Lepr Rev (2012) **83,** 154–163

A comparison of the change in clinical severity scale score and a retrospective physician assessment of neurological outcome in individuals with leprosy associated nerve function impairment after treatment with corticosteroids

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Accepted for publication 14 February 2012

Summary

Objectives: To determine whether the measured change in score of a validated clinical severity scale reflected physician assessed improvement in individuals who had received corticosteroid therapy for leprosy associated nerve damage.

Design: Patients with nerve function impairment who participated in a randomised controlled trial of corticosteroids were classified into two groups using a retrospectively determined physician assessment of improvement. One group consisted of patients who had recovered or improved the other of patients who were unchanged or had deteriorated. The change in the clinical severity scale scores of these two groups was compared.

Results: The change in the clinical severity scale scores of the 34 eligible individuals in the two groups were significantly different ($P = 0{\cdot}003$). Individuals in the group who recovered or improved had a greater change in severity score than those whose nerve function was unchanged or deteriorated.

Professor Anthony Bryceson acted as Editor for this manuscript

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0305-7518/12/064053+10 $1.00

Conclusion: The scale for measuring the severity of leprosy Type 1 reactions (T1Rs) and/or nerve function impairment reflects the clinical improvement of individuals with leprosy associated nerve damage.

Introduction

Clinical trials with appropriate outcome measures are needed to determine the most effective treatment regimens for Type 1 reactions (T1Rs) and/or nerve function impairment (NFI).[1] It has proved difficult to compare the small number of studies because of the different outcome measures used.[2] There are also difficulties in comparing the severity of T1Rs between different cohorts and even between different arms of clinical trials.[2,3]

A tool that enables clinicians to accurately assess the severity of leprosy T1Rs would be useful in defining outcomes for clinical trials. It is important that such a scale would reflect clinical outcomes following therapy and as a measure of efficacy in clinical trials. An appropriate measure would facilitate confirmation of the even distribution of patients with similar disease severity between the arms of clinical trials, could be used in treatment guidelines to define the need for therapy and may be useful in determining prognosis.

We wished to compare the change in severity score with a retrospective physician assessment of neurological outcome in leprosy patients treated with corticosteroids for T1R and/or NFI.

A scale to measure the severity of leprosy T1Rs and leprosy associated NFI was developed and validated in Bangladesh and Brazil.[4] This is a reliable 21 item scale for measuring the severity of T1Rs and NFI in leprosy patients (see Appendix 1). Neurological items are well represented and reflect the importance of NFI. The scale requires the examiner to be proficient in recognising the cutaneous signs of T1R, the assessment of motor function using voluntary muscle testing (VMT) and the use of Semmes-Weinstein monofilaments (SWM) to assess sensory function. The possible range of scores is 0–63, the lower the score the less severe the reaction (or NFI). The maximum score possible for sensory NFI and motor NFI are 24 and 30 respectively. How the scale reflects change following treatment of individuals with NFI with corticosteroids was not assessed in the validation studies. The scale was used concurrently in a Nepali cohort of leprosy patients with T1Rs and NFI in a clinical trial of corticosteroid treatment.[5] Here we further analyse the data from that study and compare a physician determined outcome (in individuals with nerve function impairment) with change in severity score. The rationale of the study is to compare a subjective physician determined assessment of improvement with a more objective, repeatable and quantifiable measure. This analysis indicates the utility of the score derived from the clinical severity scale in a clinical trial setting.

Methods

The participants were individuals with T1Rs and/or new NFI (of less than 6 months duration) who were recruited from the leprosy clinic at Anandaban Hospital in Nepal. They were enrolled between December 2005 and December 2007 in a double blind placebo controlled trial. All participants gave written informed consent. They were randomised to receive

intravenous methylprednisolone (1 g) followed by a reducing course of oral prednisolone or intravenous placebo and a reducing course of prednisolone alone for a total of 16 weeks. They were followed for a total of 337 days from enrolment. Patients with deterioration in nerve function or skin signs were treated with further prednisolone.

The methods and participants have been described previously.[5] Briefly, sensory testing (ST) was performed using two SWM (Sorri-Bauru, Bauru, São Paulo, Brazil) at designated test sites on the hands and feet. Ulnar and median nerve function was tested with 2 g and 10 g monofilaments. The posterior tibial nerve function was tested with the 10 g and 300 g monofilaments. Trigeminal nerve sensation was tested using cotton wool. VMT was assessed using the modified Medical Research Council (MRC) grading of power.[6] ST and VMT assessments were carried out by trained physio-technicians and, if necessary, repeated by the study physicians. NFI was defined as: an inability to feel the 2 g monofilament on the hand or the 10 g monofilament on the foot, or reduced power ($<$ MRC grade 5) on VMT. The clinical severity score was calculated for each participant at the time of enrolment into the study and at all subsequent assessments.

A retrospective physician assessment of neurological outcome was done at the end of the trial in those individuals who had NFI of less than 6 months duration at enrolment and who had completed the study intervention. The assessment was done by comparing participants' baseline sensory and motor examinations with their last recorded assessment (performed at day 337 of the trial or at the last assessment before being lost to follow up). The designated outcomes were: recovered, improved, unchanged or deteriorated. Recovery was defined as the ability to feel the 2 g monofilament at all test sites on the hands, the 10 g at all sites on the feet and power of grade 5 in all tested muscles. However, inclusion of an individual in the other categories was left to the discretion of the physician. The clinical severity score was not used to determine the physician assessment. Nerves with longstanding NFI of greater than 6 months at enrolment were recorded and included in the assessment. NFI of this duration would not be expected to improve with corticosteroid therapy.[7] The difference between the neurological components of the clinical severity score at baseline and their last recorded assessment were calculated. A negative value indicates deterioration in function.

The study was approved by the Nepal Health Research Council and the Ethics Committee of the London School of Hygiene and Tropical Medicine (Number 4022). The trial was registered with Current Controlled Trials Ltd (*www.controlled-trials.com*) in accordance with the policy of the International Committee of Medical Journal Editors[8] and was assigned the unique identifier ISRCTN31894035.

The data were analysed using the Statistical Package for the Social Sciences (SPSS version 16. SPSS Inc., Chicago, Illinois) and *GraphPad Prism* (version 4.02 for Windows, *GraphPad* Software, San Diego, California). Comparison between groups was made using the Mann Whitney *U* test. The threshold for accepting statistical significance was $<0{\cdot}05$.

Results

Forty-two individuals participated in the randomised controlled trial. Six individuals did not have any evidence of NFI at enrolment and two others did not complete the study intervention. Thirty-four individuals had NFI at enrolment and completed the 16 week course of corticosteroid therapy and were included in the analysis for this study (see Table 1).

Table 1. Study participants, baseline and final scores

Study Number	Gender	Age	Ridley Jopling Classification	Follow up and last assessment (Day 337 unless stated)	Retrospective physician dertermined Outcome	Intervention Received Methyl-prednisolone (MP), prednisolone alone (P)	Received additional steroids	Nerve score at baseline assessment	Nerve score at final assessment	Change in nerve score (Baseline – Final)
AN01	Male	36	BL	Complete	Improved	P	No	7·5	2·5	5
AN02	Male	28	BT	Complete	Improved	MP	No	2·5	1	1·5
AN03	Male	23	BT	Complete	Improved	MP	Yes	17·5	8·5	9
AN04	Male	49	BL	Complete	Unchanged	P	Yes	8·5	7	1·5
AN05	Male	64	LL	Complete	Recovered	MP	Yes	10	0	10
AN06	Male	24	BL	Complete	Improved	P	Yes	3	2	1
AN07	Male	16	TT	Complete	Recovered	MP		3	0	3
AN08	Male	24	BT	Complete	Improved	P	Yes	24	13·5	10·5
AN09	Male	42	BT	Complete	Improved	MP	Yes	4·5	2	2·5
AN10	Male	65	BL	Complete	Improved	P	Yes	6·5	6·5	0
AN11	Female	17	BL	Complete	Improved	MP	No	26	4·5	21·5
AN13	Male	63	BL	Complete	Recovered	MP	No	2	0	2
AN14	Female	18	BT	Complete	Unchanged	MP	No	3	1·5	1·5
AN15	Female	35	BT	Finished corticosteroids (147)	Unchanged	P	Yes	34	34	0
AN16	Female	39	BT	Complete	Improved	P	Yes	4·5	3	1·5
AN17	Female	42	BB	Complete	Improved	MP	Yes	6	3·5	2·5
AN18	Male	41	BL	Finished corticosteroids (281)	Unchanged	P	Yes	13	13	0
AN19	Male	54	BL	Finished corticosteroids (202)	Improved	MP	Yes	1	0	1
AN20	Female	54	BT	Finished corticosteroids (272)	Recovered	P	Yes	5·5	0	5·5
AN21	Male	53	LL	Complete	Improved	P	No	26	22	4
AN22	Male	16	BT	Complete	Improved	MP	No	18·5	6	12·5
AN23	Male	29	BT	Complete	Unchanged	MP	Yes	2	2	0
AN24	Male	33	BT	Complete	Improved	P	Yes	6	2	4

Table 1. *continued*

Study Number	Gender	Age	Ridley Jopling Classification	Follow up and last assessment (Day 337 unless stated)	Retrospective physician dertermined Outcome	Intervention Received Methyl-prednisolone (MP), prednisolone alone (P)	Received additional steroids	Nerve score at baseline assessment	Nerve score at final assessment	Change in nerve score (Baseline − Final)
AN25	Male	44	BT	Complete	Improved	P	Yes	17·5	7·5	10
AN26	Male	28	BT	Finished corticosteroids (119)	Unchanged	MP	No	40	30·5	9·5
AN27	Male	40	BB	Complete	Worse	P	Yes	0	2·5	−2·5
AN30	Male	35	BT	Complete	Unchanged	P	No	22	20·5	1·5
AN32	Male	36	BT	Complete	Improved	P	Yes	7	2	5
AN34	Male	40	BL	Complete	Improved	P	No	5	2	3
AN36	Male	62	BT	Complete	Unchanged	MP	No	4	3·5	0·5
AN38	Male	55	BT	Complete	Unchanged	MP	No	12·5	12	0·5
AN39	Female	40	BT	Complete	Recovered	P	No	1	0	1
AN40	Male	41	BL	Complete	Recovered	P	Yes	1	0	1
AN42	Male	22	BT	Finished corticosteroids (299)	Recovered	P	Yes	3	0	3

Twenty-eight of these had completed the full period of follow up. The remaining six had completed the 16 week study intervention and had been followed up for between 119 and 299 days in total. Twenty individuals (58·8%) required additional prednisolone.

The baseline assessment severity scores of individuals who received intravenous methylprednisolone and oral prednisolone and those who received oral prednisolone alone were not significantly different. The severity scores at enrolment between those classified as recovered or improved and those classified as unchanged or worse were not significantly different. There were no significant differences in the baseline scores of individuals who had their final assessment at day 337 and those who had their final assessment between days 119 and 299) or in the baseline scores of those who received additional prednisolone and those who did not.

Eleven (out of 34) individuals had some NFI present for more than 6 months at the time of enrolment. These 11 patients had 36 nerves (21 sensory and 15 motor) which were affected by longstanding ($>$ 6 months) NFI. At the last recorded assessment the changes in longstanding NFI were as follows: only one sensory nerve had recovered, three posterior tibial nerves had improved by a median monofilament score of 0·5. Thirteen were unchanged and four sensory nerves had deteriorated by a median score of 0·75. Four motor nerves recovered but all had the mildest possible deficit at baseline; a VMT score of one (equivalent to MRC grade 4 power). Ten motor nerves had unchanged function, including eight that had a maximal VMT score of three. The function in one motor nerve deteriorated from a scale score of two to three.

The physician assessment of neurological outcome demonstrated that seven (20·6%) individuals who had nerve damage at baseline of less than 6 months duration and had completed a 16 week course of corticosteroid therapy recovered. Only one of these seven individuals had NFI of greater than 6 months duration. This individual had mild impairment (MRC Grade 4) of the motor function of the right ulnar nerve which recovered. Seventeen individuals of 34 (50%) had an improvement in their nerve function. Five of these individuals had NFI of greater than 6 months duration but none had more than two nerves affected in this way. However, nine participants (26·5%) had nerve function that was unchanged and one individual's nerve function had deteriorated. Of the nine participants who were unchanged, five had longstanding NFI with a median number of six nerves affected in this way (Range 2–8). Table 2 shows the number of individuals in each category and the range and median change in severity scores for each category. There were no statistical differences between the groups with respect to the proportion of individuals with old nerve damage ($>$ 6 months).

Individuals were grouped according to their status with respect to the physician assessment of neurological outcome as shown in Figure 1.

Table 2. Post-hoc physician assessment of neurological outcome and change in clinical severity score (neurological items only)

	Number (n = 34)	Individuals with NFI $>$ 6 months	Median number of nerves with NFI $>$ 6 months	Range of change in severity score	Median change in severity score
Recovered	7	1	1	1–10	3
Improved	17	5	2	0–21·5	4
Unchanged	9	5	6	0–9·5	0·5
Deteriorated	1	0	–	–	−2·5

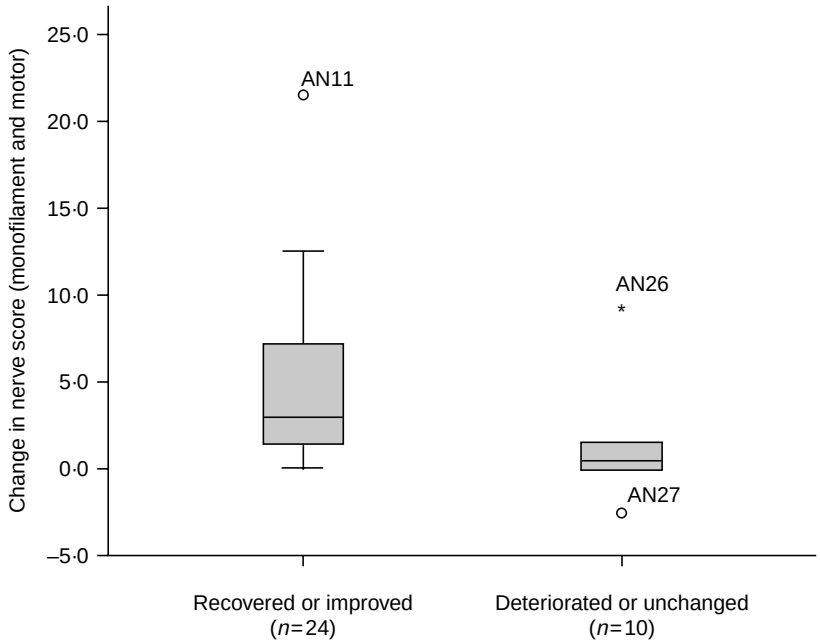

Figure 1. Change in nerve score and clinical outcome in those completing corticosteroid course ($n = 34$). (Circles denote individuals 1·5 times the interquartile range (IQR) outside the box and asterisks denote individuals 3 times the IQR outside the box).

The median change in nerve score between the baseline and the final recorded assessments were significantly different ($P = 0{\cdot}003$).The number of nerves with old NFI in the "Unchanged/Deteriorated" group was significantly greater than that in the "Recovered/Improved" group ($P = 0{\cdot}048$).

Discussion

We compared the median change in the clinical severity scores between the recovered/improved and no change/deteriorated groups identified by physician assessment and found a statistically significant difference with greater reduction in score in the improved/recovered group. The significant difference in the number of nerves affected by longstanding NFI between the two groups also supports the contention that the scale is able to discriminate outcomes as it would be expected that those with a greater number of affected nerves would have a poorer outcome. These findings should be interpreted with caution because of the small numbers in the cohort; also the scale has not been formally validated in Nepali patients and the criterion for improvement (post hoc physician assessment) is somewhat subjective. A more robust study could be designed using methodologies to prospectively assess clinical improvement and use patient centred outcomes such as minimally important difference (MID). MID is a patient centred outcome measure that quantifies the smallest change in a score that is worthwhile or important.[9] The scale needs to be assessed using MID which will allow any change in severity score to be interpreted in clinically meaningful ways. This should be performed in a population in which the scale has

been validated. Knowing the magnitude of the change in score required to achieve a MID would facilitate power calculations for clinical trials.

The retrospective physician assessment, although not a stringent outcome, reveals the high rates of persistent neurological impairment even after individuals have completed at least one prolonged course of corticosteroid therapy. In this study 70·6% (24/34) of those treated with at least 16 weeks of corticosteroid improved or recovered. This is consistent with data from Bangladesh where 67% of nerves improved after a 16 week course of prednisolone.[10] The study conducted in Nepal by Marlowe *et al.* of prednisolone and a combination of azathioprine and prednisolone reported improvement in sensory function in 57·1% of individuals with sensory impairment present for less than 6 months.[11] The figure was identical for those with motor impairment before the start of treatment.

A significant finding of the randomised controlled study of intravenous methylprednisolone was that almost 50% of those enrolled required a further course of prednisolone in addition to the study interventions.[5] The proportion receiving additional prednisolone was slightly higher (58·8%) in the sub-group of individuals who had NFI at enrolment.

The significant difference in the change in nerve score between individuals who were better or improved and those who were unchanged or worse in the Nepali cohort, although a preliminary finding, suggests that the scale reflects clinically relevant change. Further studies of the clinical severity scale are warranted to determine its utility in future clinical studies.

Conflict of Interest

None of the authors were involved in the editorial process for this paper, which was edited by Professor Anthony Bryceson.

Contributors

SLW planned and coordinated the study, enrolled and performed clinical evaluation of participants, entered and analysed the data, discussed the results, and wrote the manuscript. PGN designed the database, advised on analysis and design of the study and discussed the results. SD, KM, SR and SH enrolled and performed clinical evaluation of participants. RAH planned and coordinated the study and enrolled and performed clinical evaluation of participants. MM planned and coordinated the study. DH and KDN coordinated the study. DNJL planned the study, discussed the results, and wrote the manuscript. All authors saw and approved the final version. SLW had full access to the data used in the study, and can take responsibility for the integrity of the data and the accuracy of the data analysis. All authors had access to the processed tables and figures. SLW and DNJL act as guarantors for the paper.

Acknowledgements

We would like to thank the participants who gave up their time to be enrolled in this study. We are grateful to the staff of Anandaban Hospital for all their hard work. In particular Drs Tim and Julie Lewis, Ram Kumar Maharjan, Bijay Pandey, Mahesh Shah, Ravi Singh, and Min Thapa who helped with data collection. The physiotechnicians: Ram Babu Bista, Arjun Karki, Jaganath Maharjan and Krishna Godar Thapa who performed the bulk of the

motor and sensory examinations. Mohan Khadka, the pharmacist, who mixed the study infusions and dispensed the prednisolone. The trial monitors were Dr P S S Sundar Rao and Dr K V Krishna Moorthy and we thank them for their support.

We also wish to acknowledge Dr Wim van Brakel for his role in developing the scales used in the INFIR studies. This work was supported by grants from LEPRA, the American Leprosy Mission, the Special Trustees of the Hospital for Tropical Diseases, London, and the Geoffrey Dowling Fellowship of the British Association of Dermatologists. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Anandaban Hospital is operated by Leprosy Mission Nepal with The Leprosy Mission International.

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Appendix 1

	Criteria	0	1	2	3	Score
A1	Degree of inflammation of skin lesions Ulceration	None	Erythema	Erythema and raised		
A2	Number of raised and/or inflamed lesions	0	1–5	6–10	>10	
A3	Peripheral oedema due to reaction	None	Minimal	Visible, but not affecting function	Oedema affecting function	
A SCORE						

	HANDS	Purple 2 g Monofilament scores				Orange 10 g Monofilament scores			
	Nerves	0	0·5	1	1·5	2	2·5	3	Score
B1	RIGHT Trigeminal	Felt						Not felt	
B2	LEFT Trigeminal	Felt						Not felt	
B3	RIGHT ulnar	All sites felt	1 site not felt	2 sites not felt	3 sites not felt	1 site not felt	2 sites not felt	3 sites not felt	
B4	LEFT ulnar	All sites felt	1 site not felt	2 sites not felt	3 sites not felt	1 site not felt	2 sites not felt	3 sites not felt	
B5	RIGHT median	All sites felt	1 site not felt	2 sites not felt	3 sites not felt	1 site not felt	2 sites not felt	3 sites not felt	
B6	LEFT median	All sites felt	1 site not felt	2 sites not felt	3 sites not felt	1 site not felt	2 sites not felt	3 sites not felt	
	FEET	Orange 10 g Monofilament scores				Pink 300 g Monofilament scores			Score
	Nerves	0	0·5	1	1·5	2	2·5	3	
B7	RIGHT posterior tibial	All sites felt	1 site not felt	2 sites not felt	3 sites not felt	1 site not felt	2 sites not felt	3 sites not felt	
B8	LEFT posterior tibial	All sites felt	1 site not felt	2 sites not felt	3 sites not felt	1 site not felt	2 sites not felt	3 sites not felt	
B SCORE									

	NERVE	0	1	2	3	Score
C1	RIGHT Facial	MRC = 5	MRC = 4	MRC = 3	MRC < 3	
C2	LEFT Facial	MRC = 5	MRC = 4	MRC = 3	MRC < 3	
C3	RIGHT Ulnar	MRC = 5	MRC = 4	MRC = 3	MRC < 3	
C4	LEFT Ulnar	MRC = 5	MRC = 4	MRC = 3	MRC < 3	
C5	RIGHT Median	MRC = 5	MRC = 4	MRC = 3	MRC < 3	
C6	LEFT Median	MRC = 5	MRC = 4	MRC = 3	MRC < 3	
C7	RIGHT Radial	MRC = 5	MRC = 4	MRC = 3	MRC < 3	
C8	LEFT Radial	MRC = 5	MRC = 4	MRC = 3	MRC < 3	
C9	RIGHT Lateral Popliteal	MRC = 5	MRC = 4	MRC = 3	MRC < 3	
C10	LEFT Lateral Popliteal	MRC = 5	MRC = 4	MRC = 3	MRC < 3	
C SCORE						
Total score		Scores of A + B + C				