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Does continuous subcutaneous hydrocortisone infusion therapy improve vitality in adult patients with Addison's Disease when compared to oral hydrocortisone therapy?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
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ABSTRACT

OBJECTIVE: The objective of this selective systematic review is to determine whether or not continuous subcutaneous hydrocortisone infusion (CSHI) therapy improves vitality in adult patients with Addison's disease when compared to oral hydrocortisone therapy.

STUDY DESIGN: This systematic review used three peer reviewed articles published in English. The articles were a crossover randomized control trial, a double blind placebo controlled clinical trial, and a case series published from 2007 to 2014.

DATA SOURCES: The crossover randomized control trial and the double blind, placebo randomized control trial compared adult patients with Addison's disease vitality scores when taking oral hydrocortisone tablets to continuous subcutaneous hydrocortisone infusion therapy. The case series followed 7 patients with Addison's disease when taking continuous subcutaneous hydrocortisone infusion therapy and measured their vitality scores. The peer reviewed articles were found using PubMed and Google Scholar.

OUTCOMES MEASURED: Vitality, the primary outcome, was measured by the Short Form-36 Health Survey (SF-36).

RESULTS: Data for all three articles was continuous and p-values were reported. The Lovas et al study reported a p-value of <0.05 and concluded that vitality scores are higher in patients with Addison's disease taking CSHI therapy compared to their original therapy. The Gagliardi et al study and the Oksnes et al study report p values >0.05 suggesting that vitality scores comparing CSHI therapy to oral hydrocortisone therapy is not significantly different.

CONCLUSIONS: The data is inconclusive in determining if continuous subcutaneous hydrocortisone therapy improves vitality in patients with Addison's disease compared to oral hydrocortisone therapy.

KEY WORDS: Addison's disease, Continuous Subcutaneous Hydrocortisone Infusion Therapy, Oral Hydrocortisone, and Vitality.

INTRODUCTION

Addison's disease, also known as primary adrenal insufficiency, occurs when there is at least 90% damage to the adrenal glands leading to decreased production and secretion of hormones such as cortisol, aldosterone, and some sex hormones.¹ Due to the diffuse role of adrenal hormones, patients present with constitutional symptoms such as weakness, fatigue, weight loss, and abdominal pain. Patients can also present with decreased sex drive, signs of decreased sex hormone production, and a craving for salt.² The hallmark of the disease is hyperpigmentation in skin folds, pressure points, or in the mouth.³ Patients tend to be irritable and present with psychiatric illnesses, but the cause of this is unknown.³

In the United States, eighty percent of patients with Addison's disease are caused by an autoimmune process.² Addison's disease is rare; out of 1 million people in developed nations, 110 to 144 patients have Addison's disease.¹ In the United States, it was reported that per 1 million Americans, 40 to 60 have Addison's disease.⁴ Although Addison's disease is uncommon, patients can be treated at a primary care office, an endocrinology office, or in the ER if they present with a crisis. Considering the different specialists that attend to their care, national Addison's disease healthcare costs amount to \$2,320 per patient per year.⁵ In addition, to diagnose patients with the disease is about \$1,680 dollars per patient.⁵ Considering the condition is rare, practitioners must have a high index of suspicion to limit unnecessary testing. The number of healthcare visits per year is not recorded, however, according to a Swedish study, patients with Addison's disease have an increase in "all-cause mortality".⁶

Typical treatments for Addison's disease include oral hydrocortisone and sometimes dehydroepiandrosterone (DHEA)⁷. Currently, the gold standard treatment for patients with Addison's disease is oral hydrocortisone tablets.² However, patients with Addison's disease that take oral hydrocortisone therapy have reported decreased quality of life which is theorized to be

due to noncircadian cortisol levels.⁷ In people with normal adrenal function, cortisol levels follow the light cycle and are at the highest waking and then decrease throughout the day reaching the lowest level at midnight.⁸ Cortisol levels trigger other biological clocks of the body, which also stresses the importance of obtaining normal endogenous cortisol levels.⁸ For patients with Addison's disease, oral hydrocortisone therapy is typically 20 to 30 mg divided into three doses.⁷ Even though hydrocortisone is taken three times a day, the current dosing regimen of oral hydrocortisone does not mimic natural cortisol levels of the body.⁸ When cortisol levels are drawn, patients typically show extreme cortisol levels for that particular time of the day.⁷ Continuous subcutaneous hydrocortisone infusion (CSHI) therapy, could theoretically restore cortisol's circadian rhythm and improving vitality, or energy, in patients with Addison's disease. Using two randomized control trials and one case series, this paper compares oral hydrocortisone therapy and continuous subcutaneous hydrocortisone infusion therapy in improving vitality in patients with Addison's disease.

OBJECTIVE

The objective of this selective systematic review is to determine if continuous subcutaneous hydrocortisone infusion therapy (CSHI) improves vitality in adult patients with Addison's disease when compared to oral hydrocortisone therapy.

METHODS

All studies used for this systematic review were researched by the author in English using PubMed and Google Scholar with specific key words such as: "Addison's disease", "Continuous Subcutaneous Hydrocortisone Infusion Therapy", "Oral Hydrocortisone Therapy", "Short Form-36", and "Vitality". Criteria used to select studies was based on topic, patient characteristics, type of study conducted, and outcomes measured. Studies were considered if the subjects were

men and women with Addison’s disease and were over the age of 18. Studies were preferred if the interventions compared were oral hydrocortisone therapy and continuous subcutaneous hydrocortisone infusion therapy. The author searched for randomized control trials and case series only. Articles were selected if they considered patient oriented outcomes (POEMS) that pertained to the clinical question and were published after 2006. Articles were excluded if they did not pertain to the clinical question, did not study the effects of continuous subcutaneous hydrocortisone infusion therapy, and did not study patients’ vitality scores before and after treatment. Articles that measured vitality using the short-form 36 were preferred to establish a control for the systematic review. The articles that fit the inclusion and exclusion criteria are discussed in this select systematic review. Patient characteristics of the articles chosen are discussed in Table 1. Design and outcomes of each study are discussed in the result section of this systematic review.

Table 1 - Demographics & Characteristics of included studies

Study	Type	#Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Oksnes et al (2014) ⁹	Crossover Randomized Control Trial	33	18-70	Pts diagnosed with Addison’s disease aged 18 to 70	(-) DM, CVD, pregnancy, pharmacologic treatment with glucocorticoids or drugs that interfere with cortisol metabolism (antiepileptics, rifampicin, and St. Johns Wart)	2	Continuous Subcutaneous Hydrocortisone Infusion Therapy Compared to Oral Hydrocortisone 5 mg Tablets
Gagliardi et al (2014) ⁸	Randomized Control Trial (Randomized, double blind,	10	38- 62	“Endocrinologist-certified diagnosis of autoimmune Addison’s disease”	<18 years, bilateral adrenalectomy, secondary	0	Continuous Subcutaneous Hydrocortisone

	placebo controlled clinical trial)				adrenal insufficiency, hypopituitarism, type 1 diabetes, celiac disease, pregnancy, disturbed sleep-wake cycle, or current treatment for a major psychiatric disorder		Infusion therapy Compared to Oral Hydrocortisone
Lovas et al (2007) ⁷	Case Series (Open-labelled feasible study)	7	30- 64 years of age	“Biochemically verified Addison’s disease”	None	0	Continuous Subcutaneous Hydrocortisone Infusion Therapy

OUTCOMES MEASURED

The three studies in this select systematic review discussed vitality pertaining to the administration of CSHI therapy. In all three articles, vitality was measured using Short Form-36. Short Form-36, also known as Short Form 36 Health Survey, is a 36-question survey used for medical research.⁸ The survey has eight sections: physical functioning, emotional role functioning, social role functioning, and mental health.⁸ Scores range from 0 to 100; higher scores indicate high function.⁸

RESULTS

Two randomized control trials and one case series are discussed in this systematic review. All studies obtained vitality scores from patients after the administration of CSHI therapy. Data from all three studies were continuous data, so p values and mean change from baseline were reported.

In the randomized crossover study conducted by Oksnes et al. 33 patients with Addison's disease aged 18 to 70 participated in a study comparing CSHI therapy to oral hydrocortisone therapy. Patients were randomly selected to take either continuous subcutaneous hydrocortisone therapy or oral hydrocortisone therapy. All patients involved in the study took both regimens by the completion of the study. Initially, day 0, patients were dose adjusted for both CSHI and oral hydrocortisone therapy. Oral hydrocortisone therapy was weight adjusted using 5 mg oral hydrocortisone tablets, and was taken 3 times a day during the trial. CSHI therapy was given at an infusion rate that was standard for all participants "8:00AM to 2:00 PM, 5 mg/ m²; 2:00-8:00 PM, 0.2 mg/m²*h; 8:00 PM to 2:00 AM 0.05mg/m²*h; and 2:00-8:00 AM, 1.0 mg/m²".⁹ After three to five days, the CSHI therapy was dose adjusted based on salivary serum cortisol levels and serum cortisol levels in the morning.⁹ After dose adjustment, patients had a washout period of at least 1 month. During washout periods, patients would take pre-trial medications for their disease. After the first washout period, patients would either be randomly assigned CSHI therapy or oral hydrocortisone tablets for the first 12 weeks.⁹ Then, patients had a washout period of a minimum of 2 months. After the two months, patients would either take CSHI therapy or oral hydrocortisone therapy, whichever treatment was not administered to them during the first 12-week treatment period. The CSHI therapy was administered by an insulin pump; patients cleaned injection site prior to injection.⁹ Patients changed the infusion gear and hydrocortisone every three days. Two patients were withdrawn from the study by the researchers; one became pregnant during the trial and the other patient would not follow the guidelines set by the researchers.⁹ At each visit, patients completed the Short Form 36.

The observed mean value of vitality scores when taking oral hydrocortisone therapy for 12 weeks was 53.6, whereas, the mean value of vitality scores after 12 weeks of therapy with

CSHI therapy was 58.8.⁹ The predicted mean difference was 4.35 between the oral hydrocortisone therapy and CSHI at 12 weeks of therapy.⁹ Vitality scores in patients after 12 weeks of therapy with CSHI therapy was greater than oral hydrocortisone therapy.⁹ The difference was not significantly different, but vitality scores were higher for CSHI therapy than oral hydrocortisone therapy.

Table 2: The Observed Mean Value in Vitality Scores at 12 Weeks of Treatment

Author	Oral Hydrocortisone	CSHI therapy	Predicted Mean Difference	P for interaction
Oksnes (2014) ⁹	53.6 (44.5, 62.7)	58.8 (49.4, 67.7)	4.53 (-2.1, 11.1)	0.177

In the randomized placebo control trial conducted by Gagliardi et al. ten patients with verifiable Addison's disease participated in a trial of CSHI therapy and oral hydrocortisone therapy. The pharmacy department randomized the patients to treatment groups and also prepared the hydrocortisone and placebo capsules. Oral hydrocortisone therapy was given three times a day and was dose adjusted according to the patient's usual treatment.⁸ The infusion consisted of hydrocortisone sodium succinate diluted in water to a concentration of 50 mg/mL, and the placebo infusion was normal saline.⁸ By the completion of the study, all patients had taken both treatments, CSHI therapy and oral hydrocortisone therapy. The treatment timeframe was 4 weeks followed by a two-week wash-out period. During treatment period, patients either received oral placebo with CSHI therapy or patients had oral hydrocortisone therapy with

subcutaneous placebo. No patients withdrew while the study was being performed. The Short Form-36 was completed prior to starting treatment and at the end of treatment.

The authors reported a mean change from baseline to compare the vitality scores of oral hydrocortisone therapy and CSHI therapy. There was an average increase of 10 on vitality scores when comparing CSHI vitality scores from baseline to the end of treatment.⁸ There was a decrease in vitality scores by 2 in the oral hydrocortisone treatment group when comparing baseline scores to end of treatment.⁸ The exact p-value was not reported, but the authors noted that the p-value for vitality scores was greater than 0.05 and was not considered statistically significant.⁸ However, vitality scores of CSHI therapy trend higher than oral hydrocortisone levels overall.

Table 3: The Mean Change in Vitality Scores Before and After Treatment

Author	Oral Hydrocortisone	CSHI therapy	Mean Difference	p-value
Gagliardi (2014) ⁸	-2	10	12	>0.05

In the case series conducted by Lovas et al. seven patients with Addison's disease participated in a study to determine the efficacy of CSHI and patients' satisfaction with treatment. Initially, one patient was in a three-month trial to determine the dosage of hydrocortisone for the infusion therapy. The second patient was used to determine the affects of the HTA axis by measuring cortisol in serum and saliva.⁷ Then, five patients with Addison's disease participated in an open-labeled two-week trial of using CSHI therapy for their Addison's disease treatment. If patients were satisfied with the treatment, they had the option to extend their

trial by 10 weeks.⁷ The CSHI therapy was given by using an insulin pump and was inserted into the abdominal wall subcutaneously. The insulin pump was changed every three days as well as the 50mg/mL solution of hydrocortisone therapy.⁷ Each patients cortisol therapy was measured by salivary cortisol levels on two consecutive days at the beginning of the two weeks and two consecutive days at the end of the two weeks.⁷ If patients decided to continue the trial past the two weeks, cortisol levels were measured on an as needed basis. Patients completed the Short Form-36 at each visit.

The changes from baseline were analyzed by using a paired t test and clinical significance was considered <0.05 .⁷ If patients chose not to participate after 2 weeks, their data was also used for statistical analysis. Only one participant decided to stop treatment after the two weeks.⁷ The patient was satisfied with the treatment, but decided to revert back to their original treatment. At the conclusion of the experiment, patients were satisfied overall with the CSHI therapy. Two patients decided to be treated with CSHI treatment long term for their Addison's disease.⁷ Patients vitality scores were significantly different when comparing scores before and after CSHI therapy. There was an average increase in CSHI therapy vitality scores by 23 from baseline to the end of treatment.⁷ This value is large considering the type of study. The researchers did not report the exact p-value, but noted the p value for vitality scores was <0.05 .⁷

Table 4: Baseline and After CSHI therapy Mean Vitality Scores

Author	Baseline	End of Treatment	Mean Difference	P value
Lovas (2007) ⁷	30	53	23	<0.05

DISCUSSION

Although Addison's disease is rare, patients report decreased quality of life with the gold standard therapy, oral hydrocortisone tablets.⁷ The current guideline for treatment is oral hydrocortisone tablets 15 to 25 mg divided into two to three doses a day.¹⁰ Patients are instructed to take the morning dose as soon as they wake for the day. The second dose should be either with lunch or two hours after lunch. Lastly, the third dose should be administered no later than 4 to 6 PM.¹⁰ The morning dose is the highest, and the evening dose is the lowest.¹⁰ There is currently no black box warning for oral hydrocortisone therapy. Oral hydrocortisone is currently used in almost all medical specialties for various diseases. Patients with normal adrenal function should be advised about potential hydrocortisone withdrawal. Patients may experience GI upset, dizziness, mood changes, or muscle weakness.¹⁰ Hydrocortisone withdrawal can be avoided with a slow taper to allow the adrenal glands to resume its normal function.

Currently, the FDA notes that IM and IV preparations of hydrocortisone can be used for treatment of various conditions, if oral hydrocortisone therapy is not possible.¹¹ However, the FDA does not mention approval of the use of continuous subcutaneous hydrocortisone infusion therapy in patients with Addison's disease. Numerous studies have explored the benefits of subcutaneous hydrocortisone therapy in the treatment of Addison's disease and in emergency adrenal crisis situations.

The three studies discussed in this systematic review study the use of CSHI therapy as an alternative treatment for patients with Addison's disease. All articles, except for the study conducted by Oksnes et al, had few participants in their studies which may have decreased the validity of the results. The case series, study conducted by Lovas et al, only looked at vitality scores of patients who were using CSHI therapy and did not compare vitality scores of oral

hydrocortisone therapy. The case series compared vitality scores before and after treatment, but most patients were not taking oral hydrocortisone therapy prior to CSHI therapy. Patients were also aware of the treatment they were receiving in the case series. The Gagliardi et al study had a short wash-out period of 2 weeks whereas the study conducted by Oksnes et al had a washout period of at least 1 month. Although these studies had limitations, they still shed light on patients' vitality while using CSHI therapy.

CONCLUSION

The data is inconclusive in determining whether CSHI therapy improves vitality scores in patients with Addison's disease when compared to vitality scores of patients using oral hydrocortisone therapy. The studies conducted by Gagliardi et al and Oksnes et al concluded that the mean change in vitality scores were not significantly different when comparing CSHI therapy and oral hydrocortisone therapy. Even though the mean changes were not significantly different, both studies showed higher vitality scores in patients that were taking CSHI therapy when compared to oral hydrocortisone therapy. Although the study performed by Lovas et al did not compare CSHI to oral hydrocortisone therapy, the study concluded that the vitality scores were significantly different when comparing the patients' traditional therapy to CSHI therapy. It seems that CSHI therapy improves vitality somewhat, but the data is conflicting.

More studies need to be done comparing vitality scores of patients taking CSHI therapy and oral hydrocortisone therapy. The gold standard therapy, oral hydrocortisone tablets, does not mimic the body's normal circadian rhythm of cortisol which may greatly impact patient's vitality. Studies with less patient exclusion criteria should be considered, so more patients are able to participate in future studies. With very few treatments available for patients with Addison's disease, another alternative therapy would greatly impact their lives.

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