

Oral treatment of metabolic acidosis in hemodialyzed patients and the implications on the hemodynamic status

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Abstract

Metabolic acidosis slowly develops during renal impairment natural evolution towards ESRD and represents an important contributing factor of CKD progression. Although, several clinical and experimental trials reported the major impact of metabolic acidosis on CKD evolution, the pathophysiology mechanism remains a matter of debate. Furthermore, international guidelines do not impose a specific treatment scheme for metabolic acidosis in CKD patients, and metabolic acidosis is not fully compensated once hemodialysis starts. Therefore, the aim of our study was to determine an adequate follow-up of metabolic acidosis therapy benefits and risks in HD patients. *Patients and Methods:* 164 HD patients were evaluated according to the following protocol: bioumoral laboratory tests, the measure of different important parameters (residual diuresis, UF, BP, LVMI, volemia status). The assessed data were statistic analyzed using non-paired Student's *t*-test for continuous variables and *chi*-square (χ^2) test for qualitative parameters (p -value <0.05 was considered statistically significant). *Results:* HD individuals were followed-up depending on their predialysis-alkaline reserve value. After therapy started, predialysis-alkaline reserve mean level increased from 19.4 mEq/L to 22.6 mEq/L ($p<0.001$). Furthermore, we observed a significant decrease of nitrogenous waste products values ($T=10.87<1.66$) and intradialytic hypotension events ($p<0.001$). *Conclusions:* Our findings emphasize the beneficial effects of correcting metabolic acidosis using the proposed treatment scheme with direct impact on hemodynamic status improvement.

Keywords: metabolic acidosis, ESRD, dialysis, oral bicarbonate, hemodynamic state.

Introduction

Metabolic acidosis slowly develops during renal impairment natural evolution towards end-stage renal disease (ESRD) [1–5]. Although metabolic acidosis is worldwide recognized as a uremic toxin, its implication in chronic kidney disease (CKD) pathophysiology mechanism is still unknown [6]. Some experimental studies associated increased ammonia synthesis to tubulointerstitial lesions but without clear evidence on human subjects [7, 8]. After renal replacement therapy (RRT) initiation, the short or long-term effects of blood acid ions and postdialytic alkalosis acute events persistence are not entirely understood [6, 9]. Even if it is unanimously accepted that metabolic acidosis is not fully compensated once hemodialysis (HD) therapy starts [10, 11], *K/DOQI Guidelines* do not impose a specific therapy scheme for metabolic acidosis in CKD subjects, only suggest the need of treating acidosis when serum bicarbonate levels are below 22 mEq/L [12]. Thus, there is evidence to support that low serum bicarbonate may lessen CKD progression [1, 13], future clinical trials are needed [1]. In addition, oral bicarbonate administration in HD individuals must be performed with caution due to hydrosaline retention [14]. Therefore, the aim of our study

was to determine an adequate follow-up and scheme of metabolic acidosis therapy in HD patients and to determine the consequent benefits and risks.

Patients and Methods

The trial was conducted between March 2008 and March 2011, including chronic dialysis – HD or peritoneal dialysis (PD) – patients from IHS Dialysis Center, "St. John" Emergency Clinical Hospital, Bucharest, Romania. Subjects presenting life-threatening comorbidities (severe neurological disorders, neoplasia with metastasis or recent chemotherapy, severe heart, hepatic or respiratory failure) and those who did not consent were excluded.

One hundred and ninety two individuals were selected (28 PD patients and 164 HD patients) with the succeeding demographic features (Table 1).

Table 1 – Patients demographic features

	HD patients		PD patients	
	Male	Female	Male	Female
Mean age [years]	41.3		67.2	
Gender (n)	93	71	12	16
Mean period of dialysis [months]	54		25	

The study was performed according to the following protocol:

- Biomoral laboratory tests – in agreement with *IHS Center of Dialysis Regulation Policy* (according to the Romanian legislation for dialyzed patients): at one month – complete blood count, blood glucose, urea, creatinine, calcemia, predialysis serum bicarbonate; at six months – total proteins, albuminemia, alkaline phosphatase, C-reactive protein, iPTH. Predialysis serum bicarbonate (alkaline reserve) represented the elected biomarker to evaluate acid-base balance (predialytic normal values range 22–26 mEq/L). All blood samples were taken before the dialysis session, after a short interdialytic period (44 hours).

- Constant observations of (1) residual diuresis volume, (2) required ultrafiltration (UF), (3) blood pressure (BP) values (pre- and post-dialysis), (4) left ventricular hypertrophy (LVH) – routine echocardiography to calculate left ventricular mass index (LVMI), (5) patients' volemia status (bioelectrical impedance analysis) and (6) frequency and duration of hospital stay.

- The NaHCO_3 doses were ordered for one month and changes were made if patients experienced acute episodes.

The assessed data were statistic analyzed using non-paired Student's *t*-test for continuous variables and *chi*-square (χ^2) test for qualitative parameters. A *p*-value <0.05 was considered to be statistically significant.

The structure of the research included two different studies each for a 12 months period. The first, a prospective non-intervention trial, evaluated the possible affected parameters by important interdialytic acidosis, analyzing patients' features with serum bicarbonate <20 mEq/L. In the second study, a prospective intervention one, specific treatment to correct severe acidosis was initiated and the consequences on hemodynamic status in this group of individuals were observed.

Results

Our study was exhaustive and therefore, in the present article, we will focus only on HD patients' ($n=164$) outcome and their association to alkaline reserve (AR)/predialysis serum bicarbonate values – preD-AR.

The HD subjects were followed-up, depending on their preD-AR value, in four groups presenting an annual mean value of 20.88 ± 1.94 mEq/L (Figure 1):

- Group 1: 48 patients with preD-AR <20 mEq/L;
- Group 2: 84 patients with preD-AR between 20–22 mEq/L;
- Group 3: 18 patients with preD-AR between 22–26 mEq/L;
- Group 4: 14 patients with preD-AR >26 mEq/L; this group included subjects with intermittent predialytic metabolic alkalosis.

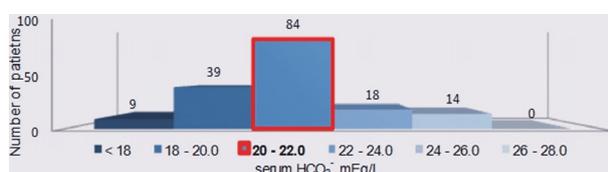


Figure 1 – Patients' distribution according to preD-AR values.

Furthermore, our manuscript highlighted Group 1 evolution, involving subjects with significant acidosis. Additionally, for an accurate comparison we included also patients to whom drug administration was contraindicated and did not receive it.

In the first 12 months, we evaluated preD-AR values and the impact on hemodynamic status. Consequently, in the following year, HD individuals received oral bicarbonate in interdialytic days, measuring, once again, the impact on their hemodynamic status. The daily dose was linked to BP, residual diuresis and preD-AR values. Tablets of 650 mg were used (two, four or six tablets per day) only in interdialytic days. The daily dose was:

- 1.3 g in patients with poor controlled BP and/or interdialytic weight gain over 3000 mL;
- 2.6 g in patients with controlled BP and/or interdialytic weight gain between 1500–3000 mL;
- 5.2 g in patients with 1000 mL residual diuresis and no need for antihypertensive treatment.

After therapy was started, a major improvement of preD-AR values was noticed in Group 1 (Figure 2).

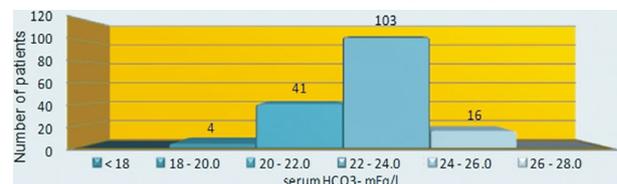


Figure 2 – PreD-AR values after treatment initiation.

The influence of oral bicarbonate therapy on preD-AR annual mean value

PreD-AR annual mean value in Group 1 was 19.4 mEq/L before treatment (bT) and 22.6 mEq/L after therapy (aT) started with statistic significance ($p < 0.001$) (Figure 3). Although four patients did not receive drug administration, the mean values after treatment initiation were ranged in normal limits.

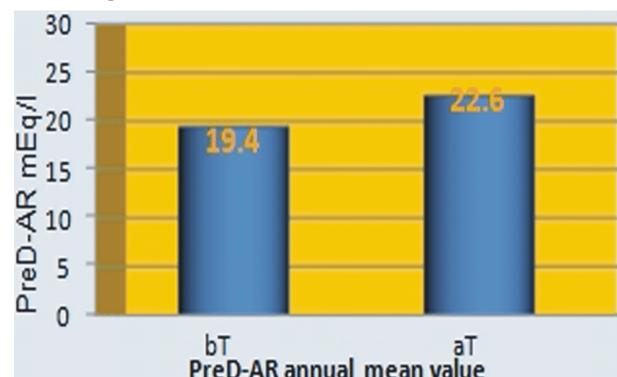


Figure 3 – The influence of oral bicarbonate therapy on preD-AR annual mean values.

The influence of oral bicarbonate therapy on UF

Before therapy, UF mean value was 2050 ± 1002 mL/dialysis session and aT the volume increased to 2230 ± 949 mL/dialysis session. UF mean quantum (Figure 4) was higher in treated patients ($n=48$) – 180 mL, comparative to all HD individuals ($n=164$) – 100 mL – insignificant increase:

$$S_p = 975.87, t_{n_1+n_2-2; 1-\alpha} = 1.66, T = 0.90 < 1.66$$

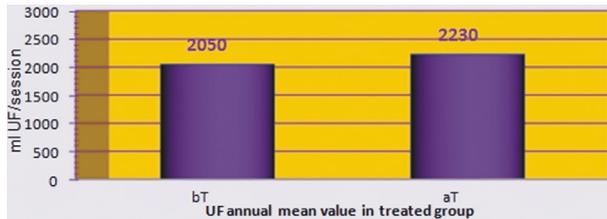


Figure 4 – The influence of oral bicarbonate therapy on UF.

The influence of oral bicarbonate therapy on nitrogenous waste products

We noticed an important decrease of urea annual mean levels (Figure 5) from 164.8+18.9 mg/dL to 126.3+15.6 mg/dL after treatment initiation – statistic significant:

$$T = 10.87, t_{n_1+n_2-2; 1-\alpha} = 1.66 \text{ and } T = 10.87 < 1.66$$

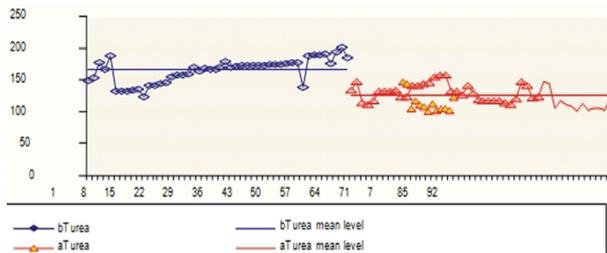


Figure 5 – The influence of oral bicarbonate therapy on nitrogenous waste products.

In addition, nitrogenous waste products decreased levels may be a consequence of hemodilution caused by predialytic fluid overload.

The influence of oral bicarbonate therapy on BP values

Comparing preD-BP means values (maximum and minimum) before and after therapy, we observed an important increase of both values: from 162 mmHg (preD-BP maximum mean level) and 86 mmHg (preD-BP minimum mean level) to 171 mmHg and 92 mmHg, respectively. Regarding postD-BP, we noticed only insignificant and uncharacteristic changes: from 142 mmHg (postD-BP maximum mean level) and 76 mmHg (postD-BP minimum mean level) to 144 mmHg and 80 mmHg, respectively. Statistically, there is an obvious increase of preD-BP and insignificant one of postD-BP.

The influence of oral bicarbonate therapy on LVH evolution

LVMI evolution during the treatment year (LVMI mean value of 19.7 g/m²) presented only a minimum modification than LVMI progression during the year without therapy (LVMI mean value of 21.9 g/m²) but higher comparing to all HD patients (n=164) LVMI mean level (Figure 6).

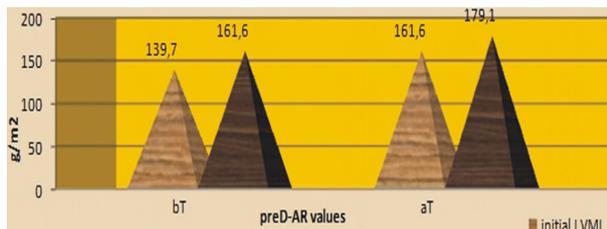


Figure 6 – Initial and at 12 months LVMI evolution before and after treatment.

The influence of oral bicarbonate therapy on the frequency of intradialytic hypotension (hBP) events

In the first year, 32 (66.6%) patients presented intradialytic hBP events and after therapy started, we observed an important decrease of intradialytic hBP episodes (19 patients – 39%). The statistic analysis emphasizes the beneficial effects of oral bicarbonate administration on lesser the frequency of intradialytic hBP events (Table 2, Figure 7).

Table 2 – Intradialytic hypotension episodes

	Intradialytic hBP	No intradialytic hBP	Total	%
Before treatment	32	16	48	0.667
After treatment	19	29	48	0.396

$$\hat{p} = 0.53 \quad Z = \frac{0,67 - 0,40}{\sqrt{\frac{0,53 * 0,47}{48 + 48}}} = 5,32$$

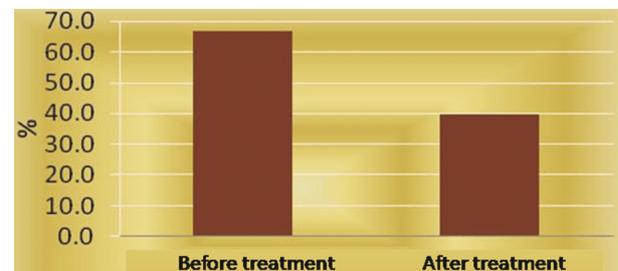


Figure 7 – Intradialytic hypotension events before and after therapy.

The influence of oral bicarbonate therapy on frequency and duration of hospital stay

After treatment initiation, the frequency and duration of hospital admission significantly decreased (duration of hospital stay dropped to a mean value of 11.8 days) (Figure 8).

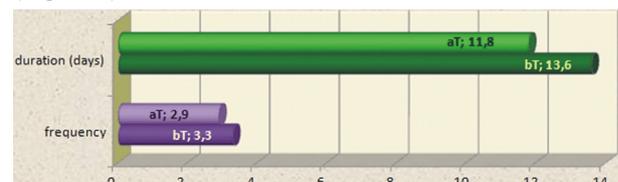


Figure 8 – The influence of oral bicarbonate therapy on frequency and duration of hospital admission.

Discussion

The aim of our study was to evaluate the benefits and the risks of oral sodium bicarbonate therapy for severe acidosis, and the consequences on hemodynamic status of hemodialyzed patients.

Our results are in agreement with literature database, highlighting the major impact of severe acidosis (preD-AR < 20 mEq/L) on the levels of nitrogenous waste products [15–18], renal osteodystrophy biomarkers [18], nutrition state [16, 19, 20], inflammation biomarkers [16, 19–22], intradialytic incidents [18], cardiovascular events [18], renal and non-renal morbidities and mortality [23–26].

We reported a diuresis mean value of 579.51 ± 511 mL in all HD patients ($n=164$) and of 495 ± 423 mL in Group 1 (preD-AR < 20 mEq/L). This statistically significant difference represents an important risk factor of elevated incidence and severity of fluid overload in patients with preD-AR values < 20 mEq/L. According to bioelectrical impedance analysis, 78% of patients with severe acidosis presented important fluid overload and therefore, a higher UF rate for each dialysis session was required. UF annual mean level was substantially increased in Group 1 (2050 ± 1002 mL) comparing with the annual mean value of all HD patients (1825 ± 1061 mL). For this reason, the need of increased UF was linked to elevated frequency and severity of intradialytic hypotension episodes. The permanent hemodynamic variations caused by “fluid overload/UF phenomena” (additionally to important pressure dynamic fluctuations in severe acidosis patients) determine alteration of vascular and myocardial walls; these structures undergo constant sudden and pathologic pressure changes [27–29].

All these modifications, additionally to anti-anabolism and pro-catabolism phenomena due to severe acidosis effect (emphasized by a decreased Kt/V value in Group 1), have a negative impact on myocardial morphology and physiology – myocardial capacity and contractility are affected and an accelerated process of ventricular hypertrophy develops [30–32].

Therefore, these contributing factors are responsible for increased duration and frequent admissions in our patients diagnosed with severe acidosis (3.31 ± 1.78 mEq/mL) comparing with all HD patients from our study and the findings from literature [24, 26, 33, 34].

After the treatment, preD-AR annual mean value was 22.6 ± 1.25 mEq/L in Group 1, emphasizing the beneficial effects of our proposed therapy scheme. In addition, after treatment initiation analyzing all HD individuals, we reached the same conclusion and we highlighted that only few subjects presented values < 20 mEq/L (patients with preD-AR > 22 mEq/mL were not influenced by drug administration).

Furthermore, therapy positive effects were linked to significant decrease of nitrogenous waste products levels and improved dialysis adequacy.

Although predialytic BP was unfavorably affected by oral bicarbonate administration (elevated BP values determining hydrosaline and interdialytic fluid overload with severe consequences on UF rate), statistically it was an insignificant increase. In addition, intradialytic hypotension events decrease correlated to therapy initiation was a major finding.

The influence on LVH evolution was inconclusive. Even if postdialytic BP was unchanged, important hemodynamic fluctuations down-regulated the favorable effects of improved acid-base balance on myocardium and consequently LVMI increased rhythm progression was maintained.

Summarizing, our findings are in concordance with literature database sustaining the positive influence of oral bicarbonate treatment to restore acid-base balance with minimum side effects and maximum wanted beneficences (the treatment is cheap, easy to tolerate and to administrate) [6, 9, 10, 14]. Based on the pre-treatment study results, the most obvious negative effects

of acidosis are within Groups 1 and 2, associating preD-AR values below 22 mEq/mL. Severe acidosis correction is imposed by its attested influences on poor dialysis outcome, favoring a bad nutritional status, alterations of vascular walls and the predisposition for intradialytic hypotensive episodes.

Therefore, our recommendations are: to immediately initiate oral bicarbonate therapy preD-AR values below < 22 mEq/mL in chronic dialyzed individuals and closely evaluate patients under treatment for hypervolemia and hypertension (possible consequences due hydrosaline retention).

Despite the theoretic risks of volume overload induced by sodium intake, we reported an insignificant improvement in patients' hemodynamic state, after treatment started. We must underline the benefit of oral sodium bicarbonate therapy in lowering the incidence and severity of intradialytic events.

Furthermore, the frequency and duration of hospital admission decreased considerable due to enhanced defense capacity against infection risk factors (the improvement of anabolism and tissue quality), decreased pro-inflammation markers synthesis and activation and improvement of Kt/V levels (without any sign of uremic intoxication and consequent complications).

☒ Conclusions

Our study highlights once again the worldwide knowledge regarding severe acidosis (preD-AR < 20 mEq/L) negative impact on dialysis patients' outcome. In addition, acidosis emphasizes preexisting pathological state and induces different comorbidities development. Severe acidosis correction by interdialytic oral bicarbonate administration improves most of clinical and bioumoral parameters, but does not significantly influence overall hemodynamic status.

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Received: April 30, 2013

Accepted: August 5, 2013