The Effects of Oral Sodium Bicarbonate Treatment on Hematological Parameters in Patients with Chronic Kidney Disease During the Predialysis Period

Tayyibe Saler[1], Mehmet Bankir[2], Serkan Duman[3], Sibel Ada[4], Betül Çavuşoğlu Türker[5], Süleyman Ahbab[6]

ABSTRACT

Introduction: Chronic renal disease (CKD) is a serious public health problem with high treatment costs, that leads to an increase in mortality and morbidity, and impairs the quality of life. This study was performed to evaluate the effect of improvement of metabolic acidosis seen in chronic renal disease by oral sodium bicarbonate treatment on hematological parameters.

Material and Methods: This study was consisted of 111 patients with chronic renal disease and datas scanned, retrospectively. Then, 62 ones in the predialysis period and received oral sodium bicarbonate treatment were followed up. Patients divided into two groups, group A (n:37) patients who had persisted metabolic acidosis though oral sodium bicarbonate treatment (HCO3<22 mEq/L) and group B (n:25) patients who were treated sufficiently (HCO3>22 mEq/L), at the end of study.

Results: Hematological parameters as hemoglobin, hematocrit, leukocyte and platelet counts of all patients were analyzed at the beginning and end of the study. Mean hemoglobin, leukocyte and platelet counts were similar between groups at the begining (p value 0.611, 0.314 and 0.840, respectively). In addition, no significant difference was found in mean hemoglobin, leukocyte and platelet counts after 3 months (p value 0.713, 0.277 and 0.937, respectively)

Conclusion: Correction of metabolic acidosis secondary to chronic renal disease by sodium bicarbonate treatment had no effect on anemia and other hematologic parameters in predialysis period.

Keywords: Chronic Renal Disease, Hematological Parameters, Metabolic Acidosis, Sodium Bicarbonate Treatment

INTRODUCTION

In the US, the prevalence of chronic kidney disease (CKD) among the general adult population is about 14% according to the 2015 USRDS Annual Data. The prevalence of CKD in the general adult population is 15.7% according to the CREDIT study in Turkey.[1] Chronic kidney disease is a multisystemic disease affects whole body. Impairment of the hematological system is common in chronic kidney disease. Anemia is the most common one, of these disorders and the frequency of anemia increases with the decrease in the glomerular filtration (GFR) rate.[2] Approximately 90% of patients with GFR below 25-30 ml/ min have anemia and in most patients the hemoglobin value is below 10 g/ dl.[3] In studies conducted with uremic patients, platelet dysfunction,as well as intrinsic platelet defects and abnormal platelet endothelial interactions have been shown.[4,5] Mild thrombocytopenia may be seen in some uremic patients.[6] Patients with CKD have also been shown to have reduced leukocyte activity. Cell mediated immunodeficiencies and hypogammaglobulinemia are known to be present in patients with chronic kidney disease.[7] Another common complication of CKD is metabolic acidosis. Metabolic acidosis develops in 80% of chronic kidney patients with glomerular filtration rate below 20% -25% of normal values.[8,9]

CKD patients with metabolic acidosis could develop a wide range of pathophysiological changes such as changes; 1-bone resorption and osteopenia, 2-increase in protein catabolism in muscles, 3-worsening of secondary hyperparathyroidism, 4-hypothyroidism, 5-decrease in respiratory reserves and insufficient buffer systems in the body leads to and increased severity of acute diseases caused by the diminished respiratory reserves and insufficient buffering systems, 6-decreased myocardial contractility and heart failure which can lead into reduced Na-K ATPase activity, 7-endocrine disorders such as growth hormone and insulin resistance, and hypertriglyceridemia in erythrocytes and myocardial cells, 8-increase in systemic inflammmation, 9-hypotension and fatigue, 10-progression of renal damage.[10-19] The results of these studies suggest that metabolic acidosis in chronic kidney disorease may be associated with hematological changes in these patients either by contributing to the progression of the disease or by its pathophysiological effects. Treating metabolic acidosis with oral sodium bicarbonate was predicted to prevent these hematological

[1]Internal Medicine Clinic, [2]Internal Medicine Clinic, [3]Internal Medicine Clinic, [4]Nephrology Clinic, Adana Numune Health Training and Research Center, University of Health Sciences, Adana, [5]Internal Medicine Clinic, [6]Internal Medicine Clinic, Istanbul Haseki Health Training and Research Center, University of Health Sciences, Istanbul, Turkey

Corresponding author: Betül Çavuşoğlu Türker, MD, Istanbul Haseki Training and Research Hospital, University of Health Sciences, Adnan Adıvar Caddesi, 34096, Fatih, Istanbul, Turkey

How to cite this article: Tayyibe Saler, Mehmet Bankir, Serkan Duman, Sibel Ada, Betül Çavuşoğlu Türker, Süleyman Ahbab. The effects of oral sodium bicarbonate treatment on hematological parameters in patients with chronic kidney disease during the predialysis period. International Journal of Contemporary Medical Research 2018;5(5):E1-E6.

DOI: http://dx.doi.org/10.21276/ijcmr.2018.5.5.2

abnormalities.[20] Studies that examine the relationship between metabolic acidosis and hematologic changes in CKD are limited in the literature. In this study, it was aimed to investigate the effect of oral sodium bicarbonate treatment of metabolic acidosis in CKD on hematological parameters.

MATERIAL AND METHODS

This study was consisted of 111 chronic kidney patients aged between 18-75 who followed up regularly from nephrology clinic of Adana Numune Health Training and Research Hospital between November 2014 and May 2015. Patients' demographic and clinical characteristic features were provided from the hospital's database system, retrospectively. Informed consent form was obtained from all participants. This study approved at Adana Numune Health Training and Research Hospital's Ethics Committee (Date 31.03.2016 and Study Approvement No. ANEAH.EK-2016/61). Sixty-two of 111 CKD patients in predialysis period with metabolic acidosis (*pH <7,35, HCO3<22*) were treated with oral sodium bicarbonate (HCO_3) treatment. Patients divided into two groups, group A (*n:37*) patients who had persisted metabolic acidosis though oral sodium bicarbonate treatment with a HCO3<22 mEq/L level and group B (*n:25*) patients who were treated sufficiently with a HCO3>22 mEq/L level, at the end of study. Exclusion criteria were morbid obesity, acute kidney damage susceptibility, hemodialysis patients, active infection, chronic liver disease, thyroid disease, pregnancy and malignancy. Hematological parameters (leucocyte, hemoglobin, hematocrit, thrombocytes counts), creatinin, urea, ferritin, parathyroid hormone (PTH), C-reactive protein (CRP), blood pH, partial carbon dioxide pressure (pCO2), and HCO3 levels were analyzed for all patients of the study.

Study of Blood Samples

Serum urea and creatinin levels were measured with Beckman Coulter Synchron LX 20 (Massachusetts, USA) using commercially available kits. Complete blood counts were analyzed with fluorescence flow cytometry using Sysmex XE 2100i (Japan). Immunoturbidimetric method was used for CRP measurement. Blood HCO3, pCO2 and pH measurements were detected from venous blood samples with blood gas analyzer (Roche cobas b 121 POC system) within 15 minutes.

Patients' (parathormone) PTH levels were measured by electrochemiluminescence immunoassay using the Abbott Architect i2000 (Illiniosis, USA) analysis system. Ferritin levels of the patients were measured by electro-chemiluminescence immunoassay using Roche C-601 (Japan) analyzer. The glomerular filtration rate of the patients was calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and the body mass index (BMI) was calculated by using body weight (kg)/height (m^2) formula.

STATISTICAL ANALYSIS

In statistical analysis, the statistical package program MedCalc 16.4.3 (MedCalc Belgium) was used. The distribution of the data was determined by the Kolmogorov-Smirnov test. Chi-square test was used to compare the frequency of demographic data and groups, independent t test or Mann-Whitney U test was used according to whether two groups had continuous distributions of normal variables or not]. A p-value of <0.05 was considered statistically significant when the results were evaluated.

RESULTS

Of the 62 patients included in the study, labeled as the control group, in their venous blood gas sample, 37 patients had hco3 value below 22 meq/l 3 months afterwards the beginning. 25 patients whose hco3 values were above 22 meq/lt in their venous blood gas analysis, 3 months after the onset, were labeled as the treatment group. When the initial demographic data of the study population were examined, the two groups were similar in terms of gender distribution (p=0,963), at the same time, no statistically significant difference was found between the groups when the groups were evaluated in terms of the mean age (p=0,451) When the body mass indexes of the groups were compared no statistically significant difference was found, (Table 1).

There was no significant difference in blood bicarbonate levels, between the groups who had received sodium bicarbonate treatment or not. (p=0,075). Treatment doses were 2,8±1,0 gr/day, 3,2±0,8 gr/day, respectively. When the average bicarbonate levels of these two groups were evaluated, mean bicarbonate level of the control group

Variables	Group A (n=37)	Group B (n=25)	p
Age (years)	55,8±17,2	58,9±13,4	0,451
Gender (women n, %)	19 (%51,4)	13 (%52)	0,963
BMI (kg/m2)	27,7±5,3	30,3±5,3	0,073

Table-1: Comparison of demographic data of the groups

Variables	Group A (n=37)	Group B (n=25)	P value
Ph	7,30±0,04	7,33±0,04	0,014
HCO3 (meq/L)	19,5±2,0	24,0±1,6	<0,001
pCO2 (mm/Hg)	41,7±6,3	43,0±5,4	0,424
eGFH (ml/min/1,73m2)	18,6±8,4	20,3±10,9	0,484
Creatinin (mg/dl)	3,6±1,3	3,4±1,3	0,576
Ferritin (ug/L)	164,6±153,6	200,4±177,7	0,221
PTH (pg/mL)	249,5±143,6	223,3±171,0	0,541
CRP (mg/L)	0,87±0,68	1,11±0,89	0,779
NaHCO3 gr/day	3,2±0,8	2,8±1,0	0,075

Table-2: Comparison of Groups' blood gas and biochemical data at the end of 3rd month

Variables	Group A (n=37)	Group B (n=25)	P value
Hgb (gr/dl)	11,3±1,6	11,5±1,7	0,713
Htc (%)	34,4±7,5	35,0±5,1	0,755
RBC (million/mm3)	3,78±0,54	3,84±0,58	0,712
Platelets (/mm3)	254810±107228	253760±82735	0,937
WBC	7812±2550	8517±2379	0,277

Table-3: Comparison of the latest hemograms of the groups

Variables	Initial	3rd month	P value
pH	7,30±0,04	7,33±0,04	0,012
HCO3 (meq/L)	19,6±2,5	23,9±1,71	<0,001
pCO2 (mm/Hg)	42,3±6,8	42,9±5,3	0,735
eGFH (ml/min/1,73m2)	20,1±11,2	20,5±10,7	0,910
Creatinin (mg/dl)	3,58±1,56	3,4±1,35	0,657
Hgb (gr/dl)	11,2±1,7	11,4±1,7	0,611
Htc (%)	34,1±5,4	34,9±5,0	0,545
RBC (millions/mm3)	3,74±0,57	3,82±0,57	0,610
Platelets (/mm3)	248692±74493	253500±81076	0,840
WBC (/mm3)	8788±2614	8528±2332	0,314
Ferritin (ug/L)	188,6±184,5	200,4±177,6	0,376
PTH (pg/mL)	233,7±172,4	223,3±171,0	0,834
CRP (mg/L)	0,74±0,74	1,11±0,89	0,809

Table-4: Comparison of laboratory data of patients who have benefited from the NaHCO3 treatment at the begining and 3rd month

(19,5±2,0 meq/L) was lower than the mean bicarbonate level of the treatment group (24,0±1,6 meq/L). This difference, comparing the two groups, was statistically significant (p=0,001)

When the mean venous blood pH values of the groups at the end of the study are evaluated, mean pH level of treatment group (7,33±0,04) was higher than the mean pH level of control group (7,30±0,04) and this difference was found to be statistically significant (p=0,014)

When the groups' end of the study mean partial CO2 pressures (pCO2) were compared, no statistically significant difference were found. (p=0,424). At the end of the study when the two groups were compared, no statistically difference was found in their final mean; 1- partial co2 pressures (p:0,424), 2-eGFR values (p:0,484), 3- creatinine values (p:0,576), 4-PTH levels (p:0,541) and 5-CRP levels (p:0,779) (table: 2). When the latest hemogram data were compared, there was no significant difference between the groups. (Table 3)

In 25 patients who benefited from oral sodium bicarbonate treatment the mean bicarbonate levels at the end of the third month (23,9 ± 1,71 meq / L) was higher than the mean bicarbonate level at the beginning of the study (19,6 ± 2,5 meq / L) and this difference was statistically significant (p = <0.001). (When the mean hemoglobin value of the patients in the treatment group was examined, there was no statistically significant difference between the study initiation and study end values (p=0,611). Also, the difference in mean platelet values of the patients between the beginning of the study and the end of the study was not statistically significant (p=0,840). In addition, no statistically significant difference was found between the mean number of leukocytes at the start and in the end of the third month in the treatment group (p=0,314) (table:4).

Also, when the mean eGFR values and the mean creatinine values at the baseline and the end of the third month of these patients were compared between themselves, there was no statistically significant difference in terms of mean eGFR (p = 0,910) and mean creatinine (p = 0,657) values. When the mean PTH levels and mean CRP levels at the baseline and at the end of the third month of the same patient group were compared between themselves, there was no statistically significant difference in terms of mean PTH (p = 0.834) and mean CRP (p = 0.809) (table:4).

DISCUSSION

In our study, we investigated the effects of oral sodium bicarbonate treatment on the hematological parameters in the metabolic acidosis that occurs in chronic renal disease patients in the predialysis period. At the end of our study, we observed that the improvement of metabolic acidosis in patients who had oral sodium bicarbonate treatment did not have any beneficial effect on hematological parameters.

Observational studies have shown that metabolic acidosis occurs in the majority of chronic renal disease patients with glomerular filtration rate (GFR) falling below 25% of normal values.[21-24] Sixty two patients included in our study had advanced renal chronic kidney disease and all had metabolic acidosis at the beginning of the treatment.

In the literature, there are many studies investigating the pathophysiological changes that may be caused by metabolic acidosis in chronic kidney disease, but the number of studies examining the relationship between metabolic acidosis and hematological changes in these patients is limited.[25-28] There is evidence in the literature that anemia is associated with nutritional status. A cross-sectional study by Ramel A et al.on this subject showed that there is a relationship between impaired nutritional status and anemia.[28] In a study that investigates the effect of metabolic acidosis on nutritional status in chronic kidney disease, conducted by Soleymanian T et al, serum bicarbonate level was correlated with serum albumin level, an important biochemical marker of nutritional status. 17 patients with a serum bicarbonate concentration of less than 22 meq / L showed lower levels of albumin when compared to patients with a bicarbonate concentration of greater than 22 mEq / L.[29] The results of these studies suggest that metabolic acidosis may be associated with anemia by affecting the nutritional status of chronic kidney patients.

Brüngger M et al have shown that metabolic acidosis reduces hormone secretion of the thyroid gland, while free T3 and free T4 levels diminish in the serum in metabolic acidosis.[30] A randomized controlled trial by Disthabanchong S et al., has been shown that correction of metabolic acidosis with oral sodium bicarbonate treatment improves thyroid functions in patients with chronic kidney disease.[31] There are studies in the literature regarding the relationship between thyroid dysfunction and anemia. In a study conducted on this subject with 8791 participants by M'Rabet-Bensalah K et al it was shown that the prevalence of anemia is higher in patients with thyroid dysfunction than in those with euthyroidism.[32] The existence of studies shows that thyroid functions can be corrected with acidosis treatment in chronic renal failure may suggest that anemia can be corrected indirectly with oral sodium bicarbonate treatment. But in our study, we did not see such an effect of sodium bicarbonate treatment on hemoglobin values.

Secondary hyperparathyroidism can lead to hematological abnormalities in chronic kidney disease.[33] In a study to investigate the effects of metabolic acidosis on parathormone, K.A. Graham et al. have shown that correcting metabolic acidosis in hemodialysis patients increases the parathyroid gland's sensitivity to calcium levels and reduces parathormone (PTH) levels by preventing secondary hyperparathyroidism.[34] In our study, it was observed that correcting metabolic acidosis with oral alkaline treatment did not have any significant effect on PTH levels in chronic kidney disease. Our study period was 3 months time, and this was not considered sufficient to correct the PTH levels though.

Inflammation can lead to the development of anemia through changes in systemic iron use, erythrocyte production, and erythrocyte life span.[35] One of two studies investigating the relationship between metabolic acidosis and inflammation was conducted by Pickering WP et al. with 8 peritoneal dialysis patients and it was found that the correction of metabolic acidosis was significantly associated with a low serum TNF α concentration.[36] A second study conducted by Shih-Hua Lin et al. divided chronic renal disease patients into three groups according to the plasma bicarbonate concentration and no significant difference was found between the groups in terms of serum CRP or IL-6 levels.[37] Our study showed that there was no correlation between metabolic acidosis and serum CRP values consistent with the findings of the second study. Low serum bicarbonate levels were found to be associated with an increase in the risk of ESRD and a 50% reduction in eGFR in the 3939 patients who participated in the CRIC study, one of the observational studies showing that low bicarbonate concentrations are associated with greater loss of renal function in chronic renal failure patients in the predialysis period. The results of a randomized controlled trial by Disthabanchong S et al. showed that treating metabolic acidosis with oral sodium bicarbonate treatment at 8-12 week periods in patients with CKD was significantly associated with higher mean eGFR levels.[31] In a single-center randomized controlled trial in which 134 patients with G4 CKD were evaluated by Rustom R. et al., patients with metabolic acidosis treated with oral sodium bicarbonate showed a less average decrease in creatinine clearance after two years of follow-up.[38] Throughout our study, e-GFR or creatinine values had no significant difference in the treated metabolic acidosis group. Similar to those have been placed in the literature, our research showed that treating metabolic asidosis is associated with slowing the progression of renal injury.

Previous studies have shown that, metabolic acidosis in chronic renal disease may contribute to hematologic changes in CKD patients by worsening the progression of the disease through possible pathophysiological effects. Alcaline treatment could alleviate the unwanted physiological changes caused by metabolic acidosis, slow the progression of renal disease and also fiz the hematological abnormalities seen in these patients.

Anemia is one of the most common hematologic impairments occurring in chronic kidney disease. In a cross-sectional multicentral study which McClellan and colleagues conducted with 5222 patients in the United States with an anemia definition of 12 g / dl hemoglobin value and below, the prevalence of anemia in chronic renal disease was found to be 47.75%. The prevalence of anemia was increased with the severity of renal damage increased, up to 75.5%.[39] In another study by Valderrábano et al., the prevalence of anemia in patients in predialysis period was found to be as high as 68%. This is based on the assumption that the definition of anemia in the study was 11mg / dl.[40] In our study, the prevalence of anemia at the beginning of the study was 80% according to the WHO's definition of anemia. This was thought to be related to the fact that all of participants had chronic kidney disease with advanced stage. Another haematological impairment that occurs in chronic kidney disease is coagulation defects. Platelet dysfunction, abnormal platelet-endothelial interactions and intrinsic platelet defects have been shown in uremic patients. Several studies have reported mild thrombocytopenia in some uremic patients. A cross-sectional study by Akbar Dorgalaleh et al found that the mean number of platelets in CKD patients was significantly lower than in healthy individuals.[41]

In an animal study conducted by Martini WZ et al investigating the effect of metabolic acidosis on platelets, blood samples were taken from the subjects whose blood pH were made acidic with HCL infusion and blood samples were taken again after the blood pHs of the same subjects were neutralized with bicarbonate infusion. The number of platelets in the acidotic blood was decreased and platelet counts remained low after pH neutralization.[42] Apart from this animal study, in our study the mean platelet counts of patients with metabolic acidosis were normal. In our study, it was observed that the treatment of metabolic acidosis with sodium bicarbonate was not related to the mean platelet count. Reduced leukocyte chemotaxis, phagocytosis and bactericidal activity have also been shown in chronic renal disease. Cell-mediated immunodeficiencies and hypogammaglobulinemia are also described in chronic renal disease. In our study, the mean leukocyte counts in both the control and treatment groups were within normal limits. In addition, the mean leukocyte counts at the beginning and at the end of the 3rd month in the treatment group were also normal. In a cross-sectional study conducted by Reza Afsar et al with a total of 100 chronic kidney disease patients (54 hemodialysis patients and 46 patients in predialysis period) the total leukocyte count was found in normal range in both groups.[43] There was no significant difference between the mean GFR and the mean daily sodium bicarbonate treatment doses of the patients receiving oral sodium bicarbonate treatment included in the treatment, but the difference in blood HCO3 levels among the groups was attributed to the possible differences in patients compliance. As in other studies, there were some limitations in our study. The main limitations of our study were retrospective planning of the study, short time period and low population.

In conclusion, treatment of oral sodium bicarbonate may

not be effective in short term correction of hematological abnormalities due to chronic renal disease, but, correction of metabolic acidosis with oral sodium bicarbonate therapy in these patients may slow the progression of the disease and reduce complications on other systems by reducing long-term progressive renal loss.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 13-04-2018; **Accepted:** 15-05-2018; **Published:** 26-05-2018