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Amiloride vs hydrochlorthiazide therapy in children with nephrotic syndrome: A clinical trial

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Abstract

Background and Objective: To assess the effectiveness and safety of oral amiloride for the treatment of edema in pediatric patients with idiopathic nephrotic syndrome.

Methods: A randomized trial of amiloride vs hydrochlorthiazide was done in 34 patients. The mean age was 4.3±0.7 years old. After a 2 week washout of diuretic therapy, nephrotic children with edema were randomized into two groups receiving amiloride vs hydrochlorthiazide. The effect of diuretics was assessed by the amount of weight reduction and the measurement of urinary fractional excretion of sodium during the first three days of diuretic therapy. The primary end point was the decrease in body weight.

Results: Of 34 patients enrolled for this trial, 17 patients were in amiloride group and 17 patients in hydrochlorthiazide group. The mean weight loss during the first three days of diuretic therapy was 1.3±0.65 kg in amiloride group and 1.19±0.4 kg in hydrochlorthiazide group (PV=0.55). The mean of maximum urinary fractional excretion of sodium during the first three days of diuretic therapy was 2.1±0.65% in amiloride group and 1.8±1% in hydrochlorthiazide group.

Conclusion: There was not any difference between amiloride and hydrochlorthiazide medications in reducing weight and increasing urinary fractional excretion of sodium in children with nephrotic syndrome.

Keywords: Fatty Liver, Obesity, Children

Introduction

Edema is the main presentation of nephrotic syndrome in children. Two mechanisms are considered as the cause of edema in these patients: Decreased oncotic pressure in the vessels and primary sodium and water reabsorption in renal tubules especially collecting ducts. These mechanisms are usually recognized as under filling and overfilling theories. In under filling theory hypoalbuminemia and thereafter hypovolemia leads to secondary sodium and water retention in kidneys. This mechanism is mainly seen in children with minimal change disease. According to overfilling theory, edema is formed due to primary sodium avidity in kidneys (1,2). This mechanism is also seen in most adult and some children with nephrotic syndrome.

These two different mechanisms result in different diuretic therapy in patients with nephrotic syndrome. To our knowledge, there is not any clinical trial having compared various diuretic therapies in children with nephrotic syndrome or any trial having compared amiloride as the main diuretic affecting collecting duct with other diuretics. This study was designed to compare the effectiveness and safety of amiloride over hydrochlorthiazide in nephrotic children.

Methods

After gaining approval of ethical group, this randomized trial was performed at Ali-Asghar Children Hospital. Patients with nephrotic syndrome aged less than 18 years old with stage 3-4 edema were enrolled in this study from January

2013. Inclusion criteria were children with idiopathic nephrotic syndrome and edema stage 3-4. Patients were excluded from the study if prednisolone and other immunosuppressive medications were started concurrently or patients had secondary form of nephrotic syndrome, renal failure, mild edema or any infection. The protocol was reviewed and approved by Iran University of medical Sciences.

The primary aims of this study were to assess the hypothesis of superiority of amiloride over hydrochlorthiazide in reducing edema in children with nephrotic syndrome and to compare the safety and tolerability of amiloride with hydrochlorthiazide. Secondary objectives were to compare amiloride with hydrochlorthiazide regarding the amount of urine sodium concentration measured by fractional excretion of sodium.

This was a randomized study. After a 2-week diuretic washout, nephrotic children were randomized to two groups: amiloride group (0.5 mg/kg/day once a day), and hydrochlorthiazide group (2 mg/kg/day once a day). During the treatment period, patients were weighted daily. Urine sodium creatinine and serum sodium, and creatinine concentration were measured daily for three consecutive days.

Results

Thirty four patients were randomized into two groups in this study. The demographic characteristics of the patients in these two groups were similar (Table1).

The mean weight loss during the first three days of diuretic therapy was 1.3±0.65 kg in amiloride group and 1.19±0.4 kg in hydrochlorthiazide group. The weight reduction was not different significantly between these two groups (Pv=0.55).

We also compared the maximum urinary fractional excretion of sodium during the first three days of diuretic therapy between amiloride and hydrochlorthiazide groups. The mean of this parameter was 2.1±0.65% in amiloride group and 1.8±1% in hydrochlorthiazide group (Pv=0.6).

Discussion

There are different mechanisms for edema formation in nephrotic syndrome. One of these mechanisms is primary increased renal reabsorption of NaCl in cortical collecting duct. Experimental studies have shown that the urine of nephrotic patients activates ENaC in cortical collecting duct. This activity is associated with serine activity in urine of these patients. The dominant serine protease in urine of nephrotic patients is plasmin which is produced during conversion of filtrated plasminogen by urokinase type plasminogen activator (3). Plasmin increases the activity of amiloride sensitive ENaC and leads to sodium retention. It has been shown that amiloride therapy in nephrotic rats increases urinary sodium concentration and restores sodium balance (4). In addition to this effect of amiloride, this drug can inhibit urokinase type plasminogen activator and, therefore, inhibits plasmin production in urine.

Descheenes et al reported 13 children with nephrotic syndrome who received amiloride or combination of amiloride and furosemide. They showed that the combination of amiloride and furosemide is superior to furosemide alone in the control of edema of these patients (5).

To our knowledge, there is not any clinical study in which amiloride was used as the first line diuretic therapy for edema in nephrotic syndrome. This study is the first randomized trial in children regarding the use of amiloride in the treatment of edema in nephrotic patients. We showed that there was not any difference between the effectiveness of amiloride and hydrochlorthiazide in reduction of edema in children with nephrotic syndrome. Our study, however, has some limitations. The mean age of our patients was low and most patients had minimal change disease. Thus it appears that the probable mechanism of edema formation in our patients was hypovolemia not primary avidity of kidneys for sodium reabsorption. We think if our trial was done in older children with non-minimal change disease, possibly, amiloride would be more effective than other diuretics in edema control.

Conclusion

We found that amiloride as the first diuretic therapy has effects as we as hydrochlorthiazide in symptomatic treatment of edema.

Conflicts of interest: None declared.

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