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## REVIEW

### Corticosteroids for treating nerve damage in leprosy. A Cochrane review

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#### *Summary*

*Objective* Corticosteroids are commonly used for treating nerve damage in leprosy. We assessed the effectiveness of corticosteroids for treating nerve damage due to leprosy.

*Methods* A systematic search was undertaken to identify randomised controlled trials (RCTs) comparing corticosteroids with placebo or with no treatment. Two authors independently assessed quality and extracted data. Where it was not possible to perform a meta-analysis, the data for each trial was summarised.

*Results* Three RCTs involving 513 people were found. Two trials compared prednisolone with placebo. One trial treated mild sensory impairment of less than 6 months duration and the other trial treated nerve function impairment of 6 to 24 months duration. Both trials examined nerve function improvement 12 months from the start of treatment, but found no significant difference between the two groups. The third trial compared three corticosteroid regimens for severe type 1 reactions. After 12 months, a significantly higher proportion of individuals on a 3 month course required extra corticosteroids compared to the groups with a high-dose and low-dose regimen of 5 months duration. Diabetes and peptic or infected ulcers were not significantly more often reported in the corticosteroid compared to the placebo group.

*Conclusions* Evidence from RCTs does not show a significant long-term effect for either long-standing nerve function impairment or mild sensory impairment. A 5 month corticosteroid regimen was significantly more beneficial than a 3 month corticosteroid regimen. Further RCTs are needed to establish the effectiveness and optimal regimens of corticosteroids and to examine new therapies.

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## Introduction

*This paper is based on a Cochrane review first published in The Cochrane Library 2007, Issue 2 (see <http://www.thecochranelibrary.com/> for information). Cochrane reviews are regularly updated as new evidence emerges and in response to feedback, and The Cochrane Library should be consulted for the most recent version of the review.*

Corticosteroids, especially prednisolone, are commonly used for treating severe reactions and nerve damage in leprosy. They work by controlling acute inflammation and relieving pain.<sup>1,2</sup> The earlier corticosteroids are given after the onset of nerve damage, the more likely permanent nerve function impairment will be prevented.<sup>3,4</sup> The recommended corticosteroid regimen for treating nerve damage starts with 40 mg prednisolone daily and lasts for 12 weeks.<sup>5</sup> Studies indicate that prolonged prednisolone treatment may be more effective in treating severe reactions and nerve damage.<sup>3,6-8</sup> Prednisolone seems to be a very effective drug, but it has some shortcomings. Long-term therapy may cause serious adverse effects, such as peptic ulcers, cataracts, or psychosis.<sup>9-11</sup> A considerable proportion of people treated for nerve damage does not benefit from corticosteroid treatment.<sup>12-15</sup> Other therapies for improving nerve function and relieving nerve pain, such as surgical decompression of nerves,<sup>16-18</sup> azathioprine,<sup>19</sup> and ciclosporin,<sup>20</sup> have been tested. These interventions are beyond the scope of this review.

Corticosteroids are the drugs of choice for acute severe reactions and nerve damage, but the long-term effect of corticosteroids is uncertain and the optimal regimen has not been established. While this review focused on evidence from randomised controlled trials (RCTs), it was expected that only a few RCTs have been conducted in this area. Therefore, the results have also been considered in the light of non-randomised evidence in the Discussion section.

## Methods

### SEARCH STRATEGY

We searched the Cochrane Neuromuscular Disease Group Register using the following terms: (leprosy or Hansen disease or Hansen's disease) AND (steroid\* or corticosteroid\* or glucocorticoid\* or (cortical hormone\*) or prednison\* or prednisolon\* or cortison\*) AND (exp peripheral nervous system diseases) or neuritis or neuropath\* or (nerve damage) or (nerve involvement) or (nerve loss) or (nerve function impairment) or (nerve problem\*) or (sensory loss) or (motor loss) or (nerve pain) or (nerve tenderness) or reaction\*. This search strategy, combined with a search strategy for identifying randomised trials, was adapted to include additional search terms where necessary and was modified to search the Cochrane Central Register of Controlled Trials (*Cochrane Library*, Issue 4, 2005), MEDLINE (from 1966), EMBASE (from 1980), CINAHL (from 1980) and LILACS (from 1982) in January 2006. References from trials and conference proceedings were searched. Trial authors were contacted and the Current Controlled Trials Register ([www.controlled-trials.com](http://www.controlled-trials.com)) was searched for ongoing trials. There were no language restrictions. Two authors independently screened the titles and abstracts of all the publications identified to examine whether studies were eligible.

#### STUDY SELECTION

Studies were eligible if they were (quasi-) randomised controlled trials (RCTs) assessing corticosteroids versus placebo or no treatment for patients with leprosy and related nerve damage or severe leprosy type 1 reaction, requiring corticosteroid treatment. Nerve damage or nerve function impairment (NFI) was defined as clinically detectable impairment of motor or sensory nerve function. It did not include impairment of nerve conduction that was only detectable by electrophysiological means.<sup>21</sup> Outcome measures of interest were: improvement in sensory nerve function as measured with graded nylon filaments<sup>22</sup> or a ball-point pen after 1 or 2 years, improvement in motor nerve function, assessed with the modified MRC grading scale<sup>23</sup> after 1 or 2 years, change in nerve pain and tenderness after 1 year, and adverse events requiring withdrawal from treatment.

#### METHODOLOGICAL QUALITY

The methodological quality of the included studies was based on the following criteria: concealment of allocation; blinding of participants and outcome assessors; loss to follow-up; clear diagnosis; baseline differences and explicit outcome measures mentioned. Each criterion was assessed as 'A': adequate, 'B': unclear or 'C': inadequate. If one of the criteria was not described in the study, it was labelled 'inadequate'. Concealment of allocation was considered adequate if the randomisation process prevented the individual making the allocation from foreseeing the treatment assignment. Blinding was considered adequate if participants and outcome assessors were unaware of the treatment given. Follow-up was considered adequate if the loss to follow-up was less than 10%. Two authors independently assessed the included studies for methodological quality.

#### DATA EXTRACTION AND ANALYSIS

Two authors extracted data regarding methodology and outcome measures from the included studies onto a data extraction form. If there were missing data, the trial authors were contacted. Authors were not blinded to trial author, journal or institution. We used the Cochrane statistical package, Review Manager, for statistical data analysis. Results were expressed as mean differences with 95% confidence intervals (CI) for continuous outcome measures and relative risks (RR) with 95% CI for dichotomous outcomes. In case of clinical heterogeneity, or if data were lacking, the results for each trial were summarised. We analysed separately participants with NFI of less than 6 months duration and participants with long-standing impairment (6 to 24 months duration). Adverse effects were expressed as the proportion of participants with major adverse events.

### Results

#### STUDY SELECTION

We identified 10 potentially relevant studies and excluded eight, because they were not randomised, compared corticosteroids plus a complementary therapy versus corticosteroids, or focused on prevention of nerve damage. One RCT became available during the review process. In total, we found three RCTs for this review.

#### INTERVENTIONS

Two studies compared corticosteroids with placebo. One of them compared prednisolone with placebo in participants with mild sensory NFI.<sup>24</sup> The other trial compared prednisolone with placebo in participants with long-standing NFI.<sup>25</sup> One study compared three different corticosteroid regimens.<sup>26</sup> This trial compared high dose corticosteroids versus low dose corticosteroids versus short regimen corticosteroids for participants with severe type 1 reactions.

#### OUTCOME MEASURES

The two trials comparing corticosteroids with placebo assessed improvement of nerve function 1 year after the start of treatment. Improvement was measured as either a change score between baseline and end of follow-up or as the proportion of participants improved. Change in nerve pain and nerve tenderness was not measured in these trials. Adverse events, requiring withdrawal of treatment were reported in both trials.

None of the pre-specified outcome measures were evaluated in the trial comparing three different corticosteroid regimens. The primary endpoint was the requirement for additional corticosteroids during the 12 month trial period. A poor outcome was defined as a failure to respond to treatment in terms of changes to skin lesions, nerve pain or tenderness, or nerve function, or recurrences of skin or nerve lesions and needing extra corticosteroids.

#### METHODOLOGICAL QUALITY

The results of the assessment of methodological quality are shown in Table 1.

Randomisation and blinding were considered adequate in all three trials. Loss to follow-up varied from 3% to 19%. Leprosy was diagnosed and classified using skin smear or number of skin lesions. Baseline characteristics in the different groups were similar. Nerve function improvement after 1 year was reported in two trials, but not after 2 years. Change in nerve pain and nerve tenderness was not measured in any of the trials. Adverse events occurred in two trials.

#### CORTICOSTEROIDS VERSUS PLACEBO FOR PARTICIPANTS WITH MILD SENSORY NERVE FUNCTION IMPAIRMENT (NFI) OF LESS THAN 6 MONTHS DURATION<sup>24</sup>

Results were available for 89% (75/84) of the participants. After 12 months the mean change in sensory score was  $-2.68 \pm 2.66$  in the prednisolone group and  $-3.00 \pm 2.75$  in the placebo group both implying a mean improvement. The improvement was slightly greater in the placebo group but the mean difference 0.32 (95% CI  $-0.91$  to 1.55) between the two groups was not significant. The proportion with sensory improvement was 80% (33/41) in the prednisolone group compared with 79% (27/34) participants in the placebo group. The difference was not significant. Major adverse events were reported in two participants. One person was diagnosed with diabetes (prednisolone) and one with an infected ulcer (placebo).

**Table 1.** Characteristics of included studies. From Van Veen, *et al.* Cochrane Database Sys Review 2007; CD005491; with permission

Study	Methods	Participants	Interventions	Outcomes	Results	Notes	
Rao 2006	Randomised, parallel group trial	334 leprosy patients with severe type 1 reactions requiring steroid treatment	(a) Prednisolone start at 60 mg/day and thereafter gradually tapered with 10 or 5 mg/2 or 4 weeks until 5 months completed (total 3500 mg)	Requirement for additional corticosteroids during the 12-month trial period	No data	Multicentre Conducted in six centres in India	
	Externally controlled computer randomisation	Persons randomised: 334	(b) Prednisolone start at 30 mg/day and thereafter gradually tapered with 5 mg/2, 4 or 8 weeks until 5 months completed (total 2310 mg)				
	Double blind	Persons analysed: 269 (a: 88, b: 91, c: 90)	(c) Prednisolone start at 60 mg/day and thereafter gradually tapered with 20 or 10 mg/2 weeks until 3 months completed (total 2940 mg) plus 2 months placebo				
Richardus 2003	Randomised, parallel group trial	95 leprosy patients with confirmed MB leprosy diagnosis having untreated sensory or motor impairment of the ulnar or posterior tibial nerve of more than 6 months up to 24 months of duration	(a) Prednisolone start at 40 mg/day and thereafter gradually tapered with 5 mg/2 weeks until 16 weeks completed (total 2520 mg)	Sensory improvement (SI) after 1 year, motor improvement (MI) after 1 year, occurrence of major adverse events	Change in SI: MD = 0.42 (95%CI -0.57; 1.41)	Multicentre Conducted in Nepal and Bangladesh	
	Externally controlled computer randomisation	Unit of randomisation: person	(b) Placebo, equivalent number of tablets for 16 weeks				% with SI: RR = 0.97 (95%CI 0.65; 1.45)
	Double blind	Unit of analysis: ulnar or posterior tibial nerve					Change in MI: MD = 0.12 (95%CI -0.76; 1.00)

Table 1. *continued*

Study	Methods	Participants	Interventions	Outcomes	Results	Notes
		Of participants with bilateral nerve function impairment, the scores of the most affected limb were used in the analysis. If both limbs were equally affected, then the scores of the right side were used in the analysis Persons randomised: 95 Nerves analysed: 92 (a: 41, b: 51)			% with AE: RR = 1.87 (95% CI 0.33; 10.64)	
Van Brakel 2003	Randomised, parallel group trial	84 leprosy patients with confirmed MB leprosy diagnosis having sensory impairment of the ulnar or posterior tibial nerve of less than 6 months duration	(a) Prednisolone start at 40 mg/day and thereafter gradually tapered with 5 mg/2 weeks until 16 weeks completed (total 2520 mg)	Sensory improvement (SI) after 1 year, occurrence of major adverse events (AE)	Change in SI: MD = 0.32 (95%CI -0.91; 1.55)	Multicentre Conducted in Nepal and Bangladesh
	Externally controlled computer randomization Double blind	Unit of randomisation: person  Unit of analysis: ulnar or posterior tibial nerve	(b) Placebo, equivalent number of tablets for 16 weeks		% with SI: RR = 1.01 (95%CI 0.81; 1.27)	
		Unit of analysis: ulnar or posterior tibial nerve  Of participants with bilateral nerve function impairment, the scores of the most affected limb were used in the analysis. If both limbs were equally affected, then the scores of the right side were used in the analysis Persons randomised: 84 Nerves analysed: 75 (a: 41, b: 34)			% with AE: RR = 0.83 (95% CI 0.05; 12.77)	TRIPOD 2

CORTICOSTEROIDS VERSUS PLACEBO FOR PARTICIPANTS WITH LONG-STANDING NERVE FUNCTION IMPAIRMENT (NFI) OF 6 TO 24 MONTHS DURATION<sup>25</sup>

Results were available for 94% (89/95) of the participants. After 12 months the mean difference in sensory score was  $-1.25 \pm 1.66$  in the prednisolone group and  $-1.67 \pm 3.02$  in the placebo group indicating a mean improvement in both. The improvement was slightly greater in the placebo group but the mean difference 0.42 (95% CI  $-0.57$  to 1.41) between the two groups was not significant. The proportion with sensory improvement was 57% (17/30) in the prednisolone group compared with 59% (24/41) in the placebo group (results available for 71 participants). The difference was not significant (relative risk 0.97, 95% CI 0.65 to 1.45). Results of motor nerve function were available for 21 participants. Of these 21 participants, three had motor NFI only and 18 had both sensory and motor NFI. After 12 months the mean difference in motor score was  $-0.18 \pm 0.98$  in the prednisolone group and  $-0.30 \pm 1.06$  in the placebo group both indicating a mean improvement. The improvement was slightly greater in the placebo group but the mean difference 0.12 (95% CI  $-0.76$  to 1.00) between the two groups was not significant.

Five participants came out of the trial due to symptoms of possible major adverse events. Three of them were in the prednisolone group (diabetes, infected ulcer, 'hypersensitivity' to the tablets), and the other two were assigned to placebo treatment (diabetes, peptic ulcer).

HIGH DOSE CORTICOSTEROIDS VERSUS LOW DOSE CORTICOSTEROIDS VERSUS SHORT REGIMEN CORTICOSTEROIDS FOR PARTICIPANTS WITH SEVERE TYPE 1 REACTIONS<sup>26</sup>

At the end of the 12 month period, 41 out of 90 participants (46%) in the short course group (2940 mg over 3 months) needed extra corticosteroids. In the group of participants receiving a low dose of prednisolone (2310 mg over 5 months) this was 28 out of 91 (31%) and 21 out of 88 participants (24%) following a high dose prednisolone regimen (3500 mg over 5 months) required additional prednisolone. The difference between the high dose and low dose 5 month regimen was not significant (relative risk 0.78, 95% CI 0.48 to 1.26). The relative risk of needing additional corticosteroids was significantly less with the high dose 5 month course than with the 3 month course (relative risk 0.52, 95% CI 0.34 to 0.81). The relative risk of needing additional corticosteroids was just significantly less with the low dose 5 month course than with the 3 month course (relative risk 0.68, 95% CI 0.46 to 0.99). No major adverse events were reported during the follow-up period of this trial.

## Discussion

Three randomised controlled trials were available for this review. The interventions and outcomes were too heterogeneous to be entered in a meta-analysis. The numbers of participants included in the trials were small and did not allow for subgroup analysis.

The variability between studies and the limitations in sample size made it difficult to draw any robust conclusions. None of the trials found a significant difference in improved nerve function between treatment and control group 12 months after the start of treatment. The question, whether corticosteroids are beneficial in treating acute NFI or type 1 leprosy reaction in a field setting in the longer term compared to placebo, remains unclear.

Several non-randomised studies have examined the effect of corticosteroids for treating severe reactions and nerve damage in leprosy. The response to corticosteroid treatment seems to depend on the severity and duration of NFI before the start of treatment.

One study found that 35% of patients having complete anaesthesia and 67% with moderate sensory impairment improved to good function 3 months after the start of corticosteroid treatment. For patients with complete motor paralysis or moderate motor impairment, respectively 11% and 55% of the patients recovered to good function.<sup>27</sup> The RCT of treating mild sensory impairment found that a significant higher proportion improved in the prednisolone group compared to the placebo group after 4 months, although the difference disappeared by the 6 month follow-up.<sup>24</sup> Another study found that it may take a long time to achieve full recovery of chronic or recurrent NFI, at least much longer than the duration of a standard steroid course.<sup>14</sup> Recovery of nerve function loss is more likely when the duration of NFI has been less than 6 months.<sup>2,3</sup> To illustrate, data from Ethiopia showed that patients with NFI for less than 6 months and treated with steroids had full recovery in 50 out of 57 nerves (88%), while in-patients with recurrent or chronic NFI only 20 out of 39 nerves (51%) had fully recovered after up to 10 years after treatment.<sup>14</sup> This is in line with the RCT of treating long-standing NFI which found that 19 out of 41 nerves (46%) treated with prednisolone improved.<sup>25</sup> However, even in the placebo group, 25 out of 51 nerves (49%) showed spontaneous improvement after 12 months. Other studies also reported spontaneous nerve function improvement in untreated individuals.<sup>12,14,15</sup>

The optimal corticosteroid regimen has not been established. Recommendations about the optimal dose and duration of steroid therapy have changed over time.<sup>8,28</sup> The principles of a steroid therapy are that it should start with a dose that is sufficient to control the inflammation rapidly. Then the dose should be tapered off until the reaction has settled. The ideal would be a steroid course adjusted and tailored to the individual's situation, but this may be only possible in referral centres.<sup>29</sup>

Currently, a standard 12 week course of prednisolone is recommended by the WHO which can be safely used in the field.<sup>5</sup> Other studies have suggested that a prolonged regimen might be more beneficial. One small retrospective study compared a short-term steroid treatment (2 months) with a prolonged steroid treatment (3 to 18 months) for type 1 reaction in borderline leprosy patients. It was found that the latter treatment gave better results on improving motor nerve function than the shorter treatment and did not increase the risk of adverse events. The critical dose to control a reaction after the initial period was considered to be 15 to 20 mg daily.<sup>7</sup> One study examined the effects of prednisolone treatment on the cellularity and cytokine profiles of leprosy skin type 1 reactions. The results showed that prednisolone treatment decreased cytokine levels significantly only after 28 days from the start of treatment. Some patients continued to have cytokine production for 1 to 6 months. This study illustrates the slow response to steroid therapy and continuing activity for several months.<sup>6</sup> While these non-randomised studies already suggested the benefits of a prolonged steroid course, the RCT comparing three corticosteroid regimens confirms this in reporting that a longer duration of prednisolone treatment gave less poor outcomes than a short course of prednisolone.<sup>26</sup>

According to other authorities, a substantial proportion of individuals treated for nerve damage do not respond to corticosteroids. The overall nerve function improvement levels vary approximately between 60% and 80% after steroid therapy.<sup>12</sup> This study reported that 27 out of 83 treated nerves with motor impairment (33%) and 53 out of 166 treated nerves with sensory impairment (32%) did not improve or had deteriorated 12 months after the start of



treatment. In a study in Thailand, 27 out of 77 patients who were treated with prednisolone (35%) showed no improvement or a worsening of NFI.<sup>15</sup> One randomised controlled trial examined the effect of prophylactic use of steroids in 636 newly diagnosed multibacillary patients.<sup>30</sup> This study showed that a low dose prophylactic steroid regimen reduced the risk of NFI at the end of 4 months, but the effect was not sustained at 1 year. Repeat use of steroid prophylaxis for a longer period than 4 months may sustain the benefit, but this needs to be further examined.

An alternative therapeutic approach for treating nerve damage in leprosy has been surgical decompression of acutely inflamed nerves. There is an ongoing search for new therapies, because steroids are not always effective, and may cause serious adverse effects and because their long-term effect is unclear. A quasi-randomised controlled trial compared an 8 week course of prednisolone combined with azathioprine with a 12 week course of prednisolone alone for treating severe type 1 reactions.<sup>19</sup> The trial did not find a significant difference between the two treatment groups, but the study was limited in size ( $n = 40$ ). A recent non-randomised follow-up study assessed the effects of ciclosporin treatment in 33 Ethiopian and 10 Nepali leprosy patients with severe type 1 reactions and the authors suggested that ciclosporin monotherapy may be an effective treatment for severe type 1 reactions with few adverse effects.<sup>20</sup> Therapies which are used for other immune-mediated conditions, such as ciclosporin or combinations of immunosuppressants may be promising. It is plausible that these therapies may be effective for treating nerve damage in leprosy, but evidence from RCTs is lacking.<sup>1</sup>

## Conclusion

### IMPLICATIONS FOR PRACTICE

Evidence from the three randomised controlled trials is insufficient to draw robust conclusions about the long-term effect of corticosteroids for treating nerve damage in leprosy. Two trials, of which one treated long-standing nerve function impairment and the other mild sensory impairment, did not show significantly better outcomes with corticosteroids than placebo for treating nerve damage in leprosy in the long term. However in a third trial, a 5 month corticosteroid regimen was significantly more beneficial than a 3 month corticosteroid regimen. Standard corticosteroid regimens are not significantly more harmful than placebo treatment, despite known adverse effects of corticosteroids.

### IMPLICATIONS FOR RESEARCH

There is a need for high-quality randomised controlled trials to establish the value and optimal dose of corticosteroid regimens and to examine the efficacy and safety of new therapies. Future trials should pay more attention to non-clinical aspects, such as costs and impact on quality of life, because these are highly relevant indicators for both policy makers and participants.

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