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Treatment with corticosteroids of long-standing nerve function impairment in leprosy: a randomized controlled trial (TRIPOD 3)

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Summary Some leprosy patients with long-standing nerve function impairment (NFI) appear to have responded favourably to treatment with corticosteroids. This study investigated whether patients with untreated NFI between 6 and 24 months duration and who are given standard regimen corticosteroid therapy, will have a better treatment outcome than a placebo group. A multicentre, randomized, double-blind placebo-controlled trial was conducted in Nepal and Bangladesh. Subjects were randomised to either prednisolone treatment starting at 40 mg/day, tapered by 5 mg every 2 weeks, and completed after 16 weeks, or placebo. Outcome assessments were at 4, 6, 9, and 12 months from the start of treatment. 92 MB patients on MDT were recruited, of whom 40 (45%) received prednisolone and 52 (55%) placebo treatment. No demonstrable additional improvement in nerve function, or in preventing further leprosy reaction events was seen in the prednisolone group. Overall, improvement of nerve function at 12 months was seen in about 50% of patients in both groups. Analysis of subgroups according to nerve (ulnar and posterior tibial), duration of NFI, and sensory and motor function, also did not reveal any differences between the

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treatment and placebo groups. There was however, indication of less deterioration of nerve function in the prednisolone group. Finally, there was no difference in the occurrence of adverse events between both groups. The trial confirms current practice not to treat long-standing NFI with prednisolone. Spontaneous recovery of nerve function appears to be a common phenomenon in leprosy. Leprosy reactions and new NFI occurred in a third of the study group, emphasizing the need to keep patients under regular surveillance during MDT, and, where possible, after completion of MDT.

Introduction

Nerve function impairment (NFI) in leprosy patients may lead to severe disabilities, such as muscle paralysis of face, hands and feet, and chronic plantar and palmar ulceration. For many years, the mainstay of treatment of NFI of less than 6 months duration, in particular in the presence of clinically manifest type 1 reaction, has been with corticosteroids.[1–3] For NFI of longer than 6 months duration, however, this treatment is not recommended. Beyond 6 months of NFI, nerve fibres are considered to be damaged irreversibly, and are therefore unlikely to respond to treatment.[4,5] Yet there are indications that some patients with long-standing NFI have responded favourably to treatment with corticosteroids.[6,7] If this is indeed the case, the potential for preventing (further) disability is considerable, while the risks of treatment are limited.[8] The studies in which this was found were open, uncontrolled trials and the conclusions therefore not firmly established. For this reason, evaluation of the efficacy of corticosteroids in patients with long-standing NFI was included in the TRIPOD study, a triad of randomized, controlled trials on prevention of impairment and disability in leprosy. The objective of the trial reported in this paper was to investigate whether patients who have untreated NFI which commenced between 6 and 24 months previously and are given standard-regimen steroid therapy, will have a better treatment outcome than similarly impaired patients who receive placebo treatment. An increase of 25% or more in the number of patients with improved nerve function in the treatment group, compared to those who received placebo treatment for the same condition, was considered to be a successful outcome.

Materials and methods

STUDY POPULATION

The trial was conducted in six leprosy control programmes in Nepal and Bangladesh. In Nepal the control programmes were in Dhanusha District in the Central Region, Morang District in the Eastern Region and in the Terai Districts of the Western Region. The Leprosy Division of the Ministry of Health of His Majesty's Government, Nepal, runs these programmes with technical assistance from the Nepal Leprosy Trust, Netherlands Leprosy Relief and the International Nepal Fellowship, respectively. In Bangladesh the control programmes were in Northwest Bangladesh, Dhaka and Chittagong, run by The Leprosy Mission (TLM), in co-operation with the Government of Bangladesh.

STUDY SUBJECTS

Leprosy patients aged 15–50 were included if they had a confirmed MB leprosy diagnosis (any degree of smear positivity or six or more skin lesions), and on treatment with WHO MB multidrug therapy (MDT), and who had untreated sensory or motor impairment of the *ulnar* or *posterior tibial* nerve of more than 6 months up to 24 months duration. Excluded from the study were any patients for whom steroids were indicated at study registration because of leprosy reactions, NFI of up to 6 months duration (acute NFI), or any other indication. Also, patients in whom corticosteroids at the fixed trial dose would be contraindicated, were excluded from the study.[9] Finally, patients were excluded if NFI of the eligible nerve had been treated surgically. Patients with NFI bilaterally or of both ulnar and posterior tibial nerve only contributed the least affected limb to the trial. If both limbs were equally affected, then the right side was included.

STUDY DESIGN

The study design was that of a multicentre, randomized, double-blind placebo-controlled trial. Patients were randomized to either of the two arms of the trial within each leprosy control programme. One treatment group received a standardized prednisolone regimen, the other a placebo regimen. Treatment prescribers, study coordinators, and patients were unaware of the treatment allocation. Patients receiving prednisolone started with a dose of 40 mg/day, taken in the morning. The dose was tapered by 5 mg every 2 weeks and was completed after 16 weeks. Patients receiving placebo took an equivalent number of placebo tablets for the same time period. Patients were requested to attend follow up clinics monthly for assessment while taking treatment. An outcome assessment was done at completion of treatment at 4 months, and at 6, 9, and 12 months after the start of treatment. The trial commenced on 1 April 1998, and intake of patients lasted until 30 June 2000.

EXAMINATION

The clinical assessment included a history, clinical examination for signs of reaction or neuritis and a voluntary muscle test (0–5 grading). Sensory testing was done by trained field staff using five coloured graded monofilaments: 200 mg, 2 g, 4 g, 10 g and 300 g.[10] The initial assessment was considered the ‘baseline’. One point was given for every level that the monofilament threshold was increased from normal at each test site. The points were added for each nerve. Normal thresholds used were 200 mg for the hand and 2 g for the foot.[11] The Semmes–Weinstein monofilament test was considered positive if a patient scored 3 or more points for any nerve. If at a follow up test a patient scored the same score as at their baseline test, or 1 or 2 points less or more, then their condition was considered ‘unchanged’. If the score had increased by 3 or more points, the condition was diagnosed as ‘deteriorated’; if decreased by 3 or more points, it was diagnosed as ‘improved’. If a patient’s score improved by 3 or more points, and the total score for the nerve was 2 or less then the patient’s condition was called ‘recovered’. Motor testing of the abductor digit minimi (ADM) was performed by the same trained staff, and scoring performed according to the modified MRC (0–5) system,[12] scores being inverted for the purposes of TRIPOD, and a score of 2 or more defining severe motor NFI.[13] Motor testing was not carried out for the intrinsic muscles of the foot, because of difficulties in standardization.

OTHER OUTCOMES

During follow-up, all patients were examined for the presence of adverse events of prednisolone. Minor adverse events were defined in advance and specifically looked for, namely moon face, fungal infections, acne, and gastric pain requiring antacid. These events were recorded only during the first 4 months of the trial only (the treatment phase). Patients exhibiting signs of these conditions were treated appropriately, but not removed from the trial unless the patient requested it. Major adverse events were defined as psychosis, peptic ulcer, glaucoma, cataract, diabetes and hypertension. These events were checked throughout the trial. Patients exhibiting these signs and symptoms were treated appropriately and removed from the trial. Another important reason to discontinue participation in the trial was any event leading to the prescription of prednisolone. Such events were known as 'steroid triggering events' and included type 1 or type 2 leprosy reactions and any signs of recent NFI.

STATISTICAL ANALYSIS

For each nerve entered into the study, the change in motor and sensory score between follow up and registration was calculated. Negative scores imply an improvement. This score was categorized as 'worse', 'same', 'better', 'recovered' (i.e. same as baseline score), and 'normal' (i.e. no longer an impairment). On the basis of these categories, a two-group classification was made: 'better' (all improvement groups) and 'same/worse'. Mixed outcomes such as improvement in sensory and worsening in motor function, were classified as 'mixed', which counted as a poor outcome. Because of the small numbers, only the two-group classification was tested for statistical significance.

Following a review of data at 12 months, it was decided that patients who had come out of the trial because of poor outcome (i.e. not lost to follow-up) should also have a 12-month follow-up. The primary purpose was to compare whether 'treatment of long-standing NFI' showed any benefit over 'steroid-triggering event detected early plus appropriate treatment' in terms of nerve function. The outcome measure for this review was change of nerve function status from baseline.

Statistical analysis was done in EPI INFO version 6·04. Risk ratios and 95% confidence intervals were calculated. The difference between group means was evaluated using a Student's *t*-test.

Results

In total, 95 patients were recruited into the trial from the six leprosy control centres in Nepal and Bangladesh. Of these patients, 54% were from Nepal and 46% from Bangladesh. There were 20 females and 75 males (ratio 3·8:1 males to females). For the posterior tibial nerve, 65 nerves were recruited, and 30 for the ulnar nerve. The duration of NFI was 7–12 months in 23, and 13–24 months in 42 posterior tibial nerves. For the ulnar nerve, the duration of NFI was 7–12 months in 14, and 13–24 months in 16 cases. Three cases were lost to follow up before month 1, and were subsequently excluded. The remaining 92 nerves are included in the analysis. Of these 92, 71 had sensory impairment, three motor impairment, and 18 both sensory and motor impairment.

Overall, 40 (45%) of patients received prednisolone and 52 (55%) received placebo, indicating a robustness to the randomization despite imbalance of numbers recruited by

centre and the relatively small numbers recruited in total. At 12 months, 46/92 (50%) patients were still in the trial. Thirty (33%) were out of the trial due to an event requiring treatment with prednisolone, and 16 (17%) left the trial for other reasons. Five patients were confirmed as lost to follow-up (5%), while another five (5%) did not have full data at 12 months. No patients came out of the trial with symptoms indicating possible minor adverse events. In total, nine people (10%) showed 13 symptoms at one or more follow up assessments. There was no significant association ($P > 0{\cdot}5$) with treatment and the frequency of minor adverse events. Five patients (5%) came out of the trial with symptoms indicating possible major adverse events. Two people were diagnosed with diabetes (urine glucose $\geq 2+$), 1 from each treatment group. One person (from the placebo group) had signs of peptic ulceration, and one person developed what was indicated as 'hypersensitivity' to the trial tablets. This individual was taking prednisolone. There was also no significant association ($P > 0{\cdot}5$) with treatment and the frequency of major adverse events. Finally, one unrelated death was registered in the placebo arm.

In Table 1, the reasons for taking a patient out of the trial are shown for each point of follow-up. Steroid-triggering events are shown by treatment group, together with the relative risk of having a steroid-triggering event for each of the two treatment groups. At the 4-month time point, there appears to be a lower risk of a steroid-triggering event in the group treated with prednisolone. However, the difference is not statistically significant. At the 6, 9 and 12 months follow-up, there is no suggestion at all of differences between the treatment groups for the occurrence of steroid-triggering events.

Table 2 shows the proportion of patients in both treatment groups who fall into the 'improved nerve function' category at each point of follow-up. With these proportions, a breakdown is given of the relative risk according to nerve, duration of NFI, and sensory and motor function. The relative risks do not reach statistical significance in any of these groupings. The most remarkable finding is that around 50% of patients in the placebo group show some improvement at 12 months. This percentage was maintained throughout the follow-up period and was not exceeded by the prednisolone group. A 'final outcome' was calculated, incorporating all patients for whom 12-month follow up data were available, including those who came 'out' because of requiring prednisolone during the trial. In total, 30 patients came out of the trial before the 12-month follow-up and it was possible to include 24 of these in the analysis of the final outcome. Further improvement was seen in the percentage

Table 1. Number and percentage of patients taken out of the trial during the treatment and at each point of follow up because of steroid-triggering events and other reasons ($n = 92$)

Month	Steroid-triggering events (cumulative)	Steroid-triggering events by treatment (cumulative)		Relative risk[a] (all data) $n = 92$	Other reasons for leaving trial (cumulative)	Still in trial (cumulative)
		Prednisolone $n = 40$	Placebo $n = 52$			
0	0	0	0	0	0	92 (100%)
4	14 (15%)	4 (10%)	10 (19%)	2·01 (0·68–5·94)	8 (9%)	70 (76%)
6	20 (22%)	10 (25%)	10 (19%)	0·80 (0·37–1·74)	10 (11%)	62 (67%)
9	28 (30%)	13 (33%)	15 (29%)	0·93 (0·50–1·72)	10 (11%)	54 (59%)
12	30 (33%)	15 (38%)	15 (29%)	0·80 (0·45–1·44)	16 (17%)	46 (50%)

[a] A relative risk of > 1 implies a relative benefit in favour of the prednisolone group.

Table 2. Percentage of patients in both treatment groups who fall into the 'improved nerve function' category at each point of follow up, together with a breakdown of the relative risk (RR) according to nerve, duration of NFI, and sensory and motor function

	Improved (cumulative %)									
Month	Pred.	Placebo	Overall $n = 92$ RR[c]	PT[a] $n = 62$ RR	Ulnar[b] $n = 30$ RR	7–12 months $n = 37$ RR	13–24 months $n = 55$ RR	Sensory $n = 71$ RR	Motor $n = 3$ RR	Sensory and motor $n = 18$ RR
4	39%	47%	0·87 (0·61–1·24)	0·98	0·73	0·83	0·90	1·01	0·50	0·63
6	34%	47%	0·80 (0·57–1·13)	0·86	0·73	0·68	0·90	0·86	0·50	0·83
9	34%	49%	0·77 (0·55–1·10)	0·77	0·82	0·62	0·90	0·77	–	0·83
12	41%	51%	0·84 (0·57–1·23)	0·77	1·00	0·75	0·90	0·83	–	0·83
Final[d]	54%	51%	0·95 (0·64–1·41)	0·90	1·10	1·02	0·90	0·96	–	0·97

[a] Posterior tibial nerve.
[b] Ulnar nerve.
[c] A relative risk of >1 implies a relative benefit in favour of the prednisolone group.
[d] A 'final outcome' was calculated incorporating all patients for whom 12-month follow up data were available, including those who came 'out' because of requiring prednisolone during the trial.

of patients originally assigned to prednisolone (54%), but not in the placebo group (51%). The differences, however, are never statistically significant, overall or in a sub-group.

Of the patients included in the trial, only three had pure motor function impairment. Excluding these, the changes in sensory score can be calculated, both overall and stratified for nerve and duration of NFI. These figures are shown in Table 3, where the mean changes in sensory score are given for each treatment group at each time period, together with range in score. The prednisolone group shows less variation in change of scores compared to the placebo group, and the mean improvement in score is often less. There were no indications of systematic differences in improvement in favour of the steroid or the placebo group, either overall or in the subgroups. It is noteworthy that the variance of the scores in the placebo group is always higher. At the final outcome, the variance in the placebo group was 9·1, compared with 2·8 in the prednisolone group. Also in this analysis an improvement in the placebo arm can be observed.

Table 3. Changes in sensory score at each point of follow-up

	Overall $n = 89$		
Month	Prednisolone difference[a]	Placebo difference[a]	*P*-value
4	Mean –0·98 Range –6, +2	Mean –1·4 Range –8, +9	0·23
6	Mean –0·80 Range –9, +4	Mean –1·3 Range –7, +9	0·07
9	Mean –0·78 Range –6, +4	Mean –1·3 Range –7, +9	0·15
12	Mean –1·1 Range –9, +4	Mean –1·6 Range –8, +9	0·11
Final	Mean –1·3 Range –6, +1	Mean –1·7 Range –8, +7	0·30

[a] Negative scores imply an improvement in nerve function.

Discussion

The main objective of the trial was to investigate whether patients who have untreated NFI of 6–24 months duration and are given standard regimen steroid treatment, will have a better treatment outcome than similarly impaired patients who receive placebo treatment. In other words, will these patients with long-term NFI benefit from steroid treatment? One of the underlying assumptions was that these patients are a relatively stable group. In the study sample at least this is clearly not the case, with very significant numbers of patients in the placebo group showing spontaneous improvement in nerve function, and many patients developing new reactions and NFI, in both arms of the trial. As a result, at no point in the trial was any difference demonstrated in terms of percentage improved nerve function. There was no evidence of any added improvement in function in the prednisolone group, rather a persistent but not-significant difference in favour of the placebo arm. Sub-analysis, by duration of NFI, and by nerve involved, failed to identify any group more likely to benefit. Further analysis was not possible because of the small number of subjects in the trial. Only the degree of variability in nerve function appeared to be affected by prednisolone treatment, in that very few nerves in the prednisolone group had deteriorated during follow-up.

Perhaps the most remarkable finding of the study is the magnitude of spontaneous improvement (51%) in the placebo arm. A degree of spontaneous recovery of nerve function has been reported in previous studies,[3,14] but the extent was never firmly established in a randomized controlled trial. The current finding is an important addition to the body of knowledge on the natural history of nerve damage in leprosy. The degree of spontaneous recovery found in this group with untreated but old NFI also raises the important question of how much spontaneous recovery occurs in those with NFI of recent onset, though it would now be considered unethical to study this prospectively in a controlled trial.

The lack of any significant difference in minor or major adverse events between prednisolone and placebo groups is further reassurance of the safety of standard reaction treatment regimens under field conditions and should give further impetus to making such treatment available to those requiring it. Further analysis of adverse events is presented in a combined report on all subjects enrolled in the three TRIPOD studies.[9]

A shortcoming of the trial is that the number of subjects (92) fell short of the original target sample of 200. This was the number required to test the hypothesis of a difference of 25% improvement in favour of the prednisolone group. The main reason for the paucity of patients was the preferential recruitment of patients into the prophylaxis trial. The lower intake decreased the statistical power of the study, in particular for the analysis of subgroups. However, there is no indication that a larger number of patients would have led to a different overall result. No systematic differences were observed in favour of the steroid group. The initial reduction in risk of a reaction of new neural impairment seen at 4 months was not sustained. At 12 months, few nerves in the prednisolone group had deteriorated, but it is not certain whether this can be attributed to the steroid treatment. Another limitation of this study is the focus on only ulnar and posterior tibial nerves. These were chosen because they are most commonly affected in leprosy. It is possible that other nerves with longstanding impairment of function would show more response to corticosteroids. Also, the current study is clearly dominated by sensory NFI.

The most likely reason why previous studies indicated that prednisolone in long-standing NFI had beneficial results is inappropriate study design. Several factors can be mentioned, such as small number of patients, absence of a control group, lack of blinding and too short a

follow up time. The most likely reason is the absence of a control group, due to which the extent of spontaneous recovery of nerve function could not be assessed. This was never anticipated to be in as high as 50%. Long-term follow-up is shown to be of great importance. While initial results during and immediately after a course of prednisolone appeared to be promising, they were often not sustained in the long term. The same was seen in the second trial within the TRIPOD study.[10]

The results of this trial confirm current practice not to treat long-standing NFI with prednisolone. On the other hand, in this study group, leprosy reactions and new NFI occurred in a third of the patients. It is therefore very important that this group of patients, mostly with MB leprosy, is kept under close surveillance during, and, where possible, following the completion of MDT. Surveillance should include regular assessment of nerve function and the provision of appropriate treatment with prednisolone in case new NFI is detected.

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