

# ACUTE CHANGES IN PLASMA ENDOTHELIN LEVELS AFTER ACETATE OR BICARBONATE BASED HEMODIALYSIS IN CHILDREN

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## SUMMARY

**Purpose:** The aim of this study is to investigate the acute changes of endothelin immediately after hemodialysis and if this change differs using acetate or bicarbonate dialysate. **Methods :** Ten children were included in the study. Hemodialysis was performed in all cases both with acetate based dialysate and bicarbonate based dialysate. In all cases, blood samples were obtained before the initiation of dialysis and after the end of dialysis. BUN, serum creatinine and plasma endothelin levels were measured. **Results :** Pre-and post-hemodialysis plasma endothelin levels of the patients with acetate based dialysate were  $33.68 \pm 11.51$  pg/ml and  $28.27 \pm 12.85$  pg/ml, respectively. Drop after acetate based hemodialysis was statistically significant, but in bicarbonate based hemodialysis we didn't observe a statistically significant difference after dialysis. There were no correlations observed between the plasma endothelin levels and BUN, serum creatinine, mean arterial pressures, age of the patients, or duration of hemodialysis therapy. **Conclusion :** As a result, acetate based hemodialysis is more effective than bicarbonate based dialysis in decreasing the plasma endothelin levels.

**Key Words :** Acetate-based Hemodialysis, Bicarbonate-based Hemodialysis, Children, Endothelin.

## INTRODUCTION

Endothelin (ET), a novel 21-residue vasoconstrictor peptide, was discovered by Yanagisawa et al. in 1988 (1). Over 2000 papers have been published on this peptide in the fields of biochemistry, molecular biology, physiology, pharmacology, anatomy, or clinical medicine (2). The kidney is one of the most important organs for ET research because high concentrations of ET are present in the kidney (3,4) and a variety of cell types in the kidney are able to produce ET (5). High-affinity and a large number of endothelin binding sites are present in the kidney (6). ET has potent biological actions on the kidney (7). ET affects the

secretion of hormones which are related to renal function (7, 8). The presence of ET in human plasma was first demonstrated in patients undergoing maintenance hemodialysis (9).

The aim of this study is to investigate the answers of three questions : 1) What is the acute effect of hemodialysis on plasma ET concentrations? 2) Is there any difference between the effects of acetate based and bicarbonate based dialysate on plasma ET concentrations? 3) Are there any correlations between plasma ET levels and BUN, serum creatinine, blood pressure, age of the patient, or duration of hemodialysis therapy.

## PATIENTS AND METHODS

Ten patients were studied. There were 4 boys and 6 girls aged from 9 to 15 years (mean  $12.2 \pm 2.8$  years). They had been hemodialysed for an average of  $37.3 \pm 18.7$  months before the start of the study. During the study, hemodialysis was performed on all patients both with acetate based dialysate and bicarbonate based dialysate. In all cases blood samples were obtained before the initiation of dialysis and after the end of the dialysis session.

For ET measurements, blood samples were collected in tubes containing aprotinin (500 KIU/ml of blood) and EDTA (7.5 mmol/ml of blood) and immediately centrifuged at  $+4^\circ\text{C}$ . The plasma samples were stored at  $-70^\circ\text{C}$  until assayed. Plasma ET concentrations were measured by radioimmunoassay using a commercially available kit (Amersham International) after extraction with amprep C18 columns that were preequilibrated with methanol and water. BUN and serum creatinine were analyzed in duplicate with a Cobas Mira Plus Autoanalyzer. The statistical significance of differences was tested via two tailed paired t test and correlations between variables were investigated by linear regression analysis. The results are expressed as mean values  $\pm$  standard deviation. A  $p < 0.05$  value was considered statistically significant.

## RESULTS

1) Pre- and post-dialysis ET levels of the patients treated with acetate based dialysate were  $33.68 \pm 11.51$  pg/ml and  $28.27 \pm 12.85$  pg/ml respectively. Drop after hemodialysis was statistically significant ( $t=2.99$ ,  $p=0.015$ ). Pre- and post-hemodialysis ET levels of the patients treated with bicarbonate based dialysate were  $29.14 \pm 11.31$  pg/ml and  $24.84 \pm 3.68$  pg/ml, respectively, but drop

after hemodialysis was not statistically significant ( $t=0.29$ ,  $p > 0.05$ ) (Table 1).

2) Pre-dialysis or post-dialysis levels of BUN and serum creatinine did not significantly differ between the two types of hemodialysis ( $p > 0.05$ ).

3) There was no correlation observed between the plasma ET levels and BUN or serum creatinine ( $r=0.27$  and  $r=0.28$ , respectively,  $p > 0.05$ ).

4) There was no correlation observed between the plasma ET levels and mean arterial pressure (MAP) ( $r=-0.0064$ ,  $p > 0.05$ ). Furthermore, no correlation was found between the changes in plasma ET levels (DET) and changes in MAP (DMAP) ( $r=-0.005$ ,  $p > 0.05$ ).

5) No correlation was observed between the ET levels and the age of the patients ( $r=-0.14$ ,  $p > 0.05$ ) or the duration of hemodialysis therapy ( $r=0.39$ ,  $p > 0.05$ ).

## DISCUSSION

ET is a 21-amino acid peptide with strong vasoconstricting activity (1). The renal artery is one of the most sensitive vessels to ET and intrarenal injection of ET causes acute renal failure in rats (10). In addition, ET causes the proliferation of mesangial cells (11). These findings suggest that ET plays an important role in the pathophysiology of renal disease.

Elevated ET concentrations were reported in patients with acute and chronic renal failure, patients undergoing hemodialysis and CAPD therapy, but the causes which elevate plasma ET concentrations have not been clarified (9, 12, 13). While one possible cause is endothelial cell damage, another possible explanation is acute hemodynamic changes as observed in shock and acute renal failure. Hypoxia is another factor to

	Endothelin (pg/ml)	BUN (mg/dl)	Creatinine (mg/dl)
<b>P</b> Acetate	$33.68 \pm 11.51^*$	$73.1 \pm 25.79$	$8.22 \pm 2.79$
<b>R</b>			
<b>E</b> Bicarbonate	$29.14 \pm 11.31$	$69.9 \pm 23.36$	$8.29 \pm 2.43$
<b>P</b> Acetate	$28.27 \pm 12.85^*$	$27.8 \pm 16.25$	$4.04 \pm 1.71$
<b>O</b>			
<b>S</b> Bicarbonate	$24.84 \pm 3.68$	$22.80 \pm 7.88$	$3.66 \pm 0.97$
<b>T</b>			

\*  $t = 2.99$ ,  $p = 0.015$

Table 1 : Patients' pre and post dialysis plasma endothelin, serum creatinine and BUN values and standard deviations.

stimulate endothelin production and cytokines such as transforming growth factor- $\beta$ , interleukins, or tumor necrosis factor cause ET release from cultured endothelial cells (2). In this study we investigated the roles of different types of hemodialysis solutions in acute changes in ET levels. There are different reports about acute changes of ET on hemodialysis in the literature. While Peco-Antic and collaborators (14) reported that post-hemodialysis levels of ET were increased, Niwa and colleagues (15) reported that post-hemodialysis levels of ET were decreased. They also found that the decrease of ET with high flux membranes was more than that with cellulose membranes. In the literature, we couldn't find an article investigating the role of different dialysis solutions in acute changes of ET on hemodialysis. In this study, we found that with acetate based dialysate, plasma ET levels decreased significantly after dialysis but with bicarbonate based dialysate, this drop is not significantly different when compared with the pre-dialysis levels. This may be due to more efficient removal or decreased generation of ET by the endothelium during hemodialysis with acetate based dialysate. We also investigated the correlation of plasma ET with BUN, serum creatinine, blood pressure, age of the patients or duration of hemodialysis therapy, but we could not find a correlation with any of these parameters. In the literature, there are conflicting reports about the correlation of these parameters with plasma ET levels. While Yamada et al. (16) found that plasma ET levels correlated positively with serum creatinine concentrations, Koyama et al (12) and Niwa et al. (15) were not able to find this correlation and neither could we. Blood pressure may be one of the important factors related to plasma ET concentrations. There have been several reports which suggest the positive relationship between plasma ET concentrations and high blood pressure in patients with chronic renal failure. Miyauchi et al. (17) reported that plasma ET levels significantly correlated with both the levels of systolic and diastolic blood pressure, but Totsune et al. (18) could not find this correlation. However, Totsune and colleagues (18) found that the changes in ET levels before and after hemodialysis correlated with the changes in mean blood pressure. In this study, we couldn't find either of these correlations.

Our results indicate that children undergoing hemodialysis for chronic renal failure have a

decrease in plasma ET concentrations measured immediately after hemodialysis, and acetate based hemodialysis is more effective than bicarbonate based dialysis in decreasing the plasma ET levels. We suggest that this acute change in ET concentrations is related to multiple factors and further studies are needed to determine them.

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