INVESTIGATING THE EFFECT OF HYDROCORTISONE ON DEPRESSIVE SYMPTOM SEVERITY: A DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSSOVER STUDY

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RESEARCH QUESTION

In participants with major depressive disorder (MDD), does treatment with hydrocortisone, compared to placebo, reduce depressive symptoms when measure by the Quick Inventory of Depressive Symptomatology scale (QIDS-C)?

BACKGROUND

Major depressive disorder (MDD), characterized by altered cortisol levels, has been a subject of extensive research. Recent studies, such as those conducted using the UK Biobank data, have shown that both systemic and inhaled glucocorticoid use is associated with changes in brain volume and white matter microstructure, impacting cognitive and emotional outcomes. This study is an interim, secondary analysis of a double-blind, placebo-controlled clinical trial with treatment crossover, examining the effects of hydrocortisone on the human hippocampus (NCT03896659). This manuscript is focusing on an interim secondary analysis of a larger trial. While the main study is interested in understanding whether hydrocortisone has a differential effect on the hippocampus of depressed versus non-depressed individuals, we are investigating if depressed patients will experience a reduction in depressive symptoms, measured by the Quick Inventory of Depressive Symptomatology (QIDS), when treated with hydrocortisone as opposed to a placebo. A meta-analysis highlighted the importance of HPA axis dysregulation in the onset and maintenance of depressive symptoms, suggesting that targeting this dysregulation could advise therapeutic strategy.[1] The manipulation of cortisol levels has been shown to have a significant impact on depression symptoms. According to DeBattista et al. (2000), acute hydrocortisone infusion significantly reduced the severity of depression in patients with major depression, suggesting that cortisol modulation may be of therapeutic benefit in depression.[2]

RESULTS

Building on existing research indicating altered brain structures and cognitive functions in glucocorticoid users, this study's preliminary insights suggest a nuanced response to hydrocortisone in the modulation of depressive symptoms. The expected outcomes, based on initial data, indicate that depressed patients might exhibit a more significant change in QIDS scores following hydrocortisone treatment compared to placebo, aligning with clinical trial findings. However, our results revealed no significant difference in QIDS-C scores when treated with hydrocortisone versus the placebo among the depressed cohort. The female sex was significantly associated with decreased QIDS-C scores when controlling for treatment on multivariate analysis however, their interaction was not significant. Similarly, while the baseline depressed cohort was significantly older than the control group, age was not associated with QIDS-C scores when controlling for treatment.

Predictors	Estimates	CI	P-value
(Intercept)	8.74	6.87 – 10.61	**<0.001**
Hydrocortisone	0.35	-1.13 – 1.84	0.637
Random Effects			
σ^2	8.26		
$\tau_{00\ record\_id}$	10.09		
ICC	0.55		
N_{record_id}	17		
Observations	63		
Marginal R^2 / Conditional R^2	0.002 / 0.551		

Table 1. Linear Mixed Effects Model Estimating the Effect of Treatment on QIDS

FUTURE DIRECTIONS

Future research should consider stratifying by age and psychosocial factors that impact cortisol levels when selecting the cohort. Additionally, future trials should consider the duration of treatment, along with pharmacokinetic and pharmacodynamic implications. Incorporating the measures of cortisol levels at baseline and post-treatment could also provide further insight.

METHODS

This study is an interim, secondary analysis of an NIH-funded (5R01MH115932-05) double-blind, placebo-controlled clinical trial with treatment crossover, examining the effects of hydrocortisone on the human hippocampus (NCT03896659). Eligible participants were allocated into two groups based on their baseline QIDS-C: the "depressed" arm (QIDS-C 11-20), consisting of individuals diagnosed with Major Depressive Disorder (MDD), and the "healthy control" arm (QIDS-C ≤ 5), individuals with no history of MDD diagnosis. Of the 54 potentially eligible participants, 12 participants were lost to follow up or screen failed. Therefore, a total of 42 participants were included in this study. For each group, participants were randomized by a statistician to receive either hydrocortisone (160 mg tablet) or a matching placebo tablet for three days, followed by MRI and cognitive testing, with a subsequent washout period and treatment cycle repeat. The study was conducted over a total of five visits.

CONCLUSION

Unlike previous studies, treatment with glucocorticoids did not have a therapeutic effect on depressive symptoms. Thus, this study serves to further our understanding around cortisol's nuanced role in depression, as it highlights the complex relationship between the HPA axis and the development of MDD. Additionally, our observations offer insight to the heterogeneity of depressive disorders and challenges we face when targeting the HPA axis to improve symptoms. Furthermore, given the influence of demographic factors, such as age and sex, that we observed in this study, our findings emphasize the importance of an individualized approach to studying and treating MDD.

1. Stetler C, Miller GE. Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. Psychosom Med. 2011;73(2):114-126. doi:10.1097/PSY.0b013e31820ad12b
2. DeBattista C, et al. "Acute Antidepressant Effects of Intravenous Hydrocortisone and CRH in Depressed Patients: A Double-Blind, Placebo-Controlled Study." Am J Psychiatry. 2000;157(8):1334–1337.