

## CLINICAL RESEARCH

## Clinical Trials

# Effectiveness of Fludrocortisone and Salt in Preventing Syncope Recurrence in Children

## A Double-Blind, Placebo-Controlled, Randomized Trial

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<b>OBJECTIVES</b>	We sought to evaluate the effectiveness of salt and fludrocortisone versus placebo in the prevention of syncope recurrence in children.
<b>BACKGROUND</b>	Intravascular volume expansion with fludrocortisone and salt has been reported to be effective in the treatment of syncope in children. However, no pediatric placebo-controlled data are available on the effectiveness of this mode of therapy.
<b>METHODS</b>	Thirty-three children with syncope or severe presyncope were randomized in a double-blinded fashion to receive either fludrocortisone 0.1 mg/day and salt 1 g/day or placebo two capsules per day for one year. All children had a positive tilt test before enrollment.
<b>RESULTS</b>	Thirty-two children (20 female) had follow-up. Their age was (mean $\pm$ SD) $13.9 \pm 2.5$ years. The number of syncopal episodes before therapy was $4.4 \pm 4.8$ . Therapy was continued for $176 \pm 117$ days, and follow-up including time after discontinuation of medications was $1.2 \pm 0.8$ years. The demographics were similar in the 18 children treated with fludrocortisone and salt compared with the 14 children on placebo. Data for up to one year of randomization were included in analyses. Symptoms recurred in 10 of 18 children on fludrocortisone and salt and in 5 of 14 children on placebo ( $p < 0.04$ ). Children on placebo had no symptoms until they discontinued their study medications.
<b>CONCLUSIONS</b>	These data, coupled with the reported comparable effect of many medications used in the treatment of syncope, raise the potential of a significant placebo effect with pharmacologic therapy. (J Am Coll Cardiol 2005;45:484–8) © 2005 by the American College of Cardiology Foundation

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Neurocardiogenic syncope is a common and recurrent phenomenon in children, with a peak incidence in the teenage years (1). The diagnosis is established by history, often confirmed by tilt testing (2), and therapy is aimed at preventing or reducing the recurrence of syncope. Initial reports of effective therapeutic interventions include fludrocortisone and salt (3), fludrocortisone alone (4), beta-adrenergic blocking agents (3–5), and pacemakers (6). However, all of these studies used an open-label design. Fludrocortisone and salt are commonly used in the treatment of syncope in children. To our knowledge, there are no pediatric studies that have compared the efficacy of this combination with placebo. Thus, we designed a prospective, randomized, double-blinded, and placebo-controlled study to compare the effectiveness of fludrocortisone and salt with placebo. Our hypothesis was that fludrocortisone and salt would be more effective than placebo in the prevention of syncope recurrence in children.

## METHODS

Children under the age of 18 years were eligible for the study if they presented between December 1995 and January 1999. Children with  $\geq 1$  episode of syncope or severe presyncope were eligible. All children had a normal heart by examination, electrocardiography, and echocardiography. During the study period, all children underwent an active tilt test. No drugs were used during the tilt test protocol. No child had had any previous therapy for syncope. A positive tilt test was defined as the induction of symptoms associated with a decrease in systolic blood pressure (BP) by more than 20 mm Hg and/or heart rate increase by more than 25 beats/min and/or significant bradycardia. We utilized a previously reported active tilt test protocol where the child is asked to stand for 20 min after 1 h in the supine position (7). The institutional review boards of the University of Tennessee and LeBonheur Children's Medical Center approved our study protocol. An informed parental consent and the child's assent were obtained in every patient.

All patients and parents were educated about the mechanisms of syncope and factors that may worsen the child's symptoms. The children were instructed to avoid prolonged standing without motion and to avoid stressful situations that previously resulted in syncope as well as increase their intake of fluids.

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**Abbreviations and Acronyms**

BP = blood pressure  
 NaCl = sodium chloride

Therapy was limited to one year. Our patients were randomized to receive either: 1) one fludrocortisone acetate 0.1-mg tablet and a sodium chloride (NaCl) 1-g tablet daily, or 2) two placebo capsules daily. None of the children were treated previously for syncope; therefore, they were not aware of the shape and taste of the active drugs. All patients were told that the medications given were either meant to taste salty (in the fludrocortisone and salt group) or that the medications were coated to avoid detection by their taste (placebo group). Initially, the fludrocortisone acetate (Florinef) used in the study was donated by the manufacturer (Apothecicon, Princeton, New Jersey). After the first year of the study, medications were purchased through an institutional grant. Children randomized to the treatment arm received 100 tablets of NaCl and 100 tablets of fludrocortisone every three months. Those randomized to the placebo group received two forms of placebo tablets or capsules (100 each). Patients were asked to return the unused portion of their medications as a means to gauge compliance with therapy. It was assumed that those who did not return any medication consumed the total number of pills.

Our primary outcome variable was recurrence of syncope. Presyncopal symptoms were not considered failure of therapy if they were not associated with frank syncope in children who previously had syncope. However, recurrent presyncope was considered a failure of therapy in children who previously had only presyncope.

Follow-up in the cardiology clinic was at 1, 3, 6, 9, and 12 months of therapy and 1 to 3 months after therapy was discontinued. We asked children and parents to report any syncopal events during or after therapy. Side effects of therapy were also assessed during each clinic visit, and a diary was provided to record any syncopal episodes. For the children who did not return for follow-up visits, data were obtained using a written questionnaire that was mailed to the last known address and/or a telephone interview. In the case of recurrent syncope or intolerable side effects, the patients were given the option of continuing the same medications or dropping out of the study and receiving an open-label therapy.

**Statistical analysis.** Two-sample Student *t* test was used to compare means of continuous variables between the two groups, and the chi-square test was used to assess proportions between the two groups. The probability of being syncope-free was estimated using the Kaplan-Meier method. Survival curves among groups were compared by the Wilcoxon test. Intention-to-treat analysis was used. A *p* value <0.05 was considered statistically significant. Data are displayed as mean values ± 1 SD. All analyses were

**Table 1.** Demographics of the Treatment Groups

	Salt/		p Value
	Fludrocortisone	Placebo	
Age at first symptom (yrs)	12.2 ± 2.9	13.0 ± 3.1	0.4
Age at tilt test (yrs)	13.7 ± 2.7	14.0 ± 2.4	0.7
Syncopal episodes	4.1 ± 3.6	5.1 ± 6.0	0.6
Weight (kg)	54.3 ± 15.9	52.6 ± 15.1	0.7
Height (cm)	165 ± 16	158 ± 8	0.1
Duration of therapy (days)	189 ± 108	159 ± 130	0.4
Duration of follow-up (yrs)	1.3 ± 1.1	1.2 ± 0.3	0.5
Total pills consumed	381 ± 209	308 ± 217	0.3
Race (African American/ Caucasian)	7/11	8/6	0.6
Male/female ratio	8/10	4/10	0.3

performed using SAS version 8 (SAS Institute, Cary, North Carolina).

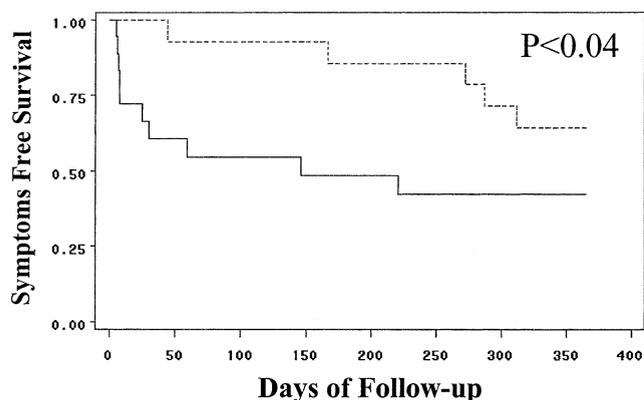
**RESULTS**

Thirty-three children and parents consented to participate in the study. There were 20 females; the racial mix was 18 Caucasian and 15 African American. The number of syncopal/presyncopal episodes before tilt testing was 4.4 ± 4.8 (range 1 to 20), and the age at first symptoms was 12.6 ± 3.0 years (range 4.4 to 16.8 years). Their age at the time of tilt test was 13.9 ± 2.5 years (range 9.0 to 17.2 years). The duration of therapy for the entire group was 176 ± 117 days (range 13 to 407 days). Follow-up from the initial clinic visit to the last contact with the patients was 1.2 ± 0.8 years (range 0.1 to 5 years). Overall, 18 patients were randomized to receive salt and fludrocortisone and 15 were randomized to receive placebo. One of the patients on placebo was lost to follow-up after randomization and was not included in the analyses.

Overall follow-up was available on 32 of 33 children (97%). There were no significant differences between the two treatment groups with regard to: age at first symptoms, age at tilt test, number of syncopal episodes before tilt test, weight, height, male to female ratio, race, duration of therapy and follow-up, or in the number of pills of either salt and fludrocortisone or placebo consumed while on the study (Table 1).

Presyncope was the presenting symptom in five children; four of them were in the salt and fludrocortisone group. The children with presyncope were indistinguishable from those with syncope for age at presentation or age at tilt test, weight, and height from the larger group. Two of the four children with presyncope on salt and fludrocortisone had recurrence of their symptoms while on therapy. The one patient with presyncope on placebo reported no recurrence of symptoms while on therapy.

The intention was to treat all children for one year. However, there was a wide range of treatment duration and follow-up. We used a one-year cutoff from the start of therapy as the time for comparison between the two groups. If a patient had a follow-up shorter than one year, then the events during that time were included in the analysis.



**Figure 1.** Symptom-free survival. Dashed line = placebo; solid line = salt and fludrocortisone.

However, for patients with a follow-up longer than one year, only the events during the first year were considered for analysis. The Kaplan-Meier curve for symptom-free survival is depicted in Figure 1. Symptoms (syncope: 8; presyncope: 2) were reported in 10 children assigned to the salt and fludrocortisone group and 5 children (syncope: 4; presyncope: 1) assigned to the placebo group ( $p < 0.04$ ). All 5 of the placebo group children reported symptoms only after their placebo was discontinued, whereas all 10 of the salt and fludrocortisone group children who reported symptoms did so during active therapy. Symptoms recurred in two of the children in the salt and fludrocortisone group after therapy was discontinued; both patients had recurrence while on therapy.

Side effects on therapy were minimal. No BP abnormalities were noted in either group. One patient on placebo had diarrhea two weeks into the study, which was attributed to the treatment, and the patient chose to terminate participation in the study. Another patient on placebo complained of headaches. In the group of children on salt and fludrocortisone, one complained of palpitations, nausea, dizziness, chest pain, and another of swelling of his arms and legs. Two patients also complained of fatigue while on salt and fludrocortisone.

## DISCUSSION

This study demonstrates, contrary to our hypothesis, for the first time in a randomized, double-blinded, placebo-controlled fashion that 1 g of salt and 0.1 mg of fludrocortisone per day plus counseling is ineffective in preventing syncope or presyncope recurrence in children. Overall, 56% of the children in the salt and fludrocortisone and counseling group had recurrence of their symptoms while on medication. Furthermore, because these results are nearly identical to those previously obtained using counseling alone as the primary mode of therapy (8), it may be inferred that fludrocortisone and salt plus counseling is no better than counseling alone. For the entire cohort, only 53% had no recurrence of their symptoms after a positive tilt test. These

data are similar to those reported for the rate of recurrence in open-label studies in children (3,4). In the study by Scott et al. (4), there was no difference between fludrocortisone up to 0.2 mg per day and atenolol up to a dose of 100 mg per day in preventing the recurrence of syncope. The recurrence rate for their entire group using the standard we used in our study, that is, any recurrence, was 52% (30 of 58 children). Moreover, the recurrence rate reported herein is in agreement with the recurrence rate reported in our previous open-labeled study (52%) (9). The rate of recurrence reported in the current study is also similar to the study in children by Balaji et al. (3) (43%). In addition, randomized placebo-controlled trials in adults have produced similar results. For example, Madrid et al. (9) randomized patients with syncope regardless of the tilt test result to placebo versus atenolol and found no significant difference in the recurrence rate between groups. The initial studies in adults comparing pacemakers with pharmacologic therapy for cardioinhibitory syncope showed pacemakers to be more effective than medication (6). However, when patients with a pacemaker implanted were randomized to either placebo (inactive pacemaker) or active pacing therapy, there was no difference in the rate of recurrence between the groups (10). The syncope recurrence rate was 42% for the placebo pacemaker group versus 33% for the active pacing group, with a recurrence rate after 6 months of follow-up of 38% for the entire 100-patient cohort.

All our patients received counseling about syncope. Thus, it was expected that any responses associated with the education about syncope would have been similar in both groups. Importantly, it has been shown that counseling alone is not a very effective treatment for neurally mediated syncope, because it provides relief of symptoms in only 35% of patients (8). In addition, the placebo-counseling group had similar medication treatment as the fludrocortisone and salt-counseling group except for the use of an active pharmacologic agent. Thus, outcomes in the placebo group need to be attributed not only to the effect of counseling but also to the effect of a placebo.

The placebo effect had been attributed to manipulation of the patient's mechanisms of coping with illnesses and responding to medications or interventions with relief of symptoms. In an excellent review of the placebo effect, Stewart-Williams (11) discusses the theories put forth to explain the placebo effect. The results obtained in our patients fit the expectancy theory, which espouses the notion that with the explanation given to them regarding the nature of their illness a medication given to them would produce the desired effect. This was starkly obvious in our placebo group patients who were symptom-free while on therapy. In the classic conditioning theory, an event associated with an unrelated stimulus creates a positive response and an improvement in symptoms. The attention received by the children during tilt testing, including intravenous access, tilt, and provoking their symptoms, would create an association with previous events or visits to physicians for

other illnesses. These visits may have been associated with a positive response with relief of their symptoms. As a result, they perceive that all the work-up leading to their diagnosis and therapy would have to result in a similar improvement in their symptoms, hence it did.

Stewart-Williams (11) also discussed the emotional change theory. This theory proposes that a reduction in the anxiety experienced by the children and their family regarding syncope would lead to relief of symptoms. Thus, the understanding that syncope is a non-life-threatening condition would alleviate the child's anxiety and result in a better control of symptoms. This phenomenon may have also been operative in our patients with syncope. The schematic processing mechanism of the placebo effect leads to the perception of less severe symptoms after an intervention, even though there was no obvious change. This mechanism may have been operative in our presyncope patients who may have perceived an improvement in their symptoms while on therapy.

It is believed that salt and fludrocortisone prevent syncope recurrence by blunting the physiologic responses to the upright position. Because of gravity, the upright position reduces venous return, and thus, decreases cardiac filling and output. Syncope is a result of the failure of the compensatory mechanisms (including an increase in circulating catecholamines and peripheral vasoconstriction). Fludrocortisone and salt expand the intravascular volume and may limit the effects of gravity on venous return. The placebo effect is in part related to the patient's expectation of the medication, conditioning on medical intervention, relief of anxiety by the use of a medication, as well as, in part, to spontaneous resolution of symptoms. Our data suggest that the mechanisms that create the placebo effect may play a role in modifying the autonomic reflexes that lead to the syncopal event.

The dose of fludrocortisone used in this study was the standard dose used in adults and children. It has been shown to be safe in large studies (3,4), and we have demonstrated that it is associated with minimal electrolyte abnormalities (12). Thus, we did not obtain any blood tests on our patients. Somatic complaints such as fatigue, chest pain, and nausea were reported more in children on salt and fludrocortisone. Overall, seven of the salt and fludrocortisone group children had reported some complaints compared with only two in the placebo group.

Limitations of the study include sample size, duration of therapy, and dosage of active agent. Despite these limitations, we have demonstrated a very significant placebo effect. The observations made in our study and by other investigators raise the dilemma of determining the best therapy for these patients. Our patients on placebo fared better than those on active therapy. This was an interesting and unexpected outcome. The question must be asked: "How can an inactive agent produce a better result than an active agent?" The previously mentioned limitations may have been operative in producing this result. In addition, the natural fluctuations and frequency of symptoms could have

affected outcome. Finally, there are a number of published reports that address the issue of the character of the tablet in creating the placebo effect (13). In our study, the active agents were mere white tablets, whereas the placebos were a green capsule and an orange capsule. These capsules may have been perceived as a more effective medication. Considering the results reported herein, our understanding of the mechanism of syncope may need revision. The autonomic contribution to the syncopal episode may be consistent from patient to patient. However, the trigger to the autonomic response is probably quite variable. Whether psychological or yet to be defined factors that trigger the autonomic response are important in the pathophysiology of syncope is unknown.

## CONCLUSIONS

Because others and we have shown a significant placebo effect with either pharmacologic or pacemaker intervention in the treatment of autonomic mediated syncope, perhaps further investigation should focus on delineating the triggering mechanisms of these troublesome events. If these mechanisms can be defined, a more rational and possibly more effective treatment plan can be devised.

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