Combination Therapy with Hydrocortisone and Fludrocortisone Does Not Improve Symptoms in Chronic Fatigue Syndrome


Study Overview

Objective. To evaluate the efficacy of hydrocortisone and fludrocortisone combination for the symptomatic treatment of chronic fatigue syndrome (CFS).

Design. Randomized, double-blind, placebo-controlled crossover study.

Setting and participants. Consecutive adults presenting to an outpatient general internal medicine clinic at a tertiary care hospital in Belgium. Participants met the 1994 Centers for Disease Control criteria for CFS.

Main outcome measures. Primary outcome was subjective fatigue measured by a visual analog scale (VAS) ranging from 0 to 10 and a fatigue questionnaire. Other outcomes included general well-being (also on a 0 to 10 visual analog scale), a version of the 36-item Short Form (SF-36) survey, and the intensity of anxiety and depression.

Main results. 20 of the 100 patients enrolled dropped out, leaving 80 patients available for analysis. Mean age was 38 years and nearly all patients were women. There was no difference in fatigue between the intervention and control groups. Patients who received hydrocortisone/fludrocortisone combination had similar fatigue scores on the VAS than those who received placebo (6.6 versus 6.7 [mean difference, 0.1 [95% confidence interval (CI), –0.3–0.6]]; \( P = 0.76 \)). Similarly, there were no differences in fatigue as measured by the fatigue questionnaire (7 ± 5 versus 8 ± 5; \( P = 0.69 \)), degree of well-being (4.6 versus 5.0 [mean difference, 0.4 [95% CI, –1.0–0.1]]; \( P = 0.14 \)) or scores on depression, anxiety, or overall health.

Conclusion. Hydrocortisone/fludrocortisone combination therapy is not effective in relieving fatigue or improving overall well-being in patients with CFS.

Commentary

CFS is an important clinical disorder characterized by chronic, debilitating fatigue, somatic symptoms, and abnormal findings on neuropsychological testing [1]. Though CFS is often dismissed by many clinicians as a manifestation of depression, studies suggest that patients with CFS may have mild hypocortisolism with impaired hypothalamic-pituitary-adrenal axis [2]. Early data suggest that treatment with hydrocortisone alone may be effective in relieving some of the symptoms of CFS [3], while fludrocortisone, a mineralocorticoid, has not been shown to be effective for this disorder [4].

The authors found that the hydrocortisone/fludrocortisone combination therapy was no better than placebo. When evaluating a negative clinical trial, several features of the trial should be assessed to ensure that the findings are accurate and reliable. Small sample size, such as the one in this study, can potentially underpower a study and lead to a high rate of false-negative findings. One easy and clinically useful way to assess adequacy of a study’s sample size is to examine the effect size and the 95% CI. In this case, the difference between the active arm and the placebo arm was 0.1 on the VAS for fatigue. More importantly, the 95% CI includes all values from –0.3 to 0.6. By examining the 95% CI, we can assess the potential difference we could have found with a larger sample size. Given that the 95% CIs are narrow and represent essentially no difference between the 2 groups, we can say with confidence that a large study would have been unlikely to find a large effect.

Another interesting feature of this study is the crossover design. There are 2 important advantages and 1 serious disadvantage of such a design for a clinical trial. The first advantage is that it essentially doubles the sample size for the study. By allowing subjects to serve as both cases and controls, the authors were essentially able to have 80 patients in each arm of the trial. Further, by allowing patients to serve as their own controls, statistical precision of the analysis is improved and therefore, the power of the study to find a difference is increased if such a difference exists. Another important advantage of such a design is that it can be helpful in recruitment. Patients can be assured that they will be given the therapy at some point during the study.
which may make them more willing to participate. A serious disadvantage of this design is that it assumes that benefits or toxicity of therapy will be apparent immediately. If this assumption turns out to be incorrect, the study might erroneously conclude that there’s no benefit where there was one. In this study by Blockmans and colleagues, if patients were required to be on hydrocortisone/fludrocortisone therapy for several months for it to be effective, by the time patients responded they would have crossed over to the placebo arm, and their improved symptoms would have been erroneously credited to the placebo. In this study, it is unlikely that this would be a reason for the negative result.

Applications for Clinical Practice
This study lends further evidence that CFS is a complicated condition that is not yet understood. Despite evidence of hypocortisolism, replacing or augmenting steroids with hydrocortisone and fludrocortisone in combination does not appear to be helpful. The search for new therapeutic options for patients with CFS continues.

–Review by Ashish K. Jha, MD

References