (80.1)	261 (80.6)
Partial	17 (5.5)	25 (7.7)
Impaired	45 (14.4)	38 (11.7)
Motor impairment by voluntary muscle test:		
Normal	279 (89.4)	289 (89.2)
Partial	11 (3.5)	21 (6.5)
Impaired	22 (7.1)	14 (4.3)
Nerve tenderness:		
None	310 (99.4)	323 (99.7)
Any pre-existing impairment	73 (23.4)	80 (24.7)

Table 3 Stratification for pre-existing nerve function impairment

Month	All data (n=636)	Relative risk (95% CI)		P value for test of interaction
		Pre-existing nerve function impairment (n=153)	No pre-existing nerve function impairment (n=483)	
4 (end of treatment)	3.9 (2.1 to 7.3)	2.0 (0.8 to 4.5)	6.7 (2.6 to 16.7)	0.05
12 (end of follow up)	1.3 (0.9 to 1.8)	1.1 (0.6 to 1.8)	1.5 (1.0 to 2.1)	0.34

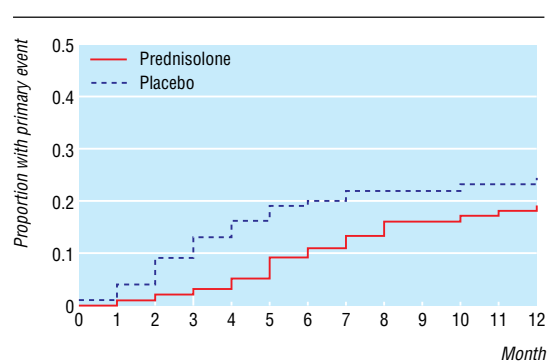


Fig 2 Time to event for all participants

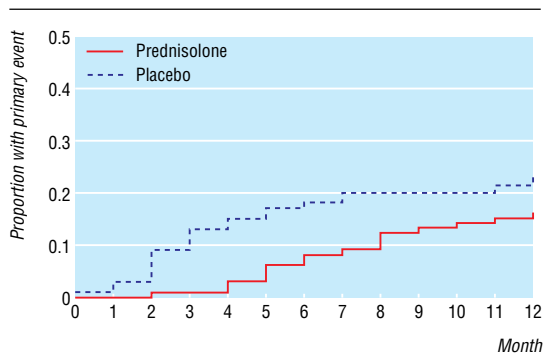


Fig 3 Time to event for participants without pre-existing nerve function impairment

Side effects and complications

We checked at each follow up during the treatment phase for evidence of minor side effects (moon face, severe fungal skin infections, severe acne, and gastric pain needing antacid), major side effects (psychosis, possible peptic ulcer, glaucoma, cataract, diabetes, and hypertension), and infection (table 4¹). Both minor and major side effects occurred more often in the prednisolone treated group. Symptoms associated with major side effects resolved on stopping prophylaxis. If patients developed infections (jaundice, typhoid, chickenpox, and infected scabies), we stopped the trial to minimise the risk to the patient. The number of people who developed an infection was not associated with the treatment groups.

One patient died during the follow up period, at seven months after the start of the trial. He was part of the placebo treated group and was no longer in the treatment phase.

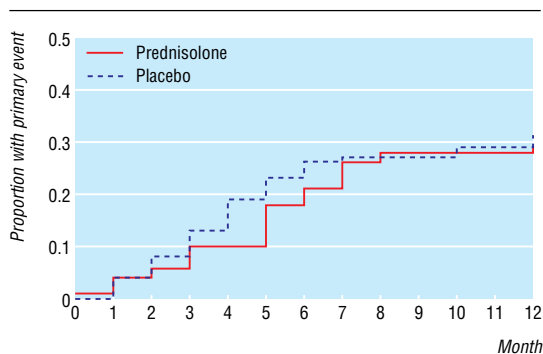


Fig 4 Time to event for participants with pre-existing nerve function impairment

Table 4 Side effects and complications. Values are numbers (percentages) unless stated otherwise

	Placebo (n=324)	Prednisolone (n=312)	P value for association
Any minor side effect:	40 (12.4)	66 (21.2)	0.002
Moon face	6 (1.9)	10 (3.2)	0.27
Acne	1 (0.3)	9 (2.9)	0.009
Fungal skin infection	0	5 (1.6)	0.028
Epigastric pain	39 (12.0)	60 (19.2)	0.01
Major side effects:	0	3 (1.0)	–
Glycosuria	0	1 (0.3)	–
Possible peptic ulcer	0	2 (0.6)	–
Infections	4 (1.2)	2 (0.6)	0.7
Dapsone allergy	12 (3.7)	8 (2.6)	0.8
Death	1 (0.3)	0	–

Discussion

Nerve damage is the most important complication of leprosy for the patient. The nerve damage affects sensory, motor, and autonomic function and progressively leads to impairments and disability. Such nerve damage is difficult to reverse,¹⁴ so any intervention that may prevent or minimise nerve damage in leprosy is worth investigating. Few studies that have explored this approach exist in the published literature,^{4, 5} but the evidence was supportive and the potential benefits substantial enough to justify proceeding to a formal trial.

The objective of this trial was to investigate whether the risk of leprosy related reaction and associated impairment of nerve function could be reduced by prophylactic oral corticosteroids. The maximum dose of prednisolone used in this trial (20 mg) was half that used in standard treatment of acute reaction and nerve function impairment.¹⁵ At four months, on cessation of the prophylaxis, a significant 75% reduction in primary outcome events occurred, more than the 50% reduction considered clinically worthwhile and hypothesised from the existing evidence. However, this significant effect was not sustained at one year. A 31% reduction in the event rate occurred in the prednisolone group compared with placebo at 12 months, but this was not statistically significant. The pattern of the survival curve (fig 2) suggests a rebound in events in the prednisolone group between four and eight months. It is unclear whether extending the duration of steroid prophylaxis from four months to eight months would block this effect and achieve a similar level of reduction at 12 months as was seen at four months.

An important consideration in the prophylactic use of steroids is the potential risk of their use in developing countries where infectious diseases still predominate. This risk, particularly that of tuberculosis, is added to the risk of hypertension, diabetes, and glaucoma associated with the use of steroids. Careful screening at entry minimised the side effects in this trial, as did monitoring at monthly intervals; this may not always be the case in routine practice. The frequency of adverse events is presented in table 4 and is reported in detail elsewhere.¹⁶ The importance of balancing the risks with the benefits of using prophylactic steroids in leprosy was a factor in setting the clinical benefit at a 50% reduction in designing this trial, an effect achieved at four months but not at 12 months.

The finding that the preventive effect in the trial in those patients with no pre-existing impairment of nerve function seemed different from the effect in those with pre-existing nerve function impairment is interesting. It highlights the importance of early detection and treatment in leprosy, a consideration at the centre of the World Health Organization's global strategy.¹⁷ The finding also suggests that small doses of steroid may be insufficient to suppress the immune response in leprosy once nerve function impairment has developed. Further research is needed to improve our understanding of the immune response in leprosy, to identify markers to predict nerve damage, and to explore new interventions to prevent and treat reactions in leprosy.

This trial is one of three trials combined in an integrated approach across six centres in two developing countries; the other two trials have been published recently.^{18, 19} The trials have shown that it is feasible to conduct high quality research in such settings and ensure high standards of quality control throughout the trial process. This trial indicates that low dose steroids can prevent reactions and impairment of nerve function in patients with multibacillary leprosy in the short term but that the benefit is not sustained at one year. These results do not support the

What is already known on this topic

Irreversible damage to peripheral nerves is a frequent complication of leprosy

Nerve damage often occurs in reactional states during antileprosy treatment and is difficult to treat and to reverse

What this paper adds

Low dose steroid can prevent nerve function impairment and reactions in the short term, but the effect is not sustained in the long term

Existing nerve function impairment may affect the outcome of steroid prophylaxis

routine use of low dose steroids for four months in the treatment of multibacillary leprosy. However, they do add to our understanding of the reaction process and indicate the need for further work in tackling this important complication of leprosy.

TRIPOD was the work of the staff of the Biratnagar subregional referral centre, the Chittagong Leprosy Control Project, the Danish Bangladesh Leprosy Mission (Nilphamari), the Dhaka Leprosy Control Project, the Nepal Leprosy Trust (Lalgadh), and the Western Region Leprosy Control Project (Nepal). The study was supported by the Leprosy Control Division of His Majesty's Government of Nepal and the People's Republic of Bangladesh. The successful completion of the study is due to these people and to the patients themselves.

Contributors: WCSS was responsible for the study conception, contributed to the interpretation and writing the paper, and is the guarantor. AMA contributed to the study design, interpretation, and writing the paper and was responsible for the execution and analysis. SGW contributed to the execution and interpretation. WHvB contributed to the study design, execution, and interpretation. RPC contributed to the study design and execution. PGN contributed to the study design, execution, and analysis and was responsible for the database design. JHR contributed to the study design and interpretation.

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Ethical approval: The study design was reviewed by the medical advisory board of LEPRA and the technical and ethical standards committee of the International Nepal Fellowship. The Nepal Health Research Council and the Bangladesh Medical Research Council gave ethical approval.

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