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Is Sodium Bicarbonate Therapy Still Up To Date?

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Abstract

Sodium bicarbonate (SB), which has a vital role in the regulation of acid-base balance of all tissues and organs, is one of the most important buffering systems of the body. SB plays an important role in the treatment of poisoning caused by numerous agents including mainly salicylate and tricyclic antidepressants. In metabolic acidosis (MA) occurred in patient with systemic and metabolic diseases, first, the primary disease should be treated and in the case of low bicarbonate levels such as diarrhea and renal tubular acidosis, missing SB should be recovered. As the kidney has an important role in acid-base balance, SB is widely used in the treatment of acute and chronic renal failure. Although there is no conclusive evidence to prevent contrast nephropathy, SB comes to the fore compared to other agents. SB is used due to MA and its effects occurring in acute renal failure. In addition, SB treatment applied to reduce the increased acid levels in chronic kidney failure may reduce mortality. While SB can be used as individualized in lactic acidosis and cardiac arrest cases, it can be used safely as a performance enhancer for athletes. SB is used widely in gastrointestinal tract diseases due to its antacid effects and its routine use is not recommended in diabetic ketoacidosis. These data demonstrate that SB is still popular and it will retain its popularity in the near future.

Keywords: Sodium bicarbonate, metabolic acidosis, toxicology, contrast induced nephropathy, lactic acidosis.

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Introduction

Acid-base balance is vital for the body as all the tissues and organs are very sensitive to pH shift. Acid-base balance in the organism is kept through the major chemical buffering system, mechanisms for respiratory adjustment and renal adjustment. Particularly, the kidney has a crucial role for keeping acid-base balance by means of many mechanisms. Bicarbonate reabsorption and regeneration, and acid excretion are some of these mechanisms. When blood pH level is high, kidneys increase excretion of bicarbonate through urine. However, it reduces urinary bicarbonate excretion when blood pH is low. Carbonic acid/ bicarbonate buffer systems, commonly available in the body, are generally extracellular liquid buffer systems and it is the most rapid buffer system of the body. When pH is 7.4, bicarbonate/carbonic acid ratio is 20, and this ratio is stable under normal conditions. Once bicarbonate/ acid ratio rises above 20, acidosis develops, whereas alkalosis occurs when it reduces lower than 20. In this ratio, bicarbonate affects kidneys, while carbonic acid demonstrates its effect on the lungs. On the other hand, changes in bicarbonate levels lead to changes in metabolic blood gas levels, and changes in carbonic acid levels cause changes in respiratory blood gas.

Sodium bicarbonate (SB) is being used therapeutically in many areas (1, 2). Treatment of metabolic acidosis (MA), occurring when bicarbonate concentration is missing, are provided through the replacement of the SB. Additionally, SB plays an important role in the treatment of poisoning which occurs due to mainly tricyclic antidepressants (TCA), and a large number of agents. SB is widely used in the treatment of acute and chronic renal failure because of its important role in maintaining acid-base balance. In this review, both the treatment areas in which SB is used will be evaluated and the actuality of SB will be discussed.

Metabolic acidosis

MA is formed when the anion load exceeds the cation load in the plasma. In the normal arterial blood, pH level varies between 7.35 and 7.45. Plasma bicarbonate concentration is generally estimated through using blood gas from pH and plasma partial carbon dioxide pressure (pCO_2) values. Blood gas measurements include three parameters as total blood carbon dioxide concentration (tCO2), pCO2 and plasma bicarbonate concentration (HCO_3^-) (3). Treatment for primary disease should be applied first as MA is a biochemical parameter of systemic diseases and metabolic disorders. Ensuring electrolyte and volume balance in cases of MA including high anion gap is often sufficient. The degree of arterial

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pH and the presence of symptoms due to acidosis are important in the SB treatment. Decreasing pH level in diabetic ketoacidosis (DKA), lactic acidosis (LA) and the development of acute conditions such as septic shock is associated with the severity of the disease and requires immediate treatment. SB treatment is required if, apart from MA, symptoms of severe hyperkalemia, hypotension not responding to volume treatment, coma, respiratory depression, respiratory acidosis and congestive heart failure are existed. There has been no clear evidence that MA, which occurs in humans, causes serious damage. (4). So, a successful treatment approach can only be possible with the treatment of underlying causes.

SB replacement is useful in cases such as diarrhea and renal tubular acidosis cases which have low bicarbonate level. On the other hand, no effect of SB, which is used symptomatically, on clinic and mortality, has been demonstrated (5, 6). However, further studies are needed to prove the beneficial effects of SB, which is used symptomatically (7, 8). In the most recent studies, it is estimated that MA worsens the kidney failure and it is just recommended to apply because of renoprotective effects (9).

Toxicology

While alternative treatment strategies in toxicology exist, SB is still the most important treatment option in several toxic actions. With SB treatment, serum alkalinization, alkalinization of urine, and sodium ions load occur (10). SB is widely used in over-dosage of drugs that cause sodium channel blockade. As a result of poisoning with sodium channel blockers (SCB), seizures and ventricular arrhythmias occur. Cardiotoxicity is the most important cause of mortality related to SCB. Electrocardiography (ECG) has a vital role in the emergency diagnosis of poisonings caused by SCB and ECG plays a more important role than of serum concentrations of the drugs. SB is the most commonly used agent in the treatment of TCA and salicylate poisoning. In TCA poisoning, with fast sodium channel blocking, it has been indicated that ECG abnormalities have occurred in the early phase and it has returned to normal with SB infusion (11). Additionally, SB treatment was reported to normalize cardiac rhythm and be effective in the treatment of cardiac rhythm disorders such as cocaine-induced ventricular dysrhythmia (12, 13). However, SB is used actively in many drugs and substance poisoning. These drugs are mainly; type 1 and type 1C antiarrhythmics, local anesthetics, antimalarials, dextropropoxyphene, propranolol, carbamazepine, phenobarbital, chlorpropamide, salicylate, diphenhydramine, propoxyphene, amantadine, cocaine, phenothiazine, quinine, thioridazine, chlorophenoxy herbicides, venlafaxine, and chlorine gas (1, 14) . There is no other accepted alternative treatment agent except SB in SCB poisoning. Alternatively, some researchers suggested sodium acetate as an agent. However, the routine use of sodium acetate is not recommended in the case where SB can be used. Although inexpensive sodium acetate has been asserted as an alternative agent, further prospective studies which verify this issue are needed (10). There are studies indicating that alternative treatment is possible by giving high dose inotropic, vasopressin or terlipressin to the patients who have hypotensive shock due to TCA intoxication. However, these studies suggested that SB treatment should be used primarily (15-16). Antidotes application is not commonly recommended in the literature (10). There are some studies indicating that SB can be used in the treatment of drug and substance poisoning even if acidosis does not exist. Indeed, it has been reported that a patient who developed arrhythmia due to TCA intoxication and had alkalosis was successfully treated by giving SB (17). In another study, however, 2 patients had deep alkalosis due to aggressive SB treatment and hyperventilation and those patients were then lost (18). Thus, pH target is important for alkalosis. 62% of the 58 members of the United Nations Poisoning Center said to believe that minimum pH value should be 7.45, and 66% said that maximum pH should be 7.55 to start SB treatment (19). For the treatment of life-threatening poisoning, 50-100 ml from 8.4% SB is applied. Doses can be repeated to keep pH level between 7.45-7.55 by following blood gas. However, in the patients who are in extravasation and have more stable condition, 500 ml from 1.26% SB is recommended due to low skin necrosis risk (20).

Contrast induced nephropathy (CIN)

Due to the increasing chronic diseases, radio-contrast procedures are becoming increasingly common in diagnosis. Therefore, physicians have difficulty in taking the decision of radiodiagnostic contrast imaging in high-risk patients. So, to protect those patients, risk assessment in terms of CIN should be done and prophylaxis protocols should be used where necessary. As well as intravenous contrast media administration, contrast-induced acute kidney injury (CI-AKI) is the most prevalent iatrogenic reason of acute kidney injury. On the other hand, in patients who have normal renal function, the incidence is generally known to be low (21).

In studies related to the pharmacological treatment protocols used for protection from CIN in the emergency room, sodium chloride and hydration, N-Acetyl Cysteine (NAC), and SB are the foremost agents. The effectiveness of those protocols has been examined under different dosing schedules. The doses can be applied at varying times between 6-24 hours. Even if some of the patients are admitted to hospitals, an important part of them are discharged. Those protocols cause a loss of considerable time and resources. In the studies, it has not been demonstrated with certainty whether the protocols are superior to each other (22, 23). In the randomized controlled study conducted by Barr et al., 353 patients including patients with diabetes mellitus, congestive heart failure, hypertension or older than 75 years old, who took coronary angiography and had glomerular filtration rate (GFR) lower than 60 ML/min, were examined. Those patients were given sodium chloride infusion or SB to protect them from CIN. In the study, after a contrast agent was given, decrease in GFR more than 25% in the following 1-4 days was accepted as CIN. Thus, the study shows that SB was not superior to sodium chloride (22). In another prospective randomized clinical study conducted by Kama et al., 107 patients who were in at risk of CIN were given NAC, sodium chloride and SB. No significant difference was found among those agents in preventing CIN (23). Koomian et al. discovered that SB and sodium chloride which were given before contrasting agent had a protective effect on kidneys and affect the quality of life (24). On the other hand, fenoldopam was found to be ineffective in a large-scale randomized study (25). Likewise dopamine was shown to be ineffective in terms of prevention strategies (26). As for hemofiltration, although it was shown to be useful, it was limited by high cost of implementation and impracticality (27). Dabarca et al. suggested that SB should be added to treatment hydration with sodium chloride after examining 266 studies including patients with cardiovascular disease who had direct contrasting agent exposure (28). However, in a meta-analysis of 19 studies, Jang et al. investigated 3609 patients and asserted that SB was superior to sodium chloride (29).

Acute renal failure (ARF)

ARF is a common, serious, but potentially treatable condition which is often accompanied by acidosis. SB treatment is a highly preferred method for patients with ARF due to MA and developing symptoms. Moreover, in people with acute acidaemia (arterial ph<7, 15), myocardial depression and systemic vasodilatation may be developed by decreasing oxygen delivery. And so, the implementation of SB can improve cardiovascular function and tissue perfusion by increasing extracellular pH (30). SB treatment is controversial in patients with ARF as MA may be caused by shock and LA occurring after the deterioration of tissue perfusion. In a review carried out by Hewitt et al., the answer to the question "what are the potential benefits and harms of SB treatment applied orally or intravenously in ARF?" was sought. Due to the lack of randomized controlled trials regarding the use of SB treatment in ARF, no claim was asserted regarding the advantages and disadvantages of SB (31). Although there is not enough evidence in favor of the use of SB, it is still widespread for the treatment ARF related acidosis, and is suggested as a supportive treatment in many nephrology textbooks (32).

Chronic renal failure (CRF)

In the treatment of many MA, which include renal tubular acidosis, SB is utilized, which has been suggested by many textbooks of nephrology. Moreover, in order to relieve symptoms and prevent uric acid stones in the kidney, SB is used with the aim of alkalizing urine in patients with cystitis (33). As Increased acid levels accelerate CRF progression, low SB level is considered as an independent risk factor of CRF progression (34). In elderly patients with CRF, high level of SB within the normal range is effective to prevent the CRF progression. Kanda et al. discovered that low (<25th percentile) SB level was related to CRF progression, and a 1-mEq/L increase in SB level (in normal range) lowered the risk of CRF progression (35).

The advantages of SB treatment in patients with CRF are being inexpensive, popular and easily accessible. On the other hand, the disadvantages are causing volume overload and the risk of high blood pressure due to the inclusion of sodium. Studies revealed that SB treatment can reduce serum potassium, which may be benefited in patients with CRF that possess the hyperkalemia risk, and get angiotensin-converting enzyme inhibitors (36). Although there is no certain scientific evidence that supports the alkalization therapy done with SB in patients with CRF, SB is commonly used for MA associated with CRF. Additionally, to keep serum bicarbonate in ≥ 22mmol/L level, SB is strongly recommended in current guidelines (36, 37).

Cardiac surgery

ARF associated with cardiac surgery occurs in 50% of patients after surgery and it increasingly causes

mortality and morbidity (38). In a double-blind randomized controlled study, Haas et al. examined 350 adult patients who underwent cardiopulmonary bypass surgery and were given sodium chloride and SB. In addition, SB was seen not to reduce the incidence of, and found to be associated with increased mortality in patients undergoing open heart surgery (39). McGuinness et al. investigated whether perioperative blood and urine alkalinization done with SB reduces acute renal failure associated with cardiac surgery. In that study conducted with 427 patients, it was discovered that SB infusion did not reduce the acute renal failure (38).

Diabetic Ketoacidosis

For many years, SB treatment has been recommended in order to keep pH level in a reliable range. However, it should be noted that the first aim of DKA treatment should not to keep pH level balanced, but to make up for the insulin, which is deficient. Studies in recent years show that bicarbonate treatment does not improve acidemia, and may even be harmful. Duho et al. found that SB treatment did not reduce glucose and ketone levels and did not increase pH (40). In a study compiling 44 works systematically, Chua et al. asserted that SB had no clinical benefit (41). In a recent study, the use of SB was claimed to cause cerebral edema in children with DKA (42). In literature, the studies related to the use of SB on patients with DKA were generally conducted on patients who had between 6.9-7.1 pH levels. No studies on patients having <6.9 pH have been carried out. However, some researchers defend the use of bicarbonate in patients with severe acidemia who have <7, 0 pH (43, 44).

Cardiac Arrest

SB was advised as a first line drug in first Standards for Cardiopulmonary Resuscitation and Advanced Cardiac Life Support written by the American Heart Association (45). In the guidelines published later, restrictions on the use of SB were imposed. In the latest one published in 2010, the use of SB was not recommended. However, SB may be advised to be used in prolonged cardiac arrest after enough alveolar ventilation and effective cardiac compression are performed. Additionally, SB may be useful in some cardiac arrest situations such as MA, hyperkalemia, and TCA overdose.

Lactic acidosis

Exogenous bicarbonate therapy in patients with LA is controversial. Although there is not any negative and positive evidence about SB in patients who have <7.1 pH, the use of SB is recommended. Because, use of the SB prevents various side effects of LA such as decreased left ventricular contractility, arrhythmia, arterial vasodilatation, venoconstriction and impaired response to vasopressors (47). The potential hazards of bicarbonate therapy are increase in arterial and tissue capillaries PCO2, increase in lactate production, decrease of ionized calcium, hypernatremia and an increase in the extracellular fluid volume (48, 49). In a study conducted with 103 patients whose mean age was 66.1, the group having LA and given SB had higher mortality rate. In this study, independent factors affecting mortality were found to be as Sequential Organ Failure Assessment score and SB treatment (50). Because of the limitations and potential side effects of bicarbonate therapy in patients with LA, efforts to find an alternative agent have been accelerated. These agents are Tromethamine, Carbicarb, and Dichloroacetate. No clinical benefit of these substances in terms of mortality could be demonstrated (51, 52). In animal studies on acute LA, it has been demonstrated that selective sodium-hydrogen exchanger 1 inhibitors help to improve hemodynamics and reduces mortality (53). As a result, correction of the underlying cause is always better than bicarbonate replacement. Bicarbonate that was given to patients may become carbon dioxide. Especially in patients with ventilation problems this situation creates serious problems. Although there is no definitive proven benefits of bicarbonate, it is recommended if pH <7.1 in LA. However, it is more effective than other alternatives.

Septic shock

In the studies conducted on patients with septic shock, SB was found to have no effect on mortality and hemodynamic changes in those patients (54). Surviving Sepsis Campaign guidelines, for patients with hypoperfusion-induced lactic acidemia with pH ≥7.15, do not recommend bicarbonate treatment to improve hemodynamic status or to reduce vasopressor requirements (55).

Rhabdomyolysis

SB is often used in preventing the destruction of myoglobin by doing urine alkalinization and its nephrotoxic metabolites (56). There has been little evidence related to the routine use of bicarbonate, mannitol and loop diuretics in rhabdomyolysis. On the other hand, today, aggressive fluid resuscitation with isotonic fluid is used in the majority of the

patients to prevent acute renal failure due to rhabdomyolysis (57).

Oral use: SB is widely used in digestive system diseases due to its antacid properties. In a randomized controlled study conducted with 92 patients, it was found that the combination of the use of SB and proton pump inhibitor had a significant effect on reflux esophagitis (58). In another study, SB with omeprazole was found to be very effective in Barrett esophagus (59).

SB is also used as a performance enhancer for athletes. In a meta-analysis examining the effects of SB, sodium citrate and ammonium chloride on performance, it was reported that SB was effective to increase performance and was recommended in short-term high-intensity exercises (60). On the other hand, in another study, SB, which was given before intermittent exercises, was found to have no significant effect on performance even if it induced metabolic alkalosis. However, individual bicarbonate intake based on the time and density of the exercises was recommended as individual performances of the subjects significantly differ from each other (61).

Consequently, SB is still used safely in especially toxicology, MA, some gastro-intestinal diseases and athletes as performance enhancers. Although, there is no conclusive evidence that SB prevents contrast nephropathy, it comes to the forefront compared to the other agents. In LA and cases of cardiac arrest, its use should be individualized. On the other hand, its routine use in DKA is not recommended. In the light of these findings, SB is still a central topic of discussion.

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