Are Corticosteroids Effective in Duchenne Muscular Dystrophy?

Manzur AY, Kuntzer T, Pike M, Swan A. Glucocorticoid corticosteroids for Duchenne muscular dystrophy. Cochrane Database of Systematic Reviews 2008; 1: CD003725. This version published online: 23 January 2008. Date of most recent substantive amendment: 14 November 2007.

INTRODUCTION

Duchenne muscular dystrophy (DMD) is the most common muscular dystrophy of childhood. The mode of inheritance is X-linked recessive thus affecting mainly males. The disease is characterized by muscle wasting and loss of walking ability leading to complete wheelchair dependence by 13 years of age. Since the disease is progressive and incurable, the outcome and quality of life of affected children is extremely poor especially in developing countries where options for rehabilitation and the facilities for the disabled are very limited. There is some evidence that humoral and cellular immune responses contribute to the pathological processes in DMD and thus it is important to evaluate the efficacy of cheap and easily available drugs such as corticosteroids for improving the function in this disease.

SUMMARY

This is an update of the Cochrane systematic review first published in 2004(1). Four double-blind randomized controlled trials (RCTs) enrolling a total of 249 patients (161 treatment group and 88 placebo group) and one randomized crossover trial enrolling 17 boys were included. The intervention included oral prednisone/prednisolone (4 studies; 3 daily use and 1 intermittent use) or deflazacort (one trial) given for a period varying from six months to 2 years. Only one study with 28 participants, addressed the primary outcome measure of prolongation of walking and did not show significant benefit. The meta-analysis from four RCTs (*N*=249) showed that corticosteroids improved muscle strength and function over six months. Analysis of pooled data from three trials demonstrated a statistically significant (Weighted mean difference [WMD] of 0.50 [95% CI 0.35 to 0.66]) improvement in average muscle score with prednisone (0.75 mg/kg/day) after six months of treatment as compared to placebo. The crossover trial using an intermittent regime of prednisone (0.75 mg/kg/day given for the first 10 days of every month, for six months) versus placebo also showed statistically significant difference in the muscle force during the prednisone phase compared to the placebo phase. Improvements were seen in time taken to rise from the floor (Gowers' time), nine meters walking time, four-stair climbing time, ability to lift weights, leg function grade and forced vital capacity. One randomized controlled trial (*N*=28) showed that glucocorticoid corticosteroids stabilize muscle strength and function for up to two years. Ability to lift standardized weights was assessed and reported in two studies and a pooled analysis demonstrated statistically significant improvement (WMD of 0.75 [95% CI 0.50 to 0.99]) in lifting weights in the prednisone group after six months of treatment as compared to placebo. The data were inadequate to compare efficacy of prednisone/prednisolone with deflazacort. Adverse effects such as excessive weight gain, behavioral abnormalities, cushingoid appearance and excessive hair growth were all more common with corticosteroids than placebo. Long-term adverse effects of glucocorticoid therapy could not be evaluated because of the short-term duration of the randomized studies.

COMMENTARY

Are the results valid?

This review addresses a sensible and specific question. The search of literature was exhaustive and the criteria for inclusion of studies were stringent. The finally included studies were acceptable in methodology though in four of the included studies allocation concealment was uncertain. The reviewers tried to include functionally important outcomes but only one included study evaluated the outcome of prolongation of walking. Other outcomes assessed

KEY MESSAGE

- Corticosteroid therapy in Duchenne muscular dystrophy improves muscle strength and function in the short-term (six months to two years) but the long-term benefits and hazards are unclear.

such as muscle strength and time taken for various activities appear to be functionally important but the direct effect of these parameters on quality of life or patient comfort is uncertain. The heterogeneity of the trials was not a major issue and the effects of treatment appeared consistent across the trials.

The authors could find 13 randomized controlled trials of corticosteroids in DMD but only 5 were finally analyzed. At least 3 studies could not be included because of incomplete information. A publication bias (studies in which an intervention is not found to be effective sometimes are not published) therefore can not be ruled out in the results of this review. The authors also found a large number of non-randomized studies on this subject, and have reported their results too in a tabular form. Majority of these unrandomized studies reported a positive impact of corticosteroids on prolongation of walking and muscle strength.

Clinical Importance and Precision of the Results

Loss of walking ability is the key milestone in the natural history of DMD and of maximal functional significance. However, none of the studies could directly answer whether use of corticosteroids would prolong walking ability. As the major contributor to the loss of walking is progressive muscle weakness, measurements of muscle strength has been used as a surrogate marker in the included studies. As this marker does not directly measure the function, assessing the quantum of benefit to the patient becomes difficult. The other functionally important outcomes such as time taken to rise from the floor (Gowers' time), nine meters walking time and four-stair climbing time improved in average by about 2 to 4 seconds by use of corticosteroids over a period of six months. Again, the impact of this in improving the quality of life and overall morbidity can not be quantified. The results are, however, consistently better in all the included studies and it can be concluded that corticosteroids improve the muscle power and bodily functions over short term (six months to two years). The long-term benefits and harms are not clear.

Most of the patients included in the studies were ambulatory at the time of start of therapy. Thus, the results are applicable only to boys with DMD in their ambulant phase.

Implications for Practice and Policy

Prednisolone has a beneficial effect on muscle strength and function in boys with Duchenne dystrophy and should be offered (at a dose of 0.75 mg/kg/day) as treatment in the ambulatory phase. If side effects require a decrease in prednisone, tapering to dosages as low as 0.3 mg/kg/day may still give significant but less robust improvement. Deflazacort can also be used for the treatment of Duchenne dystrophy in countries where it is available(2). Benefits and side effects of corticosteroid therapy however need to be monitored and the offer of treatment with corticosteroids should include a balanced discussion of potential risks. Many issues including the ideal age / functional stage for initiation of treatment, the optimal glucocorticoid regime, and the age for discontinuation of glucocorticoid treatment still need to be clarified with randomized controlled trials. Long term results on walking, respiratory and cardiac functions and, quality of life need further investigation.

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REFERENCES

1. Manzur AY, Kuntzer T, Pike M, Swan A. Glucocorticoid corticosteroids for Duchenne muscular dystrophy. Cochrane Database Syst Rev 2004; 2: CD003725.
2. Campbell C, Jacob P. Deflazacort for the treatment of Duchenne Dystrophy: a systematic review. BMC Neurol 2003; 3: 7.