

Glucocorticoid replacement regimens in the treatment of 21-hydroxylase deficiency congenital adrenal hyperplasia: a systematic Cochrane review

Sze May Ng, Karolina Stepien

¹Department of Paediatrics, Southport and Ormskirk Hospital NHS Trust, UK

²Adult Inherited Metabolic Disorders, The Mark Holland Metabolic Unit, Salford Royal NHS Foundation Trust, UK



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Background

Congenital adrenal hyperplasia (CAH) is an autosomal recessive condition which leads to glucocorticoid deficiency. During childhood, the main aims of treatment are to prevent adrenal crisis and to achieve normal stature, optimal adult height and to undergo normal puberty. In adults, the aims of treatment are to prevent adrenal crisis, ensure normal fertility and to avoid long-term consequences of glucocorticoid use. Current treatment regimens for CAH with glucocorticoids cannot optimally replicate the normal physiological cortisol level. Overtreatment or undertreatment of CAH is often reported in individuals who may be treated with different steroid treatment regimens. There is no current standard treatment for CAH and physicians often customise treatment for each individual using various regimens. It remains unclear which treatment regimen is most effective

Objectives

This Cochrane review aims to determine the efficacy and safety of different glucocorticoid replacement regimens in the treatment of congenital adrenal hyperplasia due to 21-hydroxylase deficiency in children and adults.

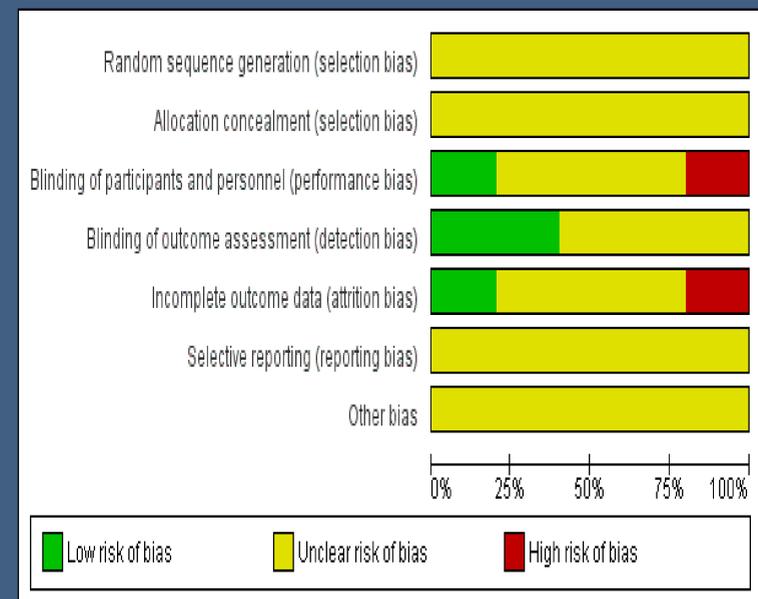
Methods

We included any RCT or quasi-RCT comparing different glucocorticoid replacement regimens in the treatment of CAH due to 21-hydroxylase deficiency in children and adults. The authors independently searched and extracted data. Data from different interventions were analysed separately. GRADE was used to assess the quality of the evidence.

Results

The initial search identified 297 records which identified 20 publications for further examination. After screening full texts of 20 selected papers, we included five RCTs with 101 people with CAH due to 21-hydroxylase deficiency. The number of participants in each trial varied from 6 to 44 with participants' ages ranging from 1.2 to 21 years. They received different glucocorticoid replacement regimens such as frequency in the day or different forms of glucocorticoids and were followed up for between six and 12 months. There were limitations to the review. The number of trials assessing different glucocorticoid regimens varied as well as the trial durations and it was difficult to draw overall conclusions from any single trial. Three trials were of a cross-over design and we did not have the appropriate information to conduct comprehensive meta-analyses. Although 17OHP and androstenedione are frequently used to monitor treatment, there is a great amount of variability in the measurements which hampers usefulness of these tests. Overall, we judged trials to be moderate to high risk of bias; lack of methodological detail led to 'unclear' risk of bias judgements across many of the domains (Figure 1).

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Discussion

The majority of the trials we included were small and many had methodological weaknesses. There are limited trials to date which compare the efficacy and safety of different glucocorticoid replacement regimens in the treatment of CAH in children and adults. This review addressed a diverse range of treatment regimens with many trials at high or unclear risk of bias. There is insufficient evidence to indicate which glucocorticoid replacement regimen results in better outcomes. There are limited trials to date which compare the efficacy and safety and no evidence to date of which regime provides optimal outcomes. There were no trials on modified-release formulation of hydrocortisone or use of 24-hour circadian continuous subcutaneous infusion of hydrocortisone. No common intervention characteristics for success were apparent among the trials included in this review.

Conclusions

Implications for Practice

The goal of glucocorticoid therapy in CAH is to replace deficient cortisol and prevent the consequences of androgen excess whilst avoiding glucocorticoid over-treatment. There are limited trials to date which compare the efficacy and safety of different glucocorticoid replacement regimens in the treatment of 21-hydroxylase deficiency congenital adrenal hyperplasia (CAH) in children and adults and no evidence to date of which regime provides optimal outcomes. There were no trials on modified-release formulation of hydrocortisone or use of 24-hour circadian continuous subcutaneous infusion of hydrocortisone. No common intervention characteristics for success were apparent among the trials included in this review.

Implications for research

This systematic review has identified the need for well-designed, adequately-powered, multicentred randomised controlled trials to assess the efficacy and safety of different glucocorticoid replacement regimens in the treatment of 21-hydroxylase deficiency CAH in children and adults. Trials should be carried out over a longer duration more than 10 years to provide further information on long-term effects of quality of life, final adult height, androgen normalisation, prevention of adrenal crisis, osteopenia, subfertility and presence of testicular rest tumours.

