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Multi-centre, double blind, randomized trial of three steroid regimens in the treatment of type-1 reactions in leprosy

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Summary
Objective: The objective of this randomized trial was to compare three different steroid regimens in treating type 1 reactions in leprosy in routine clinical practice.
Design: The study design was a multicentre, double-blind, randomized, controlled, parallel group trial in patients with acute reversal reactions. The trial was conducted in six leprosy treatment centres in India. A total of 334 participants with acute type 1 reaction were recruited to the trial and randomized to one of three prednisolone regimens: high dose (60 mg per day) or low dose (30 mg per day) both tapered over 20 weeks, and short duration (60 mg per day tapered over 12 weeks). The main outcome measure was the proportion of patients failing to respond to treatment and requiring additional steroids.
Results: At the end of 12 months, 46% on the short course required additional steroids compared with 31% on the low dose and 24% on the high dose regimen.
Conclusions: The two 20-week regimens were significantly better than the 12-week regimen. The high dose 20-week regimen was marginally and non-significantly better than the low dose regimen, but the high dose regimen contained 50% more steroid. Reactions in leprosy persist over many months and require long courses of steroids.

Introduction

Type 1, or reversal, reaction is one of the major causes of nerve function impairment in leprosy.[1] It has been shown to occur in 37% of multi-bacillary cases and predictive factors

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have been identified.[2] Type 1 reactions affect the skin and nerves due to hypersensitivity to *Mycobacterium leprae* antigens and are not associated with bacterial multiplication. The use of corticosteroids to treat reactions was first reported in 1952.[3] Steroid courses used in the 1950s and 1960s were usually short and low dose, although by the 1980s longer courses and higher doses were being recommended.[4] The next development in steroid treatment of type 1 reactions was the recommendation for standardized[5] or semi-standardized[6,7] steroid regimens. Standardized regimens were found to be useful in field conditions and for use in outpatients.[8]

More recent work has assessed the effectiveness of steroids in type 1 reactions in preventing or reversing nerve function impairments. A retrospective study reported only a 50% improvement in reactions involving nerves,[9] while other studies have reported improvement in nerve function of 60–70%.[10–12] Most of the evidence of the effectiveness of steroid therapy for reactions in leprosy is based on retrospective or prospective uncontrolled observational studies. Steroids are the established treatment for type 1 reactions and a placebo-controlled trial would be regarded as unethical although spontaneous recovery of nerve function in patients who have not received steroid treatment is observed.[12]

There is considerable debate about the optimal steroid regimen in routine clinical practice in terms of dose and duration. One study attempted to address this question using a historical control design and suggested that long term treatment was superior to short term treatment, although the study was based on only a small number of patients.[13] This paper presents the results of the first, randomized, double blind, controlled trial comparing high dose, low dose and short duration regimens in the treatment of type 1 reactions in leprosy.

Materials and methods

STUDY DESIGN

The study was a multi-centre, randomized, double blind, parallel group trial. The study was conducted in six centres spread over four different states of India (Barabanki, Chandkhuri, Karigiri, Miraj, Naini and Purulia). The study was started after a training workshop for the key personnel on all aspects of the investigation and to standardize procedures. Participating physicians from each centre met regularly throughout the trial, and one investigator visited each centre during the trial to assess quality and standardization.

OBJECTIVES AND OUTCOME MEASURES

The study tested the hypothesis that long duration, high dose steroid treatment would result in a significantly smaller proportion of people experiencing a poor outcome of treatment in routine clinical practice. We defined poor outcome as a failure to respond to treatment in terms of changes to skin lesions, nerve pain or tenderness, or nerve function, or recurrence of skin or nerve lesions such that additional steroids were clinically judged to be needed, in excess of those given as part of the trial. Our primary objective was to compare the additional steroids needed by patients allocated to three groups: long duration-high dose (High), long duration-low dose (Low) and short duration-high dose (Short).

PROTOCOL

Three regimens were tested, based on the knowledge that most leprologists[8] tend to start steroids at a dose of 30–60 mg daily and taper the dose over 3–6 months. Regimens were based on the assumption that the average weight of the patients was 60 kg.

Regimen 1 (High): Prednisolone 60 mg for 2 weeks, 50 mg for 2 weeks, 40 mg for 2 weeks, 30 mg for 2 weeks, 20 mg for 4 weeks, 10 mg for 4 weeks, 5 mg for 4 weeks. (Total steroid dose was 3·5 g, total treatment duration 5 months.)

Regimen 2 (Low): Prednisolone 30 mg for 2 weeks, 25 mg for 2 weeks, 20 mg for 8 weeks, 10 mg for 4 weeks, 5 mg for 4 weeks. (Total steroid dose was 2·31 g, total treatment duration 5 months.)

Regimen 3 (Short): Prednisolone 60 mg for 2 weeks, 50 mg for 2 weeks, 40 mg for 2 weeks, 30 mg for 2 weeks, 20 mg for 2 weeks, 10 mg for 2 weeks, and placebo for 8 weeks. (Total steroid dose of 2·94 g, total treatment duration 3 months, plus 2 months placebo.)

Prednisolone was taken as a single dose each morning. The total duration of medication (prednisolone and placebo) was 5 months. Patients were followed up for a further 7 months. In the event of worsening nerve function, and based on the clinical judgement of the clinician the dose of steroids was increased.

SAMPLE SIZE

The sample size was calculated on the hypothesis that regimen 1 (High) would be superior to the other regimens, and was set at 200 per group, total 600, to provide a power of 80% to detect a 50% requirement for supplementary steroids in one of the other groups, at an alpha of 0·05, assuming an attrition rate of 30%.

PARTICIPANTS

Participants were enrolled between 1997 and 2000. Leprosy patients with severe type 1 reactions seen at the leprosy centres or control programmes at Karigiri, Miraj, Naini, Barabanki, Purulia, and Chandkhuri were eligible for enrolment. Inclusion criteria were age 15–65 years, type 1 reactions requiring steroid treatment and willingness to consent to participate. Exclusion criteria were pregnancy, contraindications to steroids (hypertension, diabetes, severe infectious disease) and severe inter current diseases (cardiac, hepatic or renal disorders). Severe type 1 reactions were defined as nerve tenderness, any motor or sensory nerve function impairment of duration less than 3 months, or severely inflamed skin lesions. Patients were recruited into the trial on the basis of informed, voluntary consent. The trial did not raise ethical concerns since prednisolone has long been used world-wide to treat reactions in leprosy and the dosages to be used in the trial were consistent with current practice and WHO recommendations.[8] Initial assessment included history, clinical examination, nerve function tests, slit skin smear for acid fast bacilli and skin biopsy.

RANDOMIZATION, ASSIGNMENT AND MASKING

Randomization was carried out with stratification for classification into multibacillary (MB) and paucibacillary (PB) leprosy. Classification was based on the number of skin lesions and the skin smear. Randomization lists were prepared separately for each participating centre,

by Dr Rao and kept strictly confidential; authority to break the code was on the recommendation of the clinical co-ordinator (Dr Sugumaran) in case of serious side effects. The three regimens were presented in blister calendar packs containing the stipulated doses for 28 days. Each blister pack contained identical looking white tablets whatever the dose of prednisolone or placebo. The 5-month regimen for each patient according to the randomized list was prepared, supervised and boxed at the co-ordinating centre (Karigiri) and dispatched to the participating centres.

OUTCOMES AND ANALYSIS

The outcome of the trial in each patient depended upon the clinician's judgement as to whether additional steroids were required in the event of worsening of nerve function, based on the usual practice of that clinician. No specific criteria for the administration of additional steroids were spelt out in advance but the general principles were agreed and included in the protocol. The primary end point was the requirement for additional steroids during the 12-month trial period. The co-ordinating centre was responsible for data management throughout the study. The final analyses were conducted at the co-ordinating centre, Karigiri, and chi-squared tests were used to test differences between the regimens.

Results

RECRUITMENT

Recruitment was slower than expected. During the funded period we recruited 334 participants, well short of the 600 required by the trial design. Of these, 312 (93·4%) were MB and 22 (6·6%) were PB. Figure 1 shows the patient flow from recruitment to the trial. The breakdown by centre and leprosy type is given in Table 1.

BASELINE CHARACTERISTICS

The baseline characteristics of the patients recruited into the trial are shown in Table 2. There were no significant differences between the patients allocated to each of the three regimens.

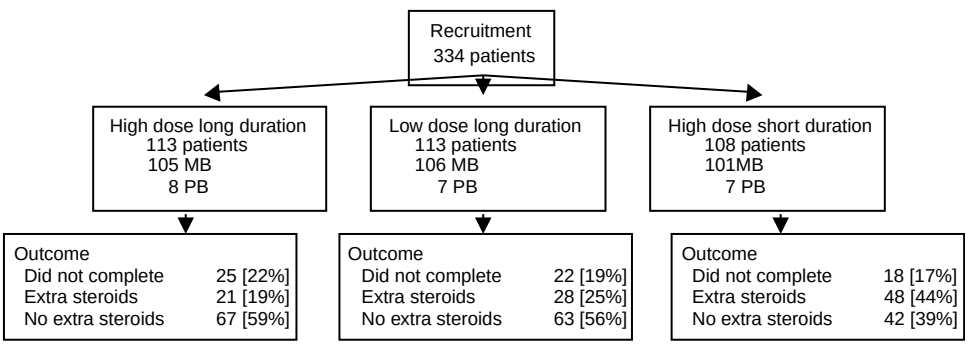

Figure 1. Participant flow.

Table 1. Recruitment intake by centre and leprosy type. MB = multibacillary, PB = paucibacillary

	Type		
Centre	MB (%)	PB (%)	Total
Barabanki	32 (96·9)	1 (3·0)	33 (100)
Chandkhuri	29 (90·6)	3 (9·4)	32 (100)
Karigiri	78 (89·7)	9 (10·3)	87 (100)
Miraj	34 (94·4)	2 (5·6)	36 (100)
Naini	125 (94·7)	7 (5·3)	132 (100)
Purulia	14 (100·0)	0 (0)	14 (100)
Total	312 (93·4)	22 (6·6)	334 (100)

TREATMENT COMPLETION

Of 334 enrolled participants, 269 (80·5%) completed the 5 months treatment and were followed up. Of those who did not complete treatment 25 (22·1%), 22 (19·5%) and 18 (16·7%) were in the High, Low and Short regimens, respectively. Table 3 shows the variation in characteristics between those who completed the study and those who did not complete treatment. More patients in the PB group failed to complete treatment, but the difference was not significant and probably reflects the small numbers of people on PB treatment. ($\chi^2 = 3{\cdot}22$, $P = 0{\cdot}07$).

ADDITIONAL STEROIDS

The number of cases who required additional steroids in the three regimens is given in Table 4. Over the whole 12-month study period, for patients completing treatment, 23·9%, 30·8% and 45·6% received additional steroids in the High, Low and Short regimens respectively. The percentages differ significantly ($\chi^2 = 9{\cdot}85$, $P = 0{\cdot}007$). More participants

Table 2. Baseline characteristics of patients recruited by steroid regimen

	Total (%)	High dose long duration (%)	Low dose long duration (%)	High dose short duration (%)
Overall	334	113 (34)	113 (34)	108 (32)
BI				
0–1	231 (69)	82 (73)	77 (68)	72 (67)
2–6	79 (24)	23 (20)	26 (23)	30 (28)
Not known	24 (7)	8 (7)	10 (9)	6 (6)
Gender				
Male	232 (69)	88 (78)	69 (61)	75 (69)
Female	102 (31)	25 (22)	44 (39)	33 (31)
Treatment				
MB	312 (93)	105 (93)	106 (94)	101 (94)
PB	22 (7)	8 (7)	7 (6)	7 (6)
Age (years)				
<30	106 (32)	39 (35)	38 (34)	29 (27)
30–44	103 (31)	34 (30)	36 (32)	33 (31)
>44	125 (37)	40 (35)	39 (34)	46 (42)

Table 3. Characteristics of patients completing treatment

	Total	Followed up (%)	Lost to follow-up (%)	Significance
Overall	334	269	65	
Regimen				
High	113	88 (78)	25 (22)	Chi-squared 1·05
Low	113	91 (81)	22 (19)	P = 0·59
Short	108	90 (83)	18 (17)	
BI				
0–1·9	231	188 (81)	43 (19)	Chi-squared = 0·16
2+	79	62 (78)	17 (22)	$P = 0·69$
Not known	24	19 (79)	5 (21)	
Gender				
Male	232	183 (79)	49 (21)	Chi-squared = 1·01
Female	102	86 (84)	16 (16)	$P = 0·31$
Treatment				
MB	312	255 (82)	57 (18)	Chi-squared = 3·22
PB	22	14 (64)	8 (36)	$P = 0·07$
Age				
<30	106	86 (81)	20 (19)	Chi-squared = 0·08
30–44	103	82 (80)	21 (20)	$P = 0·96$
>45	125	101 (81)	24 (19)	

in the Short regimen needed additional steroids than in the other regimens. However, there was no significant difference between the high and low dose regimens in the percentages that needed additional steroids. Over the 5-month treatment period, 12·5%, 15·4% and 27·8% from high, low and short regimens respectively received additional steroids, the differences being significant ($\chi^2 = 7·80$, $P = 0·020$). The proportion requiring additional steroids in the short course regimen was significantly higher than in the high dose regimen and low dose regimen.

During the 7-month follow-up period, the percentage that needed additional steroids in the short regimen was higher than in the high dose regimen ($\chi^2 = 5·53$, $P = 0·002$). Some patients received additional steroids on more than one occasion, both during the treatment and during the follow-up.

We compared the overall efficiency of the three regimens using the probability of requiring additional steroids throughout the study period (Figure 2). The short duration regimen needed more additional steroids than the other two. Although the low dose regimen curve was higher than that of the high dose regimen uniformly from the second month onwards, the gap between the curves widens after the 7th month.

Table 4. Additional steroid received by patients

	High ($n = 88$)	Low ($n = 91$)	Short ($n = 90$)	Total
During treatment (months 1–5)	11 (12·5)	14 (15·4)	25 (27·8)	50 (18·6)
During follow-up (months 6–12)	13 (14·8)	15 (16·5)	20 (22·2)	48 (17·8)
*During whole study period (months 1–12)	21 (23·9)	28 (30·8)	41 (45·6)	90 (33·5)

* Some patients received additional steroids both during treatment and also during follow-up.

Figure 3 compares the time when additional steroids were given by steroid regimen. Up to 3 months there was no difference between the proportions that received additional steroids. At 3 months, more of those with the low dose and short duration regimens received additional steroids. At the 4th, 5th and 6th months clearly more on the short duration regimen had additional steroid than others. This coincided with the short course group changing to placebo.

No serious side effects of steroids were reported in any patient from the routine clinical examinations during the follow-up period.

Discussion

The evidence of the effectiveness of steroids in treating reversal (type 1) reactions in leprosy is based on uncontrolled, observational studies. These studies report an improvement rate in nerve function of 50–70%,[9–11] although nerve function has also been shown to recover spontaneously without steroids (12). The effectiveness of steroids compared to placebo is uncertain but steroids are the generally accepted standard treatment.[9] The widespread use of steroids in out-patients and under field conditions has led to the development of standardized steroid regimens, sometimes distributed in blister packs. The debate has centred on the optimal dosage and duration of steroids in such regimens in routine clinical practice. Concerns over adverse effects of steroids when used in developing countries where infections are common[4,11] has led to pressure to keep the dose and duration of steroids to a minimum. Most information on adverse effects associated with steroids is based on evidence from developed countries but one recent study has assessed safety in developing countries.[14] This analysis showed an increase in minor adverse events associated with steroids but that major events were rare, although all patients were carefully screened for contra-indications before starting steroid therapy.[15]

Only one study has attempted to compare short and long duration steroids using a controlled design.[13] This was a small study in Ethiopia using a historical control group that suggested that long term was superior to short term.

Our paper reports the first randomized, controlled, double blind trial of different regimens (high dose, low dose and short duration) to treat type 1 reaction in leprosy. The trial used a pragmatic design to assess the benefits of the regimens in routine clinical practice.[16] The trial was designed on a larger study size, however the slow recruitment led to a shortfall in the numbers, despite an extension to the recruitment period.

Failure to complete the allocated regimen and therefore loss to follow-up was 19·5% and this was not different between the regimens. Despite these losses, the trial shows a clear superiority of longer duration (20 weeks) compared to the shorter course (12 weeks). There was a clear separation of short course from the longer courses from month 3 when the short course switched from steroid to placebo. The end point of clinically requiring additional steroids is considered a robust and relevant clinical outcome in a pragmatic trial under routine clinical conditions. The clinical assessment was based on the failure to respond to treatment in terms of nerve and skin lesions or their recurrence. The TRIPOD trial used a similar primary outcome,[17] but in addition nerve function, both sensory and motor, and nerve tenderness were assessed using standardized methods. The use of both pragmatic and detailed standardized measures of nerve function assessment is desirable as the standardized functional measures can be used to validate the clinical outcomes and provide comparability

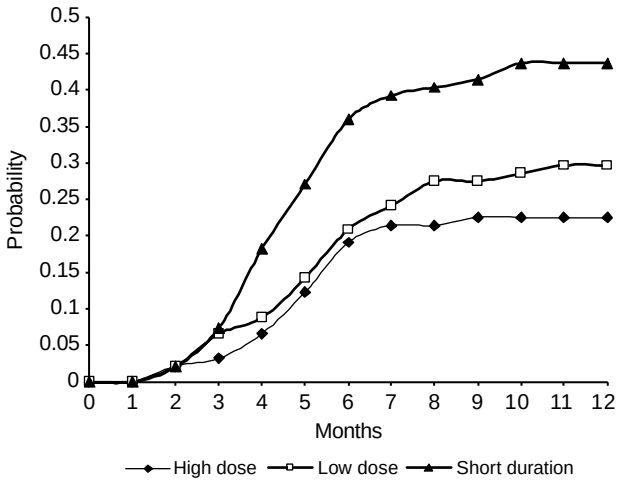

Figure 2. Probability of requiring extra steroids in each regimen over the 12-month trial period.

between studies. The use alone of multiple measures of the functions of many nerves bilaterally creates the methodological challenge of multiple end-points and requires further interpretation as to the clinical importance to the patient of small changes in function.

Of those on the short course (3 months), 46% required additional steroids by the end of 12 months compared to 31% on the low dose and 24% on the high dose regimen over 20 weeks. These results can be translated into clinical response rates to treatment with steroids of 54%, 69% and 76%, comparable to the 50–70% reported by previous studies.[9–12] The high dose regimen was associated with a trend of improved outcome compared to the low dose regimen but the difference was not statistically significant. This difference has to be seen in the light of the high dose regimen containing 50% more steroids.

This trial clearly shows the benefit of 20-week steroid regimens over 12-week regimen in terms of the requirement for additional steroids to control reactions. The non-significant difference between high and low dose regimens would not justify use of the high dose in view of the increased risk of adverse events associated with higher doses. The findings confirm that reversal reactions in MB leprosy persist over many months and suggest that duration of steroid treatment matters more than dose.

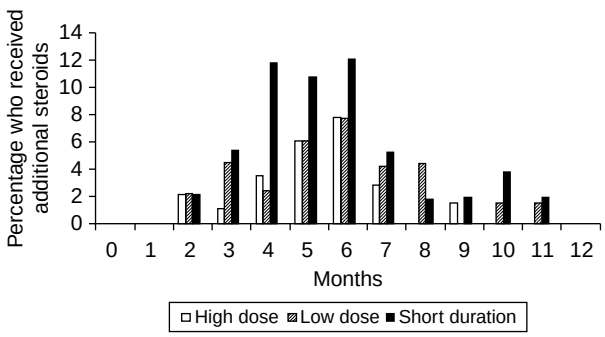

Figure 3. Actual requirement for extra steroids in each regimen over the 12-month trial period.

This trial provides new information on the treatment of reversal reactions in leprosy that should be used to inform further research. Future trials should have clear clinical end points as well as detailed standardized measures where possible to inform routine clinical practice. There are dangers in trials with multiple end points unless the primary end point is specified in advance. Given the effort involved in setting up, running and analysing a trial there would be little value in simply replicating this trial with standardized neurological function measures. Further trials are needed to address new questions building on the findings of this trial and other recent epidemiological studies.

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