

Hypotensive Episodes in Children on Hemodialysis: Role of Nitric Oxide

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ABSTRACT:

Background: In children with end stage renal disease, under regular haemodialysis therapy, hypotensive episodes during haemodialysis are the most frequent cardiovascular complications during the dialysis procedure. It has been suggested that nitric oxide (NO), a gaseous free radical derived from L-arginine that mediates important physiological processes including the regulation of cardiovascular dynamics, could be a factor in the development of these haemodialysis-related hypotensive episodes through its relaxing effect on the microvasculature. A possible cause for excessive NO production in uremia can be guanidosuccinate, a uraemic toxin, that accumulates in uraemic patients and upregulates NO synthesis from endothelial cells.

Objectives: Our aim was to investigate the possible involvement of endogenous NO in acute hypotensive episodes during maintenance haemodialysis.

Methods: This study was conducted on 25 children (16 males and 9 females) with end stage renal disease (ESRD). Their ages ranged from 6 to 18 years with mean of (14.88 ± 3.9) on regular haemodialysis therapy, following up at the Pediatric Dialysis Unit, Children's Hospital, Ain Shams University. The studied group included 13 normotensive patients (5 of them had hypotensive episodes) and 12 hypertensive patients (7 of them had hypotensive episodes). A group of 10 healthy children were selected to serve as a control group. Patients have undergone careful clinical examination with special emphasis on measurement of blood pressure: before, during and after dialysis. Plasma concentration of nitrate and nitrite ($\text{NO}_2 + \text{NO}_3$), NO stable end products, were measured in the control subjects and in the patients before, during and after dialysis sessions.

Results: It was found that in all end stage renal disease children, under regular haemodialysis, there were significant increases in plasma $\text{NO}_2 + \text{NO}_3$ levels compared to controls either before, during or after dialysis. Furthermore, there was a strong negative correlation between the mean % change of plasma $\text{NO}_2 + \text{NO}_3$ levels and mean % change of arterial blood pressure.

Before dialysis, plasma $\text{NO}_2 + \text{NO}_3$ levels were significantly lower in patients who experienced hypotensive episodes, while during dialysis, patients with hypotensive episodes showed significant increase in their plasma $\text{NO}_2 + \text{NO}_3$ levels in comparison to their level in those with no hypotensive episodes.

There was no statistically significant difference between normotensive and hypertensive patients as regards their plasma NO either before, during or after dialysis.

Conclusion: These findings suggest that hypotension during dialysis in ESRD may be related, at least in part, to the increase in NO in some patients. The basis for the rising level of NO is not well understood. From our study, it could be suggested that the low predialysis plasma level of NO in patients with hypotensive episodes may stimulate NO production and this sudden increase of plasma NO level may be the cause of hypotensive episodes during haemodialysis in those patients.

INTRODUCTION

Nitric oxide (NO), a gaseous free radical derived from L-arginine, is a potent modulator of vascular tone and platelet function⁽¹⁾. It exerts a variety of renal and

extra-renal physiological and pathophysiological effects⁽²⁾.

Nitric oxide is produced within the kidney and plays an important role in the control of many intrarenal processes, which

regulate the renal response to changes in perfusion pressure and thus help determine plasma volume and blood pressure⁽³⁾.

In end stage renal failure patients, symptomatic homodialysis-related hypotensive episodes, not explained by excessive ultrafiltration, is a frequent complication. The possibility that NO, a major regulator of cardiovascular haemodynamics, could be a factor was explored in many studies^(4, 5).

AIM OF THE WORK

This study aimed to investigate the possible involvement of endogenous NO in acute hypotensive episodes during maintenance haemodialysis through serial measurements of nitrate and nitrite anion (stable end products of NO) before, during and after the haemodialysis sessions.

SUBJECTS AND METHODS

The Patients Group:

This study was conducted on twenty five children with end stage renal disease, on regular haemodialysis therapy, following up at the Paediatric Dialysis Unit, Children's Hospital, Ain Shams University in the period from October 2000 to February 2001.

The studied group included 16 males and 9 females. Their ages ranged between 6 and 18 years with a mean of 14.88 ± 3.94 years. The duration of the disease ranged from one month to 11 years with a mean of 5.40 ± 3.31 years. Twelve children experienced hypotension episodes during haemodialysis (hypotension episodes during haemodialysis is defined as a drop of mean arterial blood pressure more than 20 mm Hg)⁽⁴⁾ and 13 patients had no hypotensive episodes during haemodialysis.

On the basis of their blood pressure, patients were classified into: -

- Group (I): which included 13 patients with normal blood pressure.

This group is further subdivided into:

Subgroup (Ia): 5 children who experienced acute hypotensive episodes during dialysis.

Subgroup (Ib): 8 children who had no hypotensive episodes.

- Group (II): which included 12 patients with high blood pressure

Also, this group is subdivided into:-

Subgroup (IIa): 7 children who experienced acute hypotensive episodes during haemodialysis.

Subgroup (IIb): 5 children who had no hypotensive episodes.

Exclusion Criteria

- Patients with active infection or bronchial asthma.
- Diabetic patients or those with underlying immune problem.

The Control Group

A group of ten clinically healthy children were selected from the general population, from the age groups and socioeconomic state to which the patients belonged, to serve as the control group.

All the patients have undergone:

History taking and careful clinical examination with special emphasis on: -

Underlying aetiology, duration of renal failure and duration of dialysis.

Frequency of dialysis and type of membrane.

All the patients were receiving 3 hours maintenance haemodialysis, three times

weekly, using cuprophane membrane.

- Medication received.

All patients received erythropoietin, iron, calcium supplement, phosphate binders, also all patients received IV heparin 2500 IU with half dose before dialysis and the other half during dialysis,

- Measurement of blood pressure; before, during and after dialysis with calculation of mean arterial blood pressure (calculated as one third of the difference between systolic and diastolic blood pressure + diastolic blood pressure) ⁽⁶⁾.

The following laboratory investigations were done

- Complete blood picture
- Serum level of creatinine, blood urea, calcium, phosphorus, sodium and potassium.
- Plasma concentration of nitrate and nitrite were measured before, during and after haemodialysis session.

The assay of total nitric oxide was based on the enzymatic conversion of nitrate to nitrite by nitrate reductase. The reaction is followed by a colorimetric detection of nitrite as an azodye product of the Griess reaction ⁽⁷⁾.

Statistics:

Mean values, standard deviation were calculated. data were analysed for measuring differences of significance ($p < 0.05$) by the unpaired t-test, correlations by simple regression analysis within 95% to 90% confidence interval ($p < 0.05$).

RESULTS

Twenty five children (16 males and 9 females) with end stage renal disease, on

regular hemodialysis therapy, were included in this study. Their age ranged between 6 and 18 years with a mean of 14.88 ± 3.94 years. The duration of the disease ranged from one month to 11 years with a mean of 5.40 ± 3.31 years (Table 1).

The mean plasma level of $\text{NO}_2 + \text{NO}_3$ in the whole patients group was 98.31 ± 79.66 μM before dialysis, fell to 76.11 ± 66.06 μM during dialysis and further down to 52.34 ± 48.78 μM after dialysis, these values were all significantly higher than that of the control group (33.93 ± 24.3 μM) (Table 2).

Correlating the mean % change of plasma $\text{NO}_2 + \text{NO}_3$ to the mean % change of the mean arterial blood pressure, either during or after to before dialysis, there was a significantly negative correlation (the greater the increase in plasma $\text{NO}_2 + \text{NO}_3$, the greater the decrease in the mean arterial blood pressure) (Figures 1 & 2).

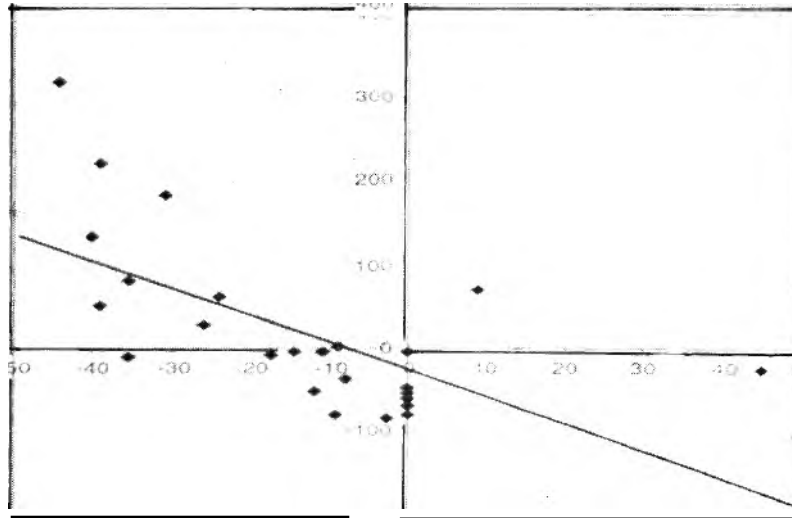
In our study, 12 patients experienced acute hypotensive episodes during dialysis that is their mean blood pressure drop more than 20 mmHg. We found that before dialysis, patients with hypotensive episodes had significantly lower mean plasma $\text{NO}_2 + \text{NO}_3$ (67.69 ± 70.70) compared to those without episodes (16.57 ± 79.41). During dialysis, patients with hypotensive episodes showed a rapid rise in the level of $\text{NO}_2 + \text{NO}_3$ reaching a significantly higher level (101.63 ± 86.97) than the rest of the patients (52.55 ± 23.29) then falling down by the end of dialysis to (67.58 ± 67.59) which was not significantly different from patients without hypotensive episodes (38.26 ± 11.20) (Fig. 3).

Table 1: Descriptive data of the patients group

	Range	Mean \pm S.D.
Age (yr)	6-18	14.88 \pm 3.94
Duration of dialysis (yr)	1/12- 10	4.16 \pm 3.29
Weight before dialysis (kg)	17.7- 50.2	30.37 \pm 9.92
Weight after dialysis (kg)	16.7- 48.6	30.06 \pm 9.43
Mean ABP before dialysis	77- 133	100.60 \pm 16.38
Mean ABP during dialysis	57- 123	85.64 \pm 19.87
Mean ABP after dialysis	70- 120	87.88 \pm 13.97

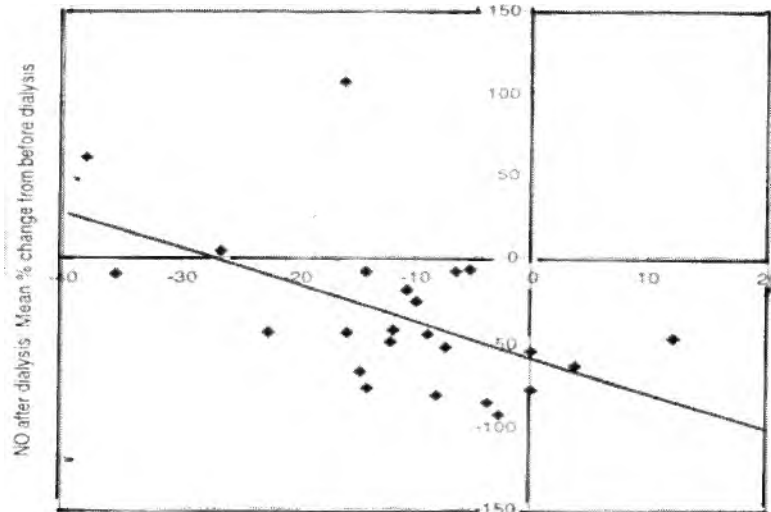
Table 2: Comparison of mean plasma NO₂+NO₃ level between different groups of patients (before, during and after dialysis) and controls

	Range	Mean \pm SD	Significance
Patients <i>before dialysis</i>	16 - 294	98.31 \pm 79.66	Z = 3.07
Controls	12.5 - 88	33.93 \pm 24.3	p < 0.01
Patients <i>during dialysis</i>	31.5 - 360	76.11 \pm 66.06	Z = 3.09
Controls	12.5 - 88	33.93 \pm 24.3	p < 0.01
Patients <i>after dialysis</i>	14 - 260	52.34 \pm 48.78	Z = 2.12
Controls	12.5 - 88	33.93 \pm 24.3	p < 0.05



$r = -0.65; p = 0.0005$

Fig. 1: Correlation between mean % change of plasma NO_2+NO_3 and mean % change of mean arterial blood pressure during dialysis in relation to before dialysis



ABP after dialysis: Mean % change from before dialysis
 $r = -0.53; p = 0.0079$

Fig. 2: Correlation between mean % change of plasma NO_2+NO_3 and mean % change of mean arterial blood pressure after dialysis in relation to before dialysis

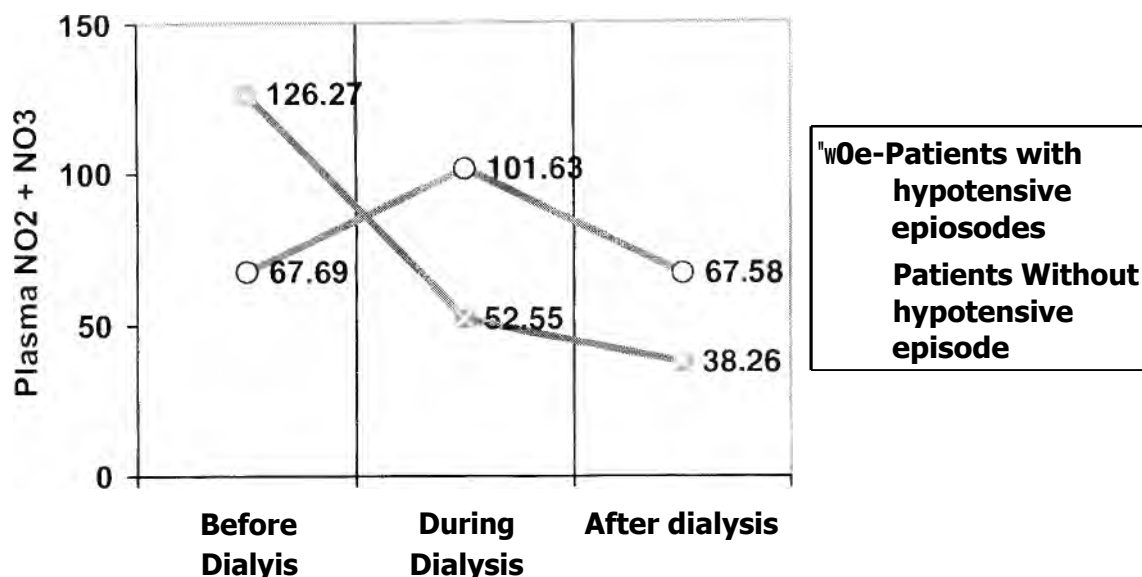


Fig 3: The change in plasma level of NO₂+NO₃ in patients with and those without hypotensive episodes during dialysis

DISCUSSION

It is well known that hypotensive episodes during haemodialysis are major cardiovascular complications of haemodialysis⁽⁴⁾. Up to one third of long term dialysis patients experience acute hypotension during haemodialysis that necessitates premature termination of the process or use of aggressive management as intravenous saline or dextran to normalize the blood pressure¹.

Nitric oxide is a mediator of important physiological processes including the regulation of cardiovascular dynamics. Nitric oxide exerts a relaxing effect on the microvasculature, contributing to both renal and systemic haemodynamic⁽⁹⁾.

Our study participants included 25 children with end stage renal disease (ESRD) on regular haemodialysis therapy, thirteen children were normotensive (5 of

them had hypotensive episodes) and 12 children were hypertensive (7 of them had hypotensive episodes) during haemodialysis.

In our study there was significant increase in plasma nitric oxide level in all ESRD children compared to controls. ESRD children had a chronic elevation in their plasma nitric oxide level either before, during dialysis or even after dialysis when compared to the controls.

This finding has been observed by other investigators^(4, 10, 1, 11) who studied groups of ESRD subjects and found that the predialysis and dialysis mean plasma NO level for all ESRD subjects was significantly higher than the mean for the controls.

The increase of plasma NO in patients with ESRD may be due to complete loss of renal clearance and so severe limitation of

the usual mechanism of removal of circulating NO by the kidney⁽¹¹⁾. A putative cause for excessive NO production in uremia can be guanidosuccinate, a uraemic toxin, that accumulates in uraemic patients and upregulates NO synthesis from endothelial cells⁽¹⁾.

In our study, there was a significantly negative correlation between the mean % change of plasma NO and mean % change of mean arterial blood pressure when comparing the levels both during and after dialysis to those before dialysis; that is the higher the percentage of the increase of plasma NO, the lower the percentage of decrease of the mean arterial blood pressure. These results suggest that enhanced NO biosynthesis may contribute to haemodialysis induced hypotension.

Beasley and Brenner, in 1992, have proposed that haemodialysis associated hypotension is mediated by increased production of nitric oxide in vascular smooth muscle cells. The majority of nitric oxide is synthesized by nitric oxygen synthase from L-arginine and molecular oxygen. Cytokines are powerful inducers of nitric oxide synthase that can result in a marked increase in nitric oxide synthesis. The membrane used in haemodialysis can activate the complement cascade with stimulation of cytokine production and so production of a large amount of nitric oxide⁽⁹⁾. It has been reported that, in uraemic patients, platelets may be a source of increased NO production, thereby leading to hypotension⁽¹²⁾. Also, in end stage renal disease there is accumulation of nitric oxide synthase inhibitors that are cleared by haemodialysis procedure resulting in

production of large amount of NO⁽¹³⁾.

From our data, comparing plasma NO level between patients with hypotensive episodes during the dialysis sessions and those with no such episodes, it was found that before dialysis, patients with acute hypotensive episodes had plasma NO level significantly lower than subjects without hypotensive episodes. This finding was surprising to us because it was expected to find high NO level in patients with hypotensive episodes compared to those with no episodes as proposed by previous authors⁽¹⁴⁾. However, during dialysis patients with hypotensive episodes showed increase in plasma NO level to levels significantly higher than those of patients without hypotensive episodes. Yokokawa and colleagues, in 1995, found that NO production at the initiation of dialysis did not differ significantly between patients who had and those who had no hypotensive episodes, but noted marked increase in plasma NO during haemodialysis in patients with hypotensive episodes, with strong negative correlation between mean plasma NO and mean arterial blood pressure⁽¹⁾.

On the other hand, in our study, patients with no hypotensive episodes had high level of NO before dialysis but during haemodialysis they showed progressive decrease in their plasma NO level through the haemodialysis session. In agreement with our results, Rysz et al. (1997) studied group of patients with end stage renal disease under haemodialysis therapy with no hypotensive episodes and found progressive decline in their nitric oxide level through the haemodialysis session⁽¹⁵⁾. They proposed that, this reduction may be

due to its elimination prevailing over production that might result from feed back inhibition of nitric oxide synthase activity or might also be related to down regulation which develops following contact to dialysis membrane. We can suggest that, the progressive decline of NO level protects these patients from hypotension episodes during haemodialysis. This suggestion could explain that sudden increase in plasma NO level in patients with hypotensive episodes who showed low predialysis plasma NO level may be the reason of the hypotensive episodes (i.e. the low NO level may stimulate production of large amount of NO through stimulation of cytokines).

In conclusion, the findings of our study suggest that hypotension during dialysis in ESRD may be related, at least in part, to the increase in NO in some patients. The basis for the rising level of NO is not well

understood. From our study, it could be suggested that the low predialysis plasma level of NO in patients with hypotensive episodes may stimulate NO production and this sudden increase of plasma NO level may be the cause of hypotensive episodes during haemodialysis in those patients.

It is recommended to further study patients with hypotensive episodes aiming to evaluate other factors which may have a role in hypotension other than NO as well as to further understand the basis for the change of NO in a subset of patients that might underlie the occurrence of hypotensive episodes during dialysis. It is worth considering studying, on experimental animals, using drugs that can stimulate production or inhibition of NO to guard against sudden elevation of NO during haemodialysis sessions and to prevent the hypotensive episodes, if possible.

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