

The prognostic importance of detecting mild sensory impairment in leprosy: a randomized controlled trial (TRIPOD 2)

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Summary This study was designed to investigate whether leprosy patients diagnosed with mild sensory impairment have a better prognosis when treated with steroids than similarly impaired patients treated with placebo. A multi-centre, randomized, double-blind, placebo-controlled trial was conducted in Nepal and Bangladesh. Patients were eligible if they had a confirmed leprosy diagnosis, were between 15 and 50 years old, had mild sensory impairment of the ulnar or posterior tibial nerve of less than 6 months duration and did not require steroids for other reasons. 'Mild impairment' was defined as 'impaired on the Semmes–Weinstein monofilament test, but testing normal on the ballpen sensory test'. Subjects were randomized to either prednisolone treatment starting at 40 mg per day, tapering over 4 months, or placebo. Nerve function was monitored monthly. Any patient who deteriorated was taken out of the trial and was put on full-dose steroid treatment. Outcome assessment was done at 4, 6, 9 and 12 months from the start of the treatment. Outcome measures were the proportion of patients needing full-dose prednisolone and the Semmes–Weinstein sum scores. Each patient contributed only one nerve to the analysis. Seventy-five patients had nerves eligible for analysis, of whom 41 (55%)

and 34 (45%) were allocated to the prednisolone and placebo arms, respectively. At 4 months, three patients in the prednisolone arm (7%) and six in the placebo arm (18%) had an outcome event requiring full dose steroids. At 12 months, these proportions had almost reversed, 11 (27%) and 6 (18%) in the treatment and placebo arms, respectively. In the latter group, 75% had recovered spontaneously after 12 months. Prednisolone treatment of sensory impairment of the ulnar and posterior tibial nerves detectable with the monofilament test, but not with the ballpen test, did not improve the long-term outcome in terms of recovery of touch sensibility, nor did it reduce the risk of leprosy reactions or nerve function impairment beyond the initial 4-month treatment phase. Two unexpected main findings were the strong tendency of mild sensory impairment to recover spontaneously and the fact that patients with mild sensory impairment without any other signs or symptoms of reaction or nerve function impairment are relatively rare.

Introduction

Testing of touch/pressure sensibility is a sensitive method for detecting nerve function impairment in leprosy.^{1–3} However, there is considerable debate about the best method of sensory testing. Most of the world's leprosy patients are treated in peripheral health clinics in resource-poor countries. Methods of clinical examination therefore need to be simple and the instruments used readily available. Indentation of the skin is currently believed to be the most quantifiable way of measuring touch perception.^{4,5}

A simple technique of skin indentation that has found widespread acceptance in the 'field' is the 'ballpen test'.^{6,7} The strength of the ballpen test is the universal availability of the testing instrument: the ballpen. Usually ten sites are tested on each palm and sole. The result is recorded as 'felt' or 'not felt' for each site tested. The main weaknesses of the test are its lack of application force control and the fact that even very light application already exceeds the human touch sensibility threshold by several multiples.⁸ Despite this, the repeatability of ballpen testing was moderate to good in the hands of trained staff.^{9,10}

The Semmes–Weinstein monofilaments provide an attractive alternative that is cheap, and can provide a (semi-)quantitative result. Graded nylon monofilaments are reported to be a sensitive and repeatable method to detect mild sensory impairment (SI) in leprosy,^{1,2,11–14} and to monitor the treatment response of SI. The validity of the Semmes–Weinstein monofilaments is well established. Johansson *et al.* showed that touch thresholds found with monofilaments correlate well with skin indentation thresholds measured with electronic testing equipment.⁴ In compression neuropathy, the monofilaments correlated very well with measurements of sensory fibre conduction and electronic vibrometry.^{15,16}

The crucial question is whether the monofilament test is 'better' in detecting SI in leprosy than the ballpen method. The underlying question is one of prognosis. 'Do the patients in whom neural impairment is detected at a mild stage with monofilaments have a better treatment prognosis than those whose impairment is detected with the ballpen test?' Since there is insufficient information in the published literature, a trial was designed to answer this question. The question was rephrased to, 'Is there a significant difference in treatment outcome, in patients diagnosed with mild SI (monofilament positive, but ballpen test negative), between those who receive a standard steroid treatment regimen and those with similar impairment who receive placebo treatment'.

The following hypotheses were formulated:

- Patients with mild sensory impairment will get worse if left untreated, i.e. 'monofilament sensory loss' will progress to 'ballpen sensory loss' if left untreated.
- Patients in the placebo group will become 'ballpen test positive' significantly more often than those in the prednisolone group.

Materials and methods

DESIGN

The study was a multi-centre double blind, placebo controlled field trial in six centres in Nepal and Bangladesh. Subjects were randomized to receive prednisolone or placebo for a duration of 16 weeks. The trial was part of a series of three trials (TRIPOD) which all used very similar design and methods. The other two trials tested the use of prophylactic steroids to prevent immunological reactions and peripheral neuropathy in leprosy and the steroid treatment of neuropathy with a duration of more than 6 months before the start of treatment.

STUDY SUBJECTS AND SAMPLE SIZE

All newly diagnosed MB patients attending one of the trial centres, who were not eligible for the prophylactic steroids trial, were potentially eligible for the trial. They were included if they had a confirmed MB leprosy diagnosis (positive skin smear or six or more skin lesions), were between 15 and 50 years old, had sensory impairment of the ulnar or posterior tibial nerve on the Semmes–Weinstein test of less than 6 months duration, a normal ballpen test, did not need steroids for any other reason, did not have a contraindication to steroids for any reason and were living within a pre-defined geographical area so as to make follow-up by home visit possible.

Based on previous experience, around 40% of patients with varying degrees of sensory impairment regain 'good' function after steroid treatment, when the impairment was diagnosed with a 'heavy' filament (~10 g for the hand, ~75 g for the foot). To detect an improvement of 50% (that is change from 40% to 60%) with a power of 80% and with a single sided 95% confidence level, the trial needed approximately 80 subjects in each arm.

TREATMENT REGIMEN AND FOLLOW-UP

Subjects were randomized to either prednisolone treatment starting at 40 mg per day, tapering over 4 months, or placebo. Nerve function was monitored monthly. Any patient who deteriorated was taken out of the trial as a 'bad outcome' and was put on full-dose steroid treatment. Outcome assessment was done at 4, 6, 9 and 12 months from the start of the treatment. Subjects developing an outcome event were taken out of the trial as 'poor outcome' and put on full-dose steroids.

EXAMINATION

The clinical assessment included a history, clinical examination for signs of reaction or neuritis and a voluntary muscle test (0–5 grading). Outcome assessment (sensory testing) was done using five coloured graded monofilaments: blue (200 mg), purple (2 g), red (4 g), orange

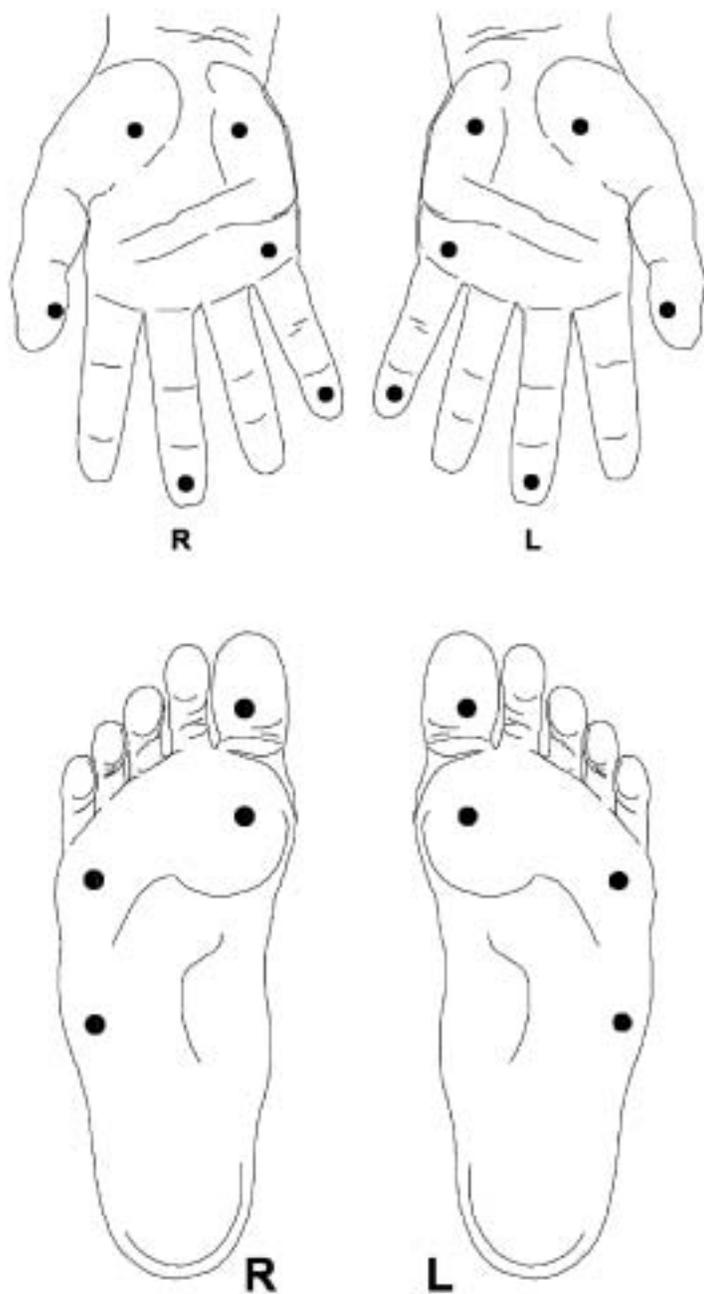


Figure 1. Monofilament and ballpen test sites and hands and feet.

(10 g) and pink (300 g). The blue, purple, red and pink filaments were used for the hand; the purple, red, orange and pink for the foot. The test sites are shown in Figure 1. The ballpen test was carried out on the same sites giving a light touch with the tip of the ballpen (just enough to indent the skin very slightly). The patient was asked to indicate, with their eyes closed,

whether they felt the stimulus by pointing to where they felt the touch or by counting the number of stimuli felt.

OUTCOME DEFINITIONS

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.^{17,18} The Semmes–Weinstein 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’.

The ballpen test was considered positive if 2 or more test sites did not feel the stimulus. A bad outcome was defined as ‘worsening of sensory impairment so that the ballpen test becomes positive’. A change in ballpen score was defined as a change of 2 or more test sites feeling or not feeling the stimulus, compared to the previous result.

STATISTICAL METHODS

Data entry and analysis was done using Epi Info software, version 6.04.¹⁹ Outcome analysis was based on a comparison of proportions (e.g. proportion of subjects recovered) or median monofilament scores between the treatment and placebo groups. The statistical significance of the difference between proportions was tested, where relevant, using a Z-test. For each nerve entered into the study, the change in monofilament score between the follow-up and registration was calculated. The significance of the difference in median sensory scores between the two groups was tested with the Kruskal–Wallis test.²⁰

Of patients with recent bilateral SI, only the *most* affected limb was included. If limbs were equally affected, the right side was included. The results for the ulnar and posterior tibial nerves were pooled in the analysis. If the patient had SI of both the ulnar and posterior tibial nerve(s), they contributed up to two nerves to the study. However, these were never both included in the same analysis.

Results

Eighty-four patients were enrolled in the trial. Nine were lost to follow-up, so the analysis was based on data from 75 subjects (41 in the prednisolone group and 34 on placebo) (Table 1). The equal distribution across the treatment and placebo group of mean age (37.2 versus 36.2), proportion of women (27% in each) and mean monofilament score at diagnosis (5.3 versus 5.2), shows that randomization was effective. Table 2 shows outcome events at the different time points during follow-up. At the end of the first 4 months, 2/41 (5%) patients in the prednisolone group and 3/34 (9%) in the placebo group had become ballpen test positive. The difference is not statistically significant. By the 12-month follow-up, three more patients in the (former) prednisolone group had become ‘ballpen positive’, bringing the total to 12%. In the placebo group, no further ballpen positivity events occurred. It is interesting that only 2/8 of the ballpen positivity events occurred during steroid treatment.

Table 1. Comparison of subject characteristics between those receiving prednisolone and those on placebo

| | Prednisolone (n = 41) | Placebo (n = 34) |
|----------------------------------|--------------------------|---------------------|
| Mean age | 37.2 | 36.2 |
| % women | 27% | 27% |
| Mean monofilament score at start | 5.3 | 5.2 |

Table 2. Details of outcome events during follow-up among patients in the TRIPOD 2 trial

| Month | Prednisolone | | | | | Placebo | | | | |
|-------|--------------|------------------|-----|--------|------|----------|------------------|-----|--------|------|
| | In trial | Ballpen positive | T1R | Others | Lost | In trial | Ballpen positive | T1R | Others | Lost |
| 0 | 41 | | | | | 34 | | | | |
| 4 | 35 | 2 | | 1 | 3 | 24 | 3 | 1 | 2 | 4 |
| 6 | 31 | 1 | 2 | 1 | | 24 | | | | |
| 9 | 29 | 1 | 1 | | | 24 | | | | |
| 12 | 26 | 1 | 1 | | 1 | 24 | | | | |
| Total | | 5 | 4 | 2 | 4 | | 3 | 1 | 2 | 4 |

Table 3. Summary of outcome events and relative risk of having an outcome event at various follow-up times during the TRIPOD 2 trial

| Month | Outcome events (cumulative) | Outcome events by treatment | | Relative risk (all data n = 75) |
|-------|--------------------------------|-----------------------------|---------|------------------------------------|
| | | Prednisolone | Placebo | |
| 0 | 0 | 41 | 34 | |
| 4 | 9 (12%) | 3 (7%) | 6 (18%) | 2.41 (0.65–8.93) |
| 6 | 13 (17%) | 7 (17%) | 6 (18%) | 1.03 (0.38–2.78) |
| 9 | 15 (20%) | 9 (22%) | 6 (18%) | 0.80 (0.32–2.03) |
| 12 | 17 (23%) | 11 (27%) | 6 (18%) | 0.66 (0.27–1.59) |

Type 1 reactions were the next frequent group of outcome events, occurring in 4/41 (10%) and 1/34 (3%) patients in the prednisolone and placebo groups, respectively (Table 2). None of these reactions occurred during steroid treatment. It is noteworthy that all patients coming out of the trial in the placebo arm did so within the first 4 months, suggesting that the mild sensory loss was possibly the first symptom of a problem that would deteriorate. By 6 months, the prednisolone arm had caught up and by 12 months, more people in the prednisolone arm had developed an outcome event. The relative risk was not significant at any point during follow-up (Table 3).

Table 4 compares the difference in baseline monofilament score and the score at the time of various outcome assessments in the placebo and prednisolone groups. The ‘final outcome’ shows data for all subjects from 12-month follow-ups, including people who

Table 4. Comparison of the difference in baseline monofilament score and the score at the time of various outcome assessments in the placebo group ($n = 34$) and prednisolone group ($n = 41$) in the TRIPOD 2 trial (a negative sign indicates improvement in score)

| Month | Difference in scores | | | Five categories ^a Significance | Two categories ^a RR |
|--------------------|---|---|--------------|--|-----------------------------------|
| | Placebo difference | Prednisolone difference | Significance | | |
| 4 | Mean -1.9 Median -2 Range -8 to ~+5 | Mean -3.3 Median -3 Range -6 to ~0 | $P = 0.01$ | $P = 0.05$ | 2.58 (1.19-5.60) |
| 6 | Mean -2.6 Median -3 Range -8 to ~+5 | Mean -2.8 Median -3 Range -7 to ~+4 | $P = 0.84$ | $P = 0.34$ | 0.99 (0.46-2.10) |
| 9 | Mean -1.9 Median -2 Range -7 to ~+5 | Mean -2.6 Median -3 Range -7 to ~+4 | $P = 0.22$ | $P = 0.22$ | 1.69 (0.86-3.31) |
| 12 | Mean -2.5 Median -2 Range -9 to ~+5 | Mean -2.6 Median -3 Range -7 to ~+5 | $P = 0.56$ | $P = 0.40$ | 1.34 (0.62-2.92) |
| Final ^b | Mean -3.0 Median -3 Range -9 to ~+3 | Mean -2.7 Median -3 Range -7 to ~+5 | $P = 0.90$ | $P = 0.41$ | 1.06 (0.43-2.61) |

^aThis score was categorized either in five groups (worse, same, better, recovered (i.e. same as before the current impairment) and normal (i.e. no longer an impairment) or in two groups (better (all improvement groups) and 'same/worse').

^bThe 'final outcome' includes data from 12-month follow-ups for people out of the trial, and is therefore the closest to the 'steroid outcome' described in the background. In total 17 patients came out of the trial before the 12-month follow up. There were 13 such 'post-trial-out' follow-ups.

were taken out of the trial because of a poor outcome, where available. This best represents the overall outcome of the result in both groups. Improvement in sensory scores was very similar in both groups, except during the first 4 months. During this period, scores improved significantly more in the prednisolone group, with none of the 41 subjects showing a worsening in monofilament score. In the placebo group, worsening of sensory scores was recorded in 12%. These differences had disappeared by the 6-month follow-up.

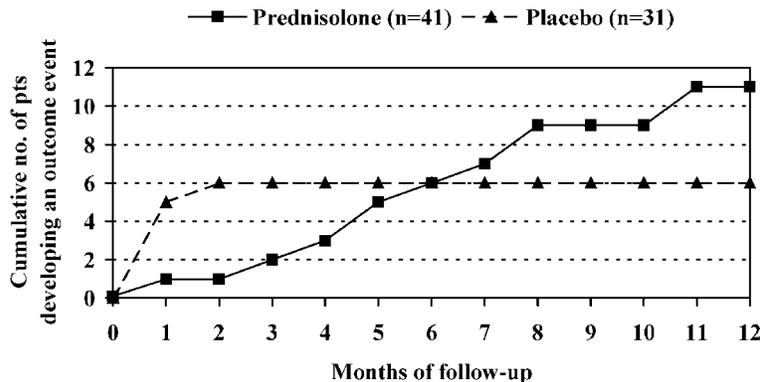


Figure 2. Occurrence of outcome events during follow-up in the TRIPOD 2 trial.

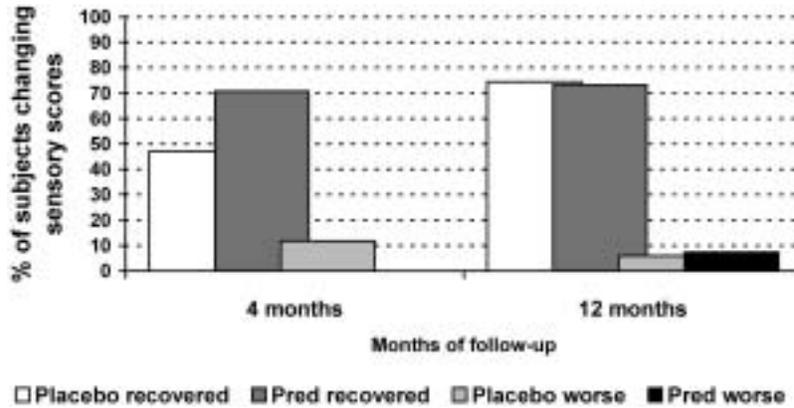


Figure 3. Changes in sensory scores during steroid treatment (4 months) and after 12 months follow-up ($n = 75$).

The occurrence of all outcome events combined is shown in Figure 2. In the prednisolone group, fewer events occurred during the treatment phase. However, 2 months after stopping steroids, the number of events has caught up with that in the placebo group. At 12 months, more subjects in the prednisolone group have experienced an event needing (additional) steroid treatment, although the difference is not statistically significant ($P = 0.52$).

Figure 3 compares the percentage of patients whose sensory function, as measured with the monofilament test, recovered or deteriorated between the prednisolone and placebo groups. During the first four months, a larger proportion of those on steroid treatment recovered (71% versus 47%). This difference is close to significance at the 5% level ($P = 0.061$). However, by 12 months the apparent disadvantage of the placebo group has completely disappeared. In both groups close to 75% of patients have now recovered and only a small number have worsened.

Figure 4 shows the progression of the mean MF scores during the different stages of the trial. For patients who had two nerves registered in the trial, a separate analysis was done for the first and second nerve. It can be seen that the pattern of improvement in sensory scores is

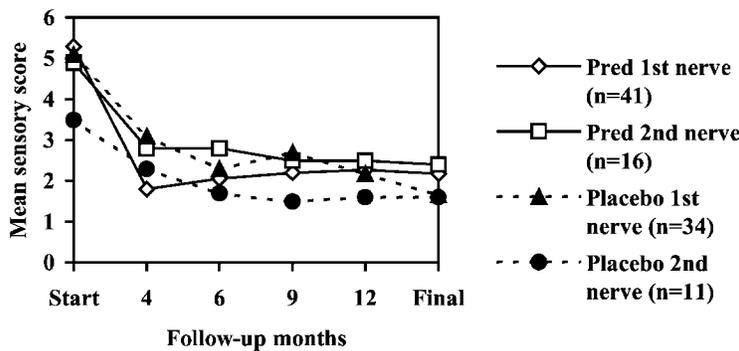


Figure 4. Mean monofilament scores at various outcome time points during follow-up. A separate analysis was done for subjects with more than one nerve involved in the trial.

very similar in both treatment and placebo categories. Improvement is slightly more gradual in the placebo-treated nerves, but the end results are very similar.

Discussion

The purpose of this study goes back to the question, ‘What is the best sensory test to screen for nerve function impairment under field conditions?’ The answer to this question depends not only on scientific considerations, but also on many operational factors. From a scientific point of view, ‘best’ would refer to ‘best for the patient’, i.e. improving the prognosis of any neuropathy detected. The monofilament test is believed to detect ‘early’ or mild sensory impairment, when the detection threshold is referenced to the normal threshold of sensation.^{2,16,17,21} In contrast, the ballpen test may only detect sensory impairment at a more advanced level, because the pressure exerted with a ballpen is variable and often much higher than the normal threshold for touch sensibility. Actual data on the pressure exerted during ballpen testing is difficult to obtain and we are not aware of any published reports on this.

Assuming that the Semmes–Weinstein test would detect sensory impairment earlier than the BP test, the question is, ‘would this early detection in fact improve prognosis?’ In other words, do people in whom sensory impairment was detected with the Semmes–Weinstein test and who were treated as soon as possible have a better prognosis than those in whom such impairment is not treated until they become ‘ballpen positive’?

The results from the present trial would suggest that this is *not* the case. While patients in the prednisolone-treated group improved slightly faster and did not show any deterioration while on steroids, those in the placebo group showed spontaneous recovery which after 12 months matched that of the former (75% versus 73% in the steroid group). After 12 months, there was no difference in mean or median monofilament sensory scores between those treated ‘early’ and those treated only when developing ‘ballpen sensory impairment’ (2.2 versus 1.6, respectively). In addition, the sensory function of some patients deteriorated after the steroids had been stopped. In both groups, sensory impairment deteriorated in only a small proportion of patients (7% versus 6%). Therefore, the current data do not indicate an advantage in detecting sensory impairment before a carefully conducted ballpen test becomes abnormal.

Whether more prolonged steroid treatment would have prevented the observed deterioration, or indeed, the occurrence of the other outcome events observed during follow-up, remains open to speculation. Many would nowadays consider a 12-week course of prednisolone too short, particularly when treating MB patients. A recently conducted prophylactic steroids trial (TRIPOD1) showed a similar pattern of results. Reactions and nerve function impairment were prevented to a large degree during the steroid prophylaxis period of 4 months, but the treatment group had an increased rate of events after stopping the prophylaxis (Anderson *et al.*, in preparation). By 12 months, the difference between the prophylaxis and the placebo groups was no longer statistically significant.

It should be noted that ‘ballpen positivity’ did not always match deterioration as measured with the monofilament test (data not shown). Some patients had worsening Semmes–Weinstein thresholds, while the ballpen test remained negative; in others the ballpen test became positive without deterioration in Semmes–Weinstein scores. This is likely to be due to the inherent variability in the application force of the ballpen. In comparative studies, the test repeatability of monofilaments was found to be better than

that of the ballpen test.^{9,10} However, the results of the latter were still moderate to good, suggesting that the test will give acceptable results if used carefully by trained staff.

The trial aimed to recruit four times as many patients as the eventual study size. An interesting lesson from this trial was that patients with isolated mild sensory impairment were difficult to find. Most patients with sensory impairment also had other reasons for needing steroids and therefore were not eligible to be included. These reasons included sensory impairment of other nerves (e.g. the median nerve), motor impairment, severe type 1 or ENL reaction or severe neuritis without NFI.

Some people would argue that the mild sensory impairment detected with the monofilament test is an artefact, caused by the subjective response of the person tested to a very small stimulus, i.e. such diagnoses are false positives resulting from random error in the test. If this were true, one would expect results similar to those observed in the current trial, namely no difference in prognosis between the treatment and placebo group and spontaneous 'recovery' in the majority of subjects due to the phenomenon of 'regression to the mean'.²⁰ However, there are two arguments that plead against the hypothesis of mild sensory impairment being false positive. The first is the excellent repeatability that has been found in both experimental and clinical studies with the monofilaments.^{9,10,13,14,22,23} Reliability coefficients were often in excess of 0.90. This pleads against random error playing a major role in monofilament testing. The second argument comes from the observations made in this trial. While the 12-month results were almost equal in the treatment and placebo groups, there was a distinct difference between the two during the time that subjects in the former group were taking prednisolone. First, the sensory function in these subjects recovered faster (Figure 3). Second, and perhaps most convincing, is the observation that the monofilament sensory scores did not deteriorate in any of the 41 subjects during steroid treatment, while deterioration was observed in 4 out of 34 subjects in the placebo group (12%). The difference is statistically significant ($P = 0.01$). The above would indicate that the changes in sensibility measured with the monofilaments are genuine.

In conclusion:

- A short (12-week) prednisolone course to treat sensory impairment of the ulnar and posterior tibial nerves detectable with the monofilament test, but not with the ballpen test, did not improve the long-term outcome in terms of recovery of touch sensibility.
- Mild sensory impairment has a strong tendency towards spontaneous recovery.
- Patients with mild sensory impairment without any other signs or symptoms of reaction or nerve function impairment are relatively rare.

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