

## Clinical Article

# The Effect of Albumin and Furosemide Therapy on Hemostatic Parameters in Nephrotic Children

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## Abstract

It has been speculated that hyperoncotic salt-poor albumin infusions with furosemide increase the tendency for thrombosis in nephrotic syndrome. In this study, 12 children with minimal change in nephrotic syndrome were treated with 20% salt-poor human albumin and furosemide. They were evaluated before, two-hours and 24-hours after therapy. Lipoprotein (a), protein C and S, factor VIII, von Willebrand factor, prothrombin time (PT), partial thromboplastin time, fibronectin, antithrombin III (AT III),  $\alpha_2$  macroglobulin ( $\alpha_2$ MG), fibrinogen,  $\alpha_1$  antitrypsin ( $\alpha_1$  AT) were measured. The decreases of AT III and  $\alpha_2$ MG during the second hour, and the decrease of fibrinogen the following day were statistically significant ( $p < 0.05$ ). Fractional excretion of these parameters were statistically insignificant before, two-hours, and 24-hours after albumin and furosemide therapy ( $p > 0.05$ ). In conclusion, a moderate decrease of AT III and  $\alpha_2$ MG with normalization during the 24<sup>th</sup> hour were the recorded significant hemostatic parameters. *Int Pediatr.* 2001;16(4):235-237.

*Key words:* nephrotic syndrome, albumin, furosemide, hemostasis

## Introduction

Thromboembolic events remain the most threatening complications of nephrotic syndrome (NS) in children. A number of anomalies of hemostasis, coagulation and fibrinolysis, have been described in NS.<sup>1,2</sup> As a result of these studies NS should be considered as a model of multifactorial thrombogenic situations. Also, the use of several types of therapeutic agents, mainly corticosteroids, increases the procoagulant activities, and powerful diuretics increases hemoconcentration and blood viscosity.<sup>2</sup>

Although albumin and diuretic therapy has been used only when indicated in nephrotic children, no report has been found about the effect of this therapy on the hypocoagulable and/or hyperfibrinolytic states of NS. Here we report the effect of albumin and furosemide therapy on some hemostatic factors in NS.

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## Patients and Methods

Twelve children with NS (5 girls, 7 boys) were studied ranging in age from 2 to 11 (mean  $7.31 \pm 2.12$ ) years. The diagnosis was minimal change NS according to the clinical findings, steroid response pattern and follow up. They were all severely edematous with proteinuria of  $156.30 \pm 100.60$  mg/m<sup>2</sup>/h (min. 42.20, max 350) and creatinine clearance of  $117.45 \pm 27.36$  ml/min/m<sup>2</sup> (min 85.90, max 164.20).

Body weight (kg), pretibial edema (- / + + + +), abdominal circumference, heart rate (/min), blood pressure (mmHg) were recorded and routine blood chemistry, whole blood count, urine chemistry, Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT), Factor VIII (F VIII) activity, von Willebrand Factor (vWF), Fibrinogen, Antithrombin III (AT III), Protein C, Protein S,  $\alpha_1$  Antitrypsin ( $\alpha_1$  AT),  $\alpha_2$  Macroglobulin ( $\alpha_2$  MG), lipoprotein (a) (Lp(a)) and fibronectin levels were measured in plasma and urine before, 2 hours and 24 hours after albumin and furosemide therapy.

During the study 0.5 g/kg, 20% salt-poor human albumin solution was infused over a one-hour period. Later, 2 mg/kg furosemide was given by IV route. Statistical analysis was performed by Wilcoxon test.

## Results

Results are presented as median and range in Table 1 and all the statistically significant results, recorded before, two-hours and 24-hours after albumin and furosemide therapy were shown for each patient on a separate graphic for each variant. Any complications were not recorded during or after therapy.

PT, aPTT, F VIII, vWF, Protein C, Protein S, Lp (a),  $\alpha_1$ AT and fibronectin measurements did not show any statistical significant difference before, two-hours and 24-hours after albumin and furosemide therapy (Table 1). Fibrinogen showed a significant decrease during the 24<sup>th</sup> hour (Fig. 1), ( $p < 0.015$ ), AT III and  $\alpha_2$  MG decreased significantly during the second hour of the therapy (Fig. 2 and 3), ( $p < 0.05$ ).

Fractional excretion of these parameters calculated from spot urine samples during therapy did not show any significant difference.

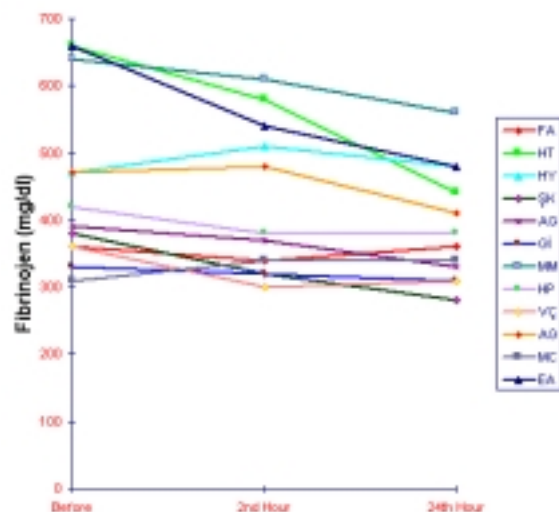


Fig. 1 - Fibrinogen levels of nephrotic children before and after albumin and furosemide therapy.

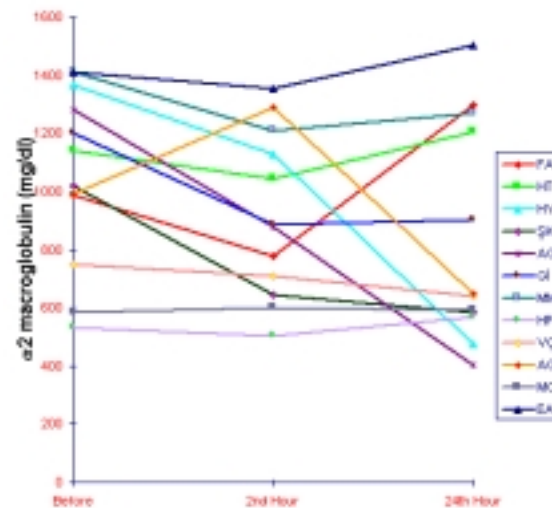


Fig. 3 -  $\alpha_2$  macroglobulin levels of nephrotic children before and after albumin and furosemide therapy.

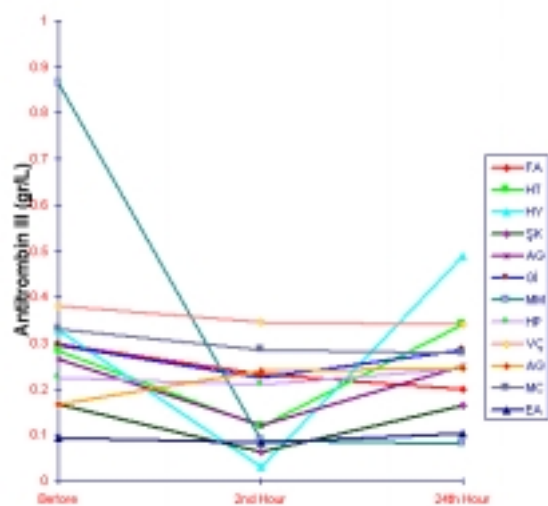


Fig. 2 - Antithrombin III levels of nephrotic children before and after albumin and furosemide therapy.

### Discussion

NS is a consequence of both altered glomerular permselectivity, allowing plasma proteins of intermediate size to escape into the urine, and the alteration in synthesis and catabolism of plasma proteins, resulting in an increased plasma concentration of many proteins of high molecular weight that are too large to be lost in the urine.<sup>1,2</sup> Total plasma protein concentration remain well preserved in the nephrotic syndrome despite significant urinary loss of some proteins and the possible increased levels of other plasma proteins could play a homeostatic role.<sup>2,3</sup> Hyper-

coagulability can be a transient feature appearing during certain phases of conditions predisposing to thrombosis.<sup>4</sup>

It has been reported that a group of proteins secreted specifically by the liver including fibrinogen, albumin, transferrin and apo A-1 was increased in the nephrotic syndrome and correlated with hypoalbuminemia.<sup>2,3</sup> Plasma fibrinogen concentration is increased and increased rate of synthesis of this protein contributes to its increased plasma concentration in nephrotic patients. Also the increased albumin synthesis was found to be associated with an increase in synthesis of a specific and coordinated group of proteins, among which was fibrinogen and speculated that plasma fibrinogen may be a better marker for albumin synthesis than proteinuria.<sup>3</sup>

Plasmatic reduction of the two inhibitors AT III and  $\alpha_1$  AT has also been reported in NS.<sup>1,2</sup>  $\alpha_2$  MG has a high molecular weight and increased concentration as a consequence of accelerated synthesis and hemoconcentration.<sup>2,3</sup> The negative relationship between AT III and  $\alpha_2$  MG is usually explained by the compensation by the increased concentration of the later. But there is no report about the relationship between albumin, furosemide therapy and these parameters.

The recorded decreases of AT III and  $\alpha_2$  MG levels during albumin and furosemide therapy in our series are not the results of increased fractional excretion. This decrease could be explained by early plasma volume expansion caused by albumin infusion.

It has also been shown that albumin infusions significantly reduced  $\alpha_2$  MG levels in the Nagase analbuminemic rats.<sup>3</sup>

## Effect of Albumin and Furosemide Therapy

Table 1 - Results of nephrotic children before and after albumin and furosemide therapy

	PT (sec)	PTT (sec)	FVIII (u/ml)	vWF (u/ml)	Fibrinogen (mg/ml)	ATIII (u/ml)	Prt C (u/ml)	Prt S (u/ml)	$\alpha_2$ AT (mg/dl)	$\alpha_2$ MG (mg/dl)	Lp(a) (mg/dl)	Fibronectin (g/l)
Before	15 (13-16)	24 (20-28)	108 (94-134)	96 (84-134)	405 (310-660)	0.288 (0.094-0.864)	81 (64-94)	80 (66-94)	76.6 (32.1-142.0)	1078.5 (532.8-1412)	46.1 (10.3-144.8)	0.444 (0.265-1.384)
2 <sup>nd</sup> hour	15 (14-18)	26 (20-30)	109 (96-128)	96 (86-126)	375 (300-610)	0.164 (0.031-0.344)	79 (64-96)	80 (62-94)	67.45 (40.8-154.0)	884.2 (504.6-1356)	60.2 (10.3-222.2)	0.481 (0.326-1.206)
24 <sup>th</sup> hour	14 (12-16)	26 (24-30)	110 (98-118)	98 (84-118)	370 (280-560)	0.247 (0.080-0.778)	79 (68-92)	88 (68-94)	124.2 (43.4-219.3)	645.5 (401.3-1502)	10.3 (10.3-159)	0.435 (0.246-2.048)

Any serious change leading to thrombotic tendency during albumin and furosemide therapy was not recorded during our study.

We concluded that although anxiety about the thrombotic tendency of albumin and furosemide therapy was not recorded during our study and the decrease of fibrinogen levels were not in accordance with this complication, early and transient ATIII and  $\alpha_2$ MG decrease were in accordance with thrombotic tendency. No absolute correlation has been found between the many biologic abnormalities and albumin and furosemide therapy.

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