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Glucocorticoid replacement regimens in the treatment of 21-hydroxylase deficiency congenital adrenal hyperplasia (Protocol)

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[Intervention Protocol]

Glucocorticoid replacement regimens in the treatment of 21-hydroxylase deficiency congenital adrenal hyperplasia

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To compare and determine the efficacy and safety of different glucocorticoid replacement regimens in the treatment of 21-hydroxylase deficiency CAH in children and adults.

BACKGROUND

Description of the condition

Congenital adrenal hyperplasia (CAH) represents a group of autosomal recessive conditions which lead to glucocorticoid deficiency. It is the most common cause of adrenal insufficiency in children, affecting 1 in 18,000 births in the UK (Khalid 2012), while in other populations, the incidence of CAH ranges from 1 in 5000 to 1 in 20,000 (Marumudi 2013; Riepe 2007). In more than 90% of cases, 21-hydroxylase enzyme deficiency is found; this is caused by mutations in the 21-hydroxylase gene (CYP21) (Marumudi 2013). In most forms of CAH, an enzyme defect blocks cortisol synthesis, thus impairing cortisol-mediated negative feedback control of adrenocorticotrophic hormone (ACTH) secretion. Oversecretion of ACTH ensues, which results in overstimulation of the adrenals and causes them to enlarge (hyperplasia). This oversecretion also stimulates excessive synthesis of the adrenal products of those pathways unimpaired by an enzyme deficiency. Control of androgens is often highly variable and metabolic abnormalities such as obesity, hypercholesterolaemia, hypertension, insulin resistance and osteopenia have been reported (Marumudi 2013). The clinical forms of 21-hydroxylase enzyme deficiency are typically categorised as classical 21-hydroxylase deficiency CAH, which is the severe form, or non-classic (NCAH), which is the mild or late-onset form. Classical 21-hydroxylase deficiency also has further subcategories of salt-wasting (SW) or simple-virilizing (SV) (also known as non-salt wasting) forms, depending on the presence of aldosterone deficiency (Khalid 2012). Clinical manifestations in classical 21-hydroxylase deficiency CAH are due to glucocorticoid deficiency, mineralocorticoid deficiency and androgen excess. The NCAH form is often under-diagnosed and may be associated with hyperandrogenic symptoms presenting either in childhood (precocious puberty) or later in adulthood (acne, infertility) (Marumudi 2013). Biochemical diagnosis of CAH relies on the determination of 17-OH progesterone; the ACTH stimulation test is the diag-

nostic test for evaluating adrenal gland function and is used for the biochemical diagnosis of NCAH due to other enzyme deficiencies. A diagnosis of CAH is often further confirmed on genetic testing and urine steroid profiling.

Description of the intervention

The management of individuals with classical 21-hydroxylase deficiency CAH involves the replacement of glucocorticoids (with oral glucocorticoids, including prednisolone and hydrocortisone), the suppression of ACTH and the replacement of mineralocorticoids to prevent salt wasting. Hydrocortisone is the preferred choice of glucocorticoid replacement in children with CAH, as prednisolone and dexamethasone are associated with growth suppression (Bonfig 2007; LWPES/ESPE 2002). The typical dosing of hydrocortisone in children is 10 to 15 mg/m² per day given in three divided doses. Hydrocortisone is rapidly absorbed from the intestine after oral intake. The bioavailability of hydrocortisone is greater than 90%, but it has a short time to maximum concentration (Tmax) of one to two hours and a short half life of 1.8 to two hours (Charmandari 2001). Hydrocortisone is highly protein-bound and there is a high clearance rate with increasing dosage (Fuqua 2010). However, conventional hydrocortisone treatment is associated with reduced quality of life (QoL) and increased side effects on bone metabolism and cardiovascular risks (Debono 2009).

Several other regimens have been proposed to mimic the normal physiological endogenous cortisol levels, such as variable intravenous infusions of hydrocortisone (Merza 2006), multiple dosing of immediate-release formulation of hydrocortisone tablets or suspension given four- to five-times daily (Hindmarsh 2009; Hindmarsh 2014), dual release (immediate-release tablet with sustained-release core) hydrocortisone tablets (Johannsson 2009), modified-release formulation tablets or suspension of hydrocortisone taken once (Verma 2010) or twice daily (Mallappa 2015) and a combination of hydrocortisone and prednisolone regimen (Ajish 2014).

During childhood, the main aims of medical treatment of 21-hydroxylase deficiency CAH are to prevent adrenal crisis and to achieve normal stature, optimal adult height and to undergo normal puberty. In adulthood, the aims of medical treatment are to prevent adrenal crisis, ensure normal fertility and to avoid the long-term consequences of glucocorticoid use.

How the intervention might work

Current treatment regimens for CAH with glucocorticoids cannot optimally replicate the normal physiological cortisol level (Merza 2006). Over-treatment or under-treatment of CAH is often reported in individuals who may be treated with different steroid treatment regimens. Conventional twice- or three-times-daily hydrocortisone replacement therapy does not replicate the normal circadian rhythm, as cortisol levels are always low in the early hours of the morning when endogenous cortisol levels are normally rising. This then drives a nocturnal rise in ACTH which increases the production of androgens (Charmandari 2001). Under-treatment and the resulting excess production of androgens causes virilization, accelerated growth, advanced skeletal maturation and early epiphyseal fusion (Riepe 2007). Conversely, a longer-acting cortisol regimen bears the risk of over-treatment and if taken at night will expose individuals to high levels of steroid at the time of the cortisol nadir. Over-treatment often leads to side effects such as obesity, hypertension and osteoporosis (Subbarayan 2014). In some regimens, reverse circadian rhythm pattern of hydrocortisone replacement has been used, where a higher dose is given at night in order to suppress overnight increases in ACTH rather thank giving the highest dose of hydrocortisone in the morning.

Why it is important to do this review

There is no standard treatment for 21-hydroxylase deficiency CAH and physicians often customise treatment for each individual using various regimens. It remains unclear which treatment regimen is most effective (Riepe 2002). The pharmacokinetics and pharmacodynamics of currently available glucocorticoid regimens do not allow the matching of the hormonal fluctuations and the physiological requirements in people with 21-hydroxylase deficiency CAH and there is much debate as to which is the most efficacious regimen used for the treatment of CAH (Merza 2006). This review aims to establish evidence of efficacy for the different treatment regimens of cortisol replacement in people with 21 hydroxylase deficiency CAH and will separately examine studies comparing the different glucocorticoid replacement regimens in the treatment of 21-hydroxylase deficiency CAH.

OBJECTIVES

To compare and determine the efficacy and safety of different glucocorticoid replacement regimens in the treatment of 21-hydroxylase deficiency CAH in children and adults.

METHODS

Criteria for considering studies for this review

Types of studies

We will include any randomised controlled trials (RCTs) or quasi-RCTs comparing different glucocorticoid replacement regimens in the treatment of 21-hydroxylase deficiency CAH in children and adults.

Types of participants

Children and adults diagnosed with 21-hydroxylase deficiency CAH according to the appropriate diagnostic criteria of the time.

Types of interventions

Any circadian, extended release or conventional hydrocortisone replacement regimen of any duration for treating congenital adrenal hyperplasia in children and adults. We will compare the following active interventions to each other:

- daily Plenadren® (an immediate-release tablet with sustained-release hydrocortisone core formulation);
- daily Chronocort® (a modified-release formulation of hydrocortisone);
- twice-daily Chronocort® (a modified-release formulation of hydrocortisone);
- three-times daily conventional immediate-release formulation of hydrocortisone;
- more than three-times daily conventional immediate-release formulation of hydrocortisone;
- 24-hour circadian continuous subcutaneous infusion of hydrocortisone;
- combination of oral hydrocortisone and prednisolone regimen.

The mineralocorticoid replacement dosing will not be compared.

Types of outcome measures

Primary outcomes

1. QoL score (as assessed by Short Form Health Survey (SF-36))
2. Androgen normalisation (defined by 17 hydroxyprogesterone monitoring)
3. Prevention of adrenal crisis

Secondary outcomes

1. Presence of osteopenia (bone mineral density (BMD) measured by dual X-ray absorptiometry (DEXA))
2. Presence of testicular or ovarian adrenal rest tumours
3. Sub-fertility (defined by history, evidence of adrenal progesterone hypersecretion, consequences of genital reconstructive surgery, secondary polycystic ovaries syndrome)
4. Final adult height in standard deviation score (SDS)

Search methods for identification of studies

Electronic searches

We will identify relevant studies from the Inborn Errors of Metabolism Trials Register.

The Inborn Errors of Metabolism Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated with each new issue of the Cochrane Library), weekly searches of MEDLINE and the prospective hand-searching of one journal - *Journal of Inherited Metabolic Disease*. Unpublished work is identified by searching through the abstract books of the Society for the Study of Inborn Errors of Metabolism conference and the SHS Inborn Error Review Series. For full details of all searching activities for the register, please see the Cochrane Cystic Fibrosis and Genetic Disorders Group's website.

The review authors will also conduct electronic database searches of the Cochrane Library, MEDLINE, Embase, PsycINFO and CINAHL using an iterative search strategy (Appendix 1; Appendix 2; Appendix 3). Furthermore, they will make efforts to identify reports relevant to the review by searching the internet using tools such as Google Scholar. They will search for interventions which contain the words congenital adrenal hyperplasia, hydrocortisone or glucocorticoid replacement, 21-hydroxylase deficiency.

We will search databases of ongoing trials: Current Controlled Trials (www.controlled-trials.com - with links to other databases of ongoing trials) and clinicaltrials.gov (Appendix 4).

Searching other resources

We will aim to identify additional studies by searching the reference lists of included trials and other (systematic) reviews, meta-analyses and health technology assessment (HTA) reports (identified from the above-detailed electronic database searches).

Data collection and analysis

One author (KS) will conduct an initial search and undertake an initial sift of the search results to identify potentially relevant articles. Both authors will then independently assess sifted articles for eligibility.

Selection of studies

To determine the studies for further assessment, two review authors (SN, KS) will independently scan the abstract, title or both sections of every record retrieved. They will review the full text of all potentially relevant articles. The authors will extract data using the Cochrane Cystic Fibrosis and Genetic Disorders Review Group's study selection, quality assessment and data extraction form, adapted to suit the outcomes of this review. They will record study design, study participant characteristics and outcome data.

They will measure inter-rater agreement for study selection using the kappa statistic (Cohen 1960). If there are any differences in opinion, the review authors will resolve these by consensus and with an independent advisor. If it is not possible to resolve a disagreement regarding study selection, the review authors will add the article to those 'Awaiting assessment' and contact the study investigators for clarification. The review authors will include an adapted QUOROM (quality of reporting of meta-analyses) flowchart of study selection and a PRISMA diagram to show the flow of study selection (Moher 1999).

Dealing with duplicate publications

In the case of duplicate publications and companion papers of a primary paper, the review authors will extract all available information from all publications. In cases of doubt, the review authors will obtain the original publication (usually the oldest version) as a priority.

Data extraction and management

The authors will extract data using the Cochrane Cystic Fibrosis and Genetic Disorders Review Group's study selection, quality assessment and data extraction form, adapted to suit the outcomes of this review. They will record study design, study participant characteristics, and outcome data and resolve any disagreements by discussion, or if required by a third party. The review authors will request any relevant missing information from the study investigators, if required. They plan to analyse the data from different interventions and undertake the comparisons separately.
The review authors will report outcome data at the following intervals:

- short term: less than 12 months;
- medium term: one to five years;
- long term: more than five years.

If studies report multiple time points within the time frames described above (e.g. three months and six months), then the review authors will present any additional individual time points, but still describe the results as 'short term', 'medium term' or 'long term' as appropriate.

Assessment of risk of bias in included studies

The authors will use the Cochrane risk of bias tool to assess the following criteria: randomisation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; and selective reporting (Higgins 2011). They will classify the risks as low, high or unclear and record each decision and their reasons for the judgement in a table; they will display the assessments in the overall risk of bias graph.

Measures of treatment effect

The authors will follow recommendations for data analysis set out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).
For dichotomous outcomes, (such as presence of osteoporosis, testicular or ovarian tumours, hypertension, hypercholesterolaemia or obesity) the authors plan to analyse the treatment effect using risk ratios (RR). Considering the outcome measures listed, authors expect that most of the data collected for this review will be continuous. There are many differing methods for measuring each of the outcome measures listed above and therefore the authors plan to analyse the treatment effect using the standardized mean difference (SMD) with 95% confidence intervals (CIs). They will present the data entered as a scale with a consistent direction effect. The authors will conduct a meta-analysis if this is meaningful (i.e. when interventions, participants and the underlying clinical outcomes are similar enough for pooling to make sense). They will describe skewed data narratively and report these as medians and interquartile ranges.
When multiple treatment arms are reported in a single study, the review authors will only include the relevant arms. If the intervention groups do not fall into the same comparison, it would be reasonable to include independent comparisons in a meta-analysis as if they were from different studies.

Unit of analysis issues

The authors will implement the following strategies to minimize the impact of non-standard designs upon the conclusions of the review. For cluster-RCTs, the review authors will take into consideration that a unit-of-analysis error can result in narrowed CIs and artificially small P values (Whiting-O'Keefe 1984). If they include any cross-over studies, they plan to incorporate only the first-arm results into the meta-analysis (Qizilbash 1998). This method would half the available sample for analysis and therefore the authors will only include data from cross-over studies after careful deliberation.

Dealing with missing data

If data are missing from the included studies, the review authors will make every effort to contact the original study authors to obtain these data. If data such as standard deviation scores (SDS) are missing, where appropriate, the authors will calculate these from standard errors (SE), CIs, T-values or P values (if reported). In the event of large scale missing data or participant attrition, authors will carry out an intention-to-treat analysis. Bias can result from the imperfect nature of estimates by imputation; to protect against this the authors plan to carry out an available-case analysis dealing with participants who completed the study. If this occurs, the authors will also conduct a sensitivity analysis. They will investigate attrition rates, e.g. dropouts, losses to follow-up and withdrawals.

Assessment of heterogeneity

Authors will assess heterogeneity using the I^2 statistic, which gives insight into the level of variability within results that is due to heterogeneity as opposed to chance alone (Higgins 2003). In order to be consistent with other Cochrane Reviews evaluating behavioural interventions (Savage 2014), the authors will assess heterogeneity in terms of overlapping percentage intervals: 0% to 40% (might not be important); 30% to 60% (may represent moderate heterogeneity); 50% to 90% (may represent substantial heterogeneity); and 75% to 100% (may represent considerable heterogeneity) (Deeks 2011). However, the authors acknowledge that closer investigation of the consistency of the direction and strength of the effect in trials is warranted to give a better interpretation of I^2 (Higgins 2003).

Assessment of reporting biases

A comprehensive search strategy, including grey literature, will protect against many forms of publication bias. The authors note, however, that this method alone will not prevent all possibility of publication bias infiltrating the review. Therefore, if the authors identify and incorporate more than 10 studies, they will further assess publication bias using funnel plots. The authors will visually assess the funnel plots they generate to assess asymmetry and consider the descriptive characteristics of the plot. Further to visual inspection, authors may also assess funnel plot asymmetry using an adaptation of the linear regression model (Eggar 1997).
In order to examine possible selective reporting bias, the review authors will request study protocols from the original study authors.

Data synthesis

If a meta-analysis is appropriate, the authors plan to use a fixed-effect model. If heterogeneity cannot be explained by the prespecified subgroup analyses, the authors will perform a sensitivity analysis using a random-effects model. If a meta-analysis is not appropriate (e.g. a substantial level of heterogeneity), the review authors will present a narrative synthesis.

Subgroup analysis and investigation of heterogeneity

The authors plan to conduct subgroup analyses based on children (younger than 18 years of age) and adults (18 years and older) within the different intervention categories if at least moderate heterogeneity (as defined above) is present.

Sensitivity analysis

If authors find data are incomplete, if they need to impute data, or if criteria limits are poorly defined (such as age ranges, or what constitutes 'standard care') they plan to undertake sensitivity analyses. They will complete the meta-analyses with and without the contentious data to assess its impact upon the overall findings. If the results of the meta-analyses are not greatly altered, the robustness of the review increases. If results of the two analyses differ greatly, then the results of the review should be interpreted with caution.The authors plan to avoid this by conducting a sensitivity analysis at the participant level and incorporating adjustment using the intra-class correlation coefficient (ICC).
If the authors identify different levels of potential bias in studies, they will conduct sensitivity analyses. If they judge some studies to contain potentially high or uncertain levels of bias, they will omit these from the analyses. This again will allow the reviewers to identify the impact of these studies upon the results of the analyses. If there is no marked difference in results due to this omission, it strengthens the conclusions of the review by indicating that they are not in fact impacted by the potential bias of the studies.
If any heterogeneity cannot be explained by the prespecified subgroup analyses, the authors will perform a sensitivity analysis using a random-effects model.

Summary of findings table

The authors will present a 'Summary of findings' table for each comparison to present the main findings of a review in a transparent and simple tabular format. In particular, to provide key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the primary and secondary outcomes listed below.

1. QoL score
2. Androgen normalisation
3. Prevention of adrenal crisis
4. Presence of osteopenia
5. Presence of testicular adrenal rest tumours (in boys)
6. Subfertility
7. Final adult height in SDS

The authors will use GRADE to evaluate the quality of the evidence (Schünemann 2011a; Schünemann 2011b).

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE (via Ovid) search strategy

1. exp congenital adrenal hyperplasia
2. exp CAH
3. exp 21-hydroxylase deficiency
4. 1 or 2 or 3
5. exp hydrocortisone
6. exp glucocorticoids
7. exp prednisolone
8. 5 or 6 or 7
9. 4 and 8
10. limit 9 to english language
11. limit to 10 humans

Appendix 2. Embase (via Ovid) search strategy

1. exp congenital adrenal hyperplasia
2. exp CAH
3. exp 21-hydroxylase deficiency
4. 1 or 2 or 3
5. exp hydrocortisone
6. exp glucocorticoids
7. exp prednisolone
8. 5 or 6 or 7
9. 4 and 8
10. limit 9 to english language
11. limit 10 to humans
12. limit 9 to (english language and exclude medline journals)

Appendix 3. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1 MeSH descriptor: [hydrocortisone, glucocorticoid replacement, congenital adrenal hyperplasia, 21-hydroxylase deficiency] explode all trees

Appendix 4. Grey literature and ongoing trials database search strategies

We will search the following databases using the terms congenital adrenal hyperplasia, hydrocortisone or glucocorticoid replacement, 21-hydroxylase deficiency:

- NICE Evidence;
- Health Canada - Clinical Trials Search;
- metaRegister of Controlled Trials (mRCT);
- ClinicalTrials.gov.

We will also search the following manufacturers' websites:

- Seven Seas;
- Abbott.

CONTRIBUTIONS OF AUTHORS

Roles and responsibilities	
TASK	WHO WILL UNDERTAKE THE TASK?
Protocol stage: draft the protocol	SMN
Review stage: select which trials to include (2 + 1 arbiter)	SMN and KS
Review stage: extract data from trials (2 people)	SMN and KS
Review stage: enter data into RevMan	AS
Review stage: carry out the analysis	SMN and KS

(*Continued*)

Review stage: interpret the analysis	SMN and KS
Review stage: draft the final review	SMN and KS
Update stage: update the review	SMN and KS

DECLARATIONS OF INTEREST

Both authors: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

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