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Orginal Article

Effect of Intravenous Acetylcysteine on Plasma Homocysteine in Hemodialysis Patients

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Abstract

Background. Cardiovascular disease is common in hemodialysis patients. The classical risk factors do not appear to be entirely responsible for cardiovascular disease and novel risk factors including hyperhomocysteinemia are suggested in this patient group.
Methods. Twentyfour patients were enrolled in the study. In the same patient group, placebo (250 ml 5% glucose solution) and acetylcysteine (5 grams in 250 ml 5% glucose solution) were administered on two consecutive hemodialysis sessions. Blood samples were taken at the beginning and at hour 4 of the placebo and acetylcysteine session for measuring the plasma homocysteine levels.
Results. Plasma homocysteine level was decreased from 24.06±9.26 to 15.75±7.33 μmol/L (38.6%) at placebo session, whereas plasma homocysteine level was decreased from 21.25±8.66 to 7.36±4.06 μmol/L (65.26%) at acetylcysteine session. The reduction of plasma homocystein level was statistically significant both placebo and acetylcysteine administered session ($p<0.001$; $p<0.001$ respectively). Homocysteine reduction at acetylcysteine session was significantly higher than that at placebo session ($p<0.001$).
Conclusions. The study demonstrated that intravenous acetylcysteine normalized plasma homocysteine levels in hemodialysis patients. However, further studies are needed to establish the long time effect of intravenous acetylcysteine on plasma homocysteine levels in hemodialysis patients.

Keywords: cardiovascular disease; hemodialysis; homocysteine

Introduction

Cardiovascular disease is common in patients with end-stage renal disease (ESRD) and is the primary cause of death. The classical risk factors do not appear to be entirely responsible for cardiovascular disease and novel risk factors including hyperhomocysteinemia are suggested in this patient group [1].

Homocysteine is a sulphur-containing amino acid formed during methionine metabolism [1].
It is known that homocysteine metabolism is impaired in patients with ESRD. In hemodialysis patients, mean plasma homocysteine levels are markedly elevated, often in range of 25-30 μmol/L (compared with a normal range of 12-15 μmol/L) [2]. Hyperhomocysteinemia contributes to the increased cardiovascular mortality in these patients [3]. A prospective study carried on hemodialysis patients demonstrated that each 1 μmol/L increase in total homocysteine levels rose the risk of vascular disease by 1% [4]. Physiopathological mechanism is not clear. However, hyperhomocysteinemia may accelerate atherosclerosis by stimulating impairment of coronary microvascular dilator function [5], smooth muscle proliferation [6], platelet activation and thrombogenesis [7], endothelial dysfunction and collagen synthesis [8].
In normal subjects, the plasma homocysteine levels can be decreased by folic acid administration. However, ESRD patients characteristically demonstrate resistance against homocysteine lowering effect of folic acid. It was shown that Vitamin B12 lowered plasma homocysteine level by 17% when given orally and, in another, by over 30% when administered subcutaneously, but its levels were not normalized [9].
Acetylcysteine has a sulphydryl containing substance with potent antioxidant characteristics [10] and improves peripheral and coronary arteriel function [11]. Acetylcysteine also reduces the plasma homocysteine levels [10]. However, a study carried on hemodialysis patients demonstrated that orally prescribed acetylcysteine did not significantly lower plasma homocysteine levels [12]. The available clinical evidence for an effect of intravenous acetylcysteine on plasma homocysteine levels in hemodialysis patients is inadequate. The purpose of this study is to determine if intravenous administration of acetylcysteine has any effect on plasma homocysteine levels in hemodialysis patients.

Patients and methods

Patients
Twentyfour patients (14 females, 10 males) undergoing routine hemodialysis for 4 hours 3 times a week for at least 3 months were enrolled in the study. The etiology of renal failure was diabetic nephropathy in eight patients, hypertension in four patients, polycystic kidney disease in four patients, glomerulonephritis in three patients, malignancy in two patients, nephrolithiasis in one patients. The etiology was unknown in two patients. Polysulphone membrane dialyzer (F8 Fresenius Medical Care) and bicarbonate-based dialysis solution were used in hemodialysis.

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Vascular access for hemodialysis was obtained via arteriovenous fistula in seventeen patients and via tunneled-cuffed hemodialysis catheters in seven patients. In the same patient group, placebo (250 ml 5% glucose solution at the first session) and acetylcysteine (5 grams in 250 ml 5% glucose solution at the second session) were administered on two consecutive hemodialysis sessions from the venous hemodialysis line for 4 hours. No side effect was observed during acetylcysteine administration. Average blood flow rate was set to 300 ml/minute and average dialysate flow rate was set to 500 ml/minute for both acetylcysteine and placebo administered session. This study was approved by Ethics Committee of Medical Faculty of Kocaeli University and all patients signed the written consent.

Biochemical investigations

Blood samples were taken at the beginning and at hour 4 of the session on the day of placebo and acetylcysteine administration for measuring the plasma homocysteine levels. Samples were centrifuged immediately and separated. The homocysteine levels were measured by a competitive immunoassay method on the Immulite 2000 Analyzer. At the first session, blood samples taken at the beginning of hemodialysis were examined for thyroid function tests, vitamin B12 and folic acid levels. Vitamin B12 and folic acid levels were determined by chemoluminescence immunoassay on Immulite 2000 using (DPC) kits. Third generation sensitive thyroid stimulating hormone (TSH) measurement was performed using two way chemoluminescence immunoassay method.

Statistical analysis

Data were expressed as the mean ± SD. Kolmogorov-Smirnov test was used to analyze whether values showed normal distribution or not. At placebo session, homocysteine values were compared by paired samples t-test due to showing normal distribution. Paired samples t-test was also used for comparison of homocysteine reduction obtained with placebo and acetylcysteine administration. However, at acetylcysteine session, homocysteine values did not show normal distribution. Therefore, the data were tested by Wilcoxon signed ranks test. Statistical analysis was performed using SPSS (Statistical Package for Social Science) for Windows version 13. A probability value <0.05 considered statistically significant.

Results

General characteristics of the patients are shown in Table 1. The most common etiology of the renal failure in the patients was diabetes mellitus (33.3%). Mean vitamin B12, folic acid and TSH levels of the patients were found within normal limits. Mean plasma homocysteine level was decreased 8.31±4.01 μmol/L (from 24.06±9.26 to 15.75±7.33 μmol/L, 38.6 %) at placebo session, whereas mean plasma homocysteine level was decreased 13.89±5.23 μmol/L (from 21.25±8.66 to 7.36±4.06 μmol/L, 65.26 %) at acetylcysteine session (Table 2). The reduction of plasma homocystein level was statistically significant both placebo and acetylcysteine administered session ($p<0.001$; $p<0.001$ respectively). Homocysteine reduction at acetylcysteine session was significantly higher than that at placebo session ($p<0.001$).

Table 1. General characteristics of the patients

Parameter	Mean±SD
Age (years)	61.5
Hemodialysis period (months)	34
Hemoglobin (g/dL)	10.38±1.42
BUN (mg/dL)	56.32±18.16
Creatinine (μmol/L)	720.46±246.63
Kt/V	1.62±0.42
Albumin (g/dL)	3.37±0.55
Calcium (mmol/L)	2.18±0.25
Phosphate (mg/dL)	5.18±1.80
PTH (pg/mL)	236.39±194.75
Vitamin B12 (pg/mL)	392.46±248.75
Folic acid (ng/mL)	7.82±5.38
TSH (μIU/mL)	2.15±1.39

Abbreviations: BUN (blood urea nitrogen); Kt/V (hemodialysis adequacy);
PTH (parathyroid hormone); TSH (thyroid stimulating hormone)

Table 2. Plasma homocysteine levels before and after hemodialysis sessions administrated placebo and acetylcysteine

	Before dialysis	After dialysis	The difference	P
Acetylcysteine session	21.25±8.66	7.36±4.06	13.89±5.23	<0.001
Placebo session	24.06±9.26	15.75±7.33	8.31±4.01	<0.001

Discussion

This study demonstrated that intravenously acetylcysteine administration during hemodialysis lowered plasma homocysteine to normal levels beyond the plasma homocysteine lowering effect of hemodialysis.

Various treatment strategies were performed to reduce the elevated plasma homocysteine levels in hemodialysis patients. It is known that folic acid and vitamin B12 administration lowers homocysteine levels by approximately one quarter to one third in general population [13]. In contrast, patients with ESRD are characteristically resistant to the homocysteine-lowering effect of folic acid [9]. Dimercaptosuccinic acid was administered orally in a study for treatment of hyperhomocysteinemia in hemodialysis patients. Therapy of 2.5 mg/kg/day dimercaptosuccinic acid was compared with placebo in this study [14]. At the end of eight-week

follow-up, there was no statistically significant difference between the dimercaptosuccinic acid group and the placebo group (p=0.45).

The use of different dialysis techniques has also been investigated to lower homocysteine concentrations. Although only modest success has been reported for high-flux and super-flux dialyzers [9], some excellent results have been reported using nocturnal dialysis [15]. A standard hemodialysis session lowers plasma homocysteine level approximately by 28% [3].

There are some data from human studies supporting the hypothesis that acetylcysteine has useful effects on plasma homocysteine level. Acetylcysteine lowered plasma homocysteine levels in healthy females when administered orally [16]. However, in the study assessed the effect of prolonged oral acetylcysteine therapy in hemodialysis patients was not provided statistically significant reduction in homocysteine levels (p=0.07). In this study, 1.2 grams of acetylcysteine was administered orally twice a day for 4 weeks [12].

It was shown that intravenous acetylcysteine administration lowered plasma homocysteine levels in healthy controls [17]. Scholze *et al*. assessed intravenous acetylcysteine use in hemodialysis patients [3]. In this study, the effect of 5 grams of intravenous acetylcysteine on homocysteine levels was compared with placebo. Mean plasma homocysteine level was decreased from 19.8±9.2 to 11.9±7.8 µmol/L on hemodialysis session administered placebo, whereas mean plasma homocysteine level was decreased from 20.1±8.5 to 2.2±1.2 µmol/L on hemodialysis session administered acetylcysteine.

In another study investigated the effect of intravenous acetylcysteine on homocysteine levels in hemodialysis patients, Thaha *et al* showed that an 88.3% reduction of plasma homocysteine concentration occured after acetylcysteine administration [18].

Our study results are consistent with these study results. That is, plasma homocysteine levels are normalized by intravenous acetylcysteine administration.

Much more reduction of plasma homocysteine levels after intravenous acetylcysteine administration is likely to be related to quick displacement of homocysteine from protein-binding sites. It has been suggested that intradialytic decline of plasma homocysteine levels in hemodialysis patients results from the removal of unbound homocysteine [3].

Conclusions

In conclusion, our study suggests that intravenous acetylcysteine normalizes plasma homocysteine levels. However, further studies are required to state that intravenous acetylcysteine may use in hemodialysis patients as a homocysteine lowering agent.

Conflict of interest statement. None declared.

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