The effect of intravenous iron on protein oxidation hemodialysis patients

Sima Abedi Azar[1], Mohammad Reza Jafari Nakhjavani[2*]

[1.] Associate Professor of Nephrology, Kidney Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
[2.] Assistant Professor of Rheumatology, Connective Tissue Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, IR Iran.
dr_mrjn@yahoo.com

Abstract: Introduction: Parenteral iron (IV Iron) as a choice treatment of iron deficiency may aggregate oxidative stress already present in hemodialysis(HD) patients. Inflammation induced and IVIR-induced protein oxidations were shown in HD patients. Oxidative stress related inflammation in HD patients can induce activation of oxidative burst enzymes in phagocytes and contribute significantly to high prevalence and severity of atherosclerosis and infections and can decrease the survival rate and affect the quality of life of HD patients. This study aimed to clarify the role of IVIR therapy on protein oxidation and its relation to inflammation in these patients. **Patients and** methods: We examined the effect of IVIR administration on markers of protein oxidation and inflammatory factors as high-sensitivity C-reactive protein (hs-CRP) in 30 HD patients(16=M,14 =F, mean age:52.37±1.20 years)given I.V iron(100 mg of iron sucrose for half hour immediately after HD) and 30 HD patients whom not received iron(m=16,f=14,mean age:48.27±9.59) as control group. Blood samples were drawn Pre-HD, Pre-IVIR, and post-IVIR (30 minute after dialysis) for iron, transferrin, ferritin, markers of free radical activities: thiol groups, Malondialdehyde (MDA) and hs-CRP. **Results**: hs-CRP in Iron group increased from7.27±7.9to 7.54±7.47 immediately after HD and to 8.34±8.22 after IVIR administration. Thiols level in Iron group decreased from 35.81±17.29 to 27.54±13.10 ($p<0.001$) immediately and increased to 37.10±15.60 ($p<0.04$) after IVIR. MDA in Iron group decreased from 3.00±1.24 to2.10±0.77 ($p<0.001$) after HD and increased to 3.28± 0.98 ($p<0.001$) after IVIR. In control group Thiols and hs-CRP and MDA decreased immediately and 30 minutes after HD. MDA levels before and end of HD and 30 minutes after HD were significantly higher in Iron group($p<0.05$).There was significant meaningful correlation between MDA and hs-CRP after HD ($p<0.001$) and after IVIR therapy ($p<0.001$)in Iron treated group. **Conclusion**: IVIR treatment increases oxidative stress in HD patients and it positively correlates with inflammatory factors like hs-CRP.

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1. Introduction

Oxidative stress and inflammation lead to an increase in the prevalence and severity of atherosclerosis, infections, and amyloidosis Beta-2 microglobulin and finally result in a decrease in the lifetime and life quality of dialysis patients (Brenner Robert, 2005).

Availability of dialysis has added to the lifetime of hundreds of patients with ESRD. Hemodialysis has numerous side effects such as hypotension, muscle cramps, anaphylactic reaction, increased oxidative stress, reduced antioxidants, and anemia (Skorecki, 2009).

Iron deficiency in patients with CRF is observed even before starting alternative treatments such as hemodialysis. Loss of blood in each dialysis intensifies iron deficiency. Iron deficiency also results in erythropoietin and since oral iron may not be able to meet the need for iron in the body it is preferred to use intravenous iron injection for hemodialysis patients. Iron infusion has its own side effects. One of the side effects of iron injection is concentration of iron in the body which can cause oxidative stress, which in turn leads to an increase in tissue damage (Singh Ajay, 2005). Injected iron directly causes oxidative damage and MDA is one of the indicators of increased oxidative damage.

High-sensitivity C-reactive protein (hs-CRP) and Hemocysteine are other indicators the growth of which leads to an increase in oxidative stress (Cavdar, 2005).

Oxidative stress is a lack of balance between toxic elements and clearing mechanisms. As a result of this imbalance the increase in the number of free radicals in blood leads to the expansion of tissue damages in different organs. Oxidative stress is often seen in chronic hemodialysis patients.

Intravenous iron injection is accompanied by increased free iron content of blood, increased number of free radicals, and reduced amount of vitamin C (which is a strong anti-oxidant)(Camerson, 1999; Herbert, 1997).

This study was aimed at studying the effect of intravenous iron injection on the oxidation of proteins in hemodialysis patients.

2. Material and Methods

In a clinical trial that was performed in the internal diseases department of Tabriz University of Medical Sciences on hemodialysis patients, the effect of intravenous iron infusion on the oxidation of proteins in hemodialysis patients was studied.

The blood samples of patients in the experimental and control groups were obtained three times:

1. Before the dialysis
2. Immediately after dialysis
3. 30 minutes after dialysis

The levels of MDR, hs-CRP and Hemocysteine were measured in all of the three blood samples of the patients.

The levels of Hemocysteine and hs-CRP were measured using the Alaysa method while the levels of MDA were measured based on the formation of complexes between MDA and Thiobarbituric acid using a spectrophotometer. The types of filters used in all dialysis sessions were the same and a comparison was drawn between the levels of MDA, hs-CRP and Hemocysteine in patients of the two groups. Results of the comparison were also analyzed.

Statistical Analysis:

The collected data were analyzed by SPSS-17 statistical software. The collected data were expressed as percentage and mean ± SD. Continuous (quantitative) variables were compared by Independent samples and Paired t test. Categorical (qualitative) variables were compared by contingency tables and Chi-square test or Fisher's exact test. P-value ≤ 0.05 was considered statistically significant.

3. Results

In this study 60 hemodialysis patients were classified in to two groups (an experimental and a control group) and the effects of iron injection on oxidative stress of the two groups was studied.

Each group consisted of 46.6% female and 5.53% female participants. The average age of patients was also 52.3 years.

In the experimental group 2 were anti-Hbs positive. Moreover, in the experimental and control groups 4 and 10 patients were anti-HCV positive, respectively.

Results of the comparison between inflammatory factors in the experimental and control groups:

The average level of pre-dialysis MDA in the experimental group was significantly higher than the control group (P=0.01). The average level of MDA 30 minutes before the dialysis was significantly higher in the experimental group than the control group (P<0.01).

The post-dialysis level of MDA in the experimental group was significantly lower than the pre-dialysis MDA level (P<0.001).

In the experimental group, the average level of MDA 30 minutes after dialysis was significantly higher than the level of MDA immediately after dialysis (P<0.001).

In the control group, the average level of MDA immediately after dialysis was significantly lower than the level of MDA prior to the dialysis (P=0.001). Moreover, the level of MDA 30 minutes after dialysis was also significantly lower than the MDA before dialysis in this group.

In the experimental group the average level of Hemocysteine immediately after dialysis was significantly lower than the average level of Hemocysteine before dialysis (P=0.001).

In addition, the average level of Hemocysteine 30 minutes after dialysis was significantly higher than the level of Hemocysteine immediately after dialysis in the experimental group.

The trend of variations in the average level of inflammatory factors in each dialysis:

In sum, the average level of inflammatory factors reduced immediately after dialysis and increased 30 minutes after dialysis in the experimental group.

However, the average level of inflammatory factors reduced gradually immediately after dialysis and 30 minutes after dialysis in the control group.

Table 1: Inflammatory factors of patients in two groups

		MDA (*μg/dl*)	hs-CRP (*mg/l*)	Hemocysteine (*mmol/l*)
Case Group	Before Hemodialysis	3	7.27	35.8
	After Hemodialysis	2	7.54	27.54
	30 minute after Hemodialysis	3.28	8.32	3.1
Control Group	Before Hemodialysis	2.31	9.67	37.07
	After Hemodialysis	1.86	8.82	33.37
	30 minute after Hemodialysis	1.5	7.6	3.13

4. Discussions

Patients in the experimental and control groups had matching age and gender. The experimental parameters of the patients in the two groups did not different significantly at the beginning of the study. Therefore, the confounding factor for the aforementioned parameters of the two groups was at its lowest value. Hence, results of the comparison between the acute phase inflammatory factors were reliable in both groups.

In a study that was conducted by Johner, Javadar and their colleagues (2002) in Turkey, 13 patients with an average age of 49.9 years were examined. The patients did not receive any iron in the first dialysis (group 1) and all the patients received 20 mg of intravenous bolus iron at the end of the second dialysis (group 2). In the third dialysis, within 30 minutes all the patients gradually received 100 mg of intravenous iron infusion which was solved in 100 cc of normal saline (group 3). The levels of MDA were also measured before dialysis, immediately after dialysis, and 30 minutes after dialysis (Cavdar, 2005). In the aforementioned study the levels of MDA in group 3 and the triple blood sample showed an increasing trend. In the experimental group of our study the levels of MDA first declined and then escalated. The increase in MDA was not significant immediately after dialysis whereas in our study the levels of MDA declined significantly immediately after dialysis. However, the level of MDA was significantly higher 30 minutes after dialysis compared to the level of MDA measured immediately after dialysis. In our study the level of MDA increased significantly 30 minutes after dialysis.

Therefore, it is concluded that intravenous iron injection leads to a significant increase in MDA.

In the aforementioned study the level of MDA decreased gradually in group 1 (similar to the control group in our study). However, the decrease in the average level of MDA in group 1 was not significant unlike our study in which the decrease in the average level of MDA immediately after dialysis was significant.

Unlike our study, in the aforementioned study the average levels of MDA before dialysis and 30 minutes after dialysis in group 3 were significantly lower than those of group 1.

In our study the levels of MDA before dialysis and 30 minutes after dialysis were higher in the experimental group than the control group.

In order to explain the significant reduction in MDA immediately after dialysis in the experimental and control groups of the present study it can be argued that uremia increases damages and finally increases MDA. On the other hand, dialysis reduces uremic toxins and therefore leads to a temporary reduction in MDA.

In the study by Leem et al. (1999), hemodialysis patients received 100 mg of iron through infusion following dialysis. Research results revealed that iron overload brings about an increase in oxidative stress (Lim, 1999).

This finding shows the adverse effect of iron on oxidative stress and complies with the results of our study in which inflammatory factors grew as a result of iron injection.

In the study by Dr. David Tovbin et al. the effect of injection of 100 mg of intravenous iron on the levels of Hemocysteine was studied. The levels of Hemocysteine before dialysis, after dialysis and 30 minutes after dialysis were also measured.

In this research, the average level of Hemocysteine escalated significantly immediately after dialysis while it declined slightly with the infusion of iron (Tovbin, 2002).

This finding is in contrast with the finding of our study in which the level of Hemocysteine of the two groups declined significantly after dialysis and escalated significantly after iron infusion.

Conclusion

Measurements of inflammatory factors before dialysis, immediately after dialysis and 30 minutes after dialysis resulted in the following findings.

In the experimental group the average values of factors declined during the first dialysis session and then grew relatively. The decrease and increase in the levels of MDA and Hemocysteine were also significant.

In the control group the values of these factors declined gradually within the first dialysis session and the reduction in the average level of MDA immediately after dialysis was more evident.

The comparison between the average values of inflammatory factors in the experimental and control groups showed that the level of MDA in the experimental group increased significantly 30 minutes after dialysis. However, since the level of MDA in the experimental group was higher than the control group before dialysis this result is not reliable.

Corresponding Author:
Dr. Mohammad Reza Jafari Nakhjavani
Emam Reza Hospital, Connective Tissue Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, IR Iran.
E-mail: dr_mrjn@yahoo.com

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