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Review

SODIUM BICARBONATE - KNOWN MEDICATION, NEW PROSPECTS?

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ABSTRACT

Critical conditions frequently involve disturbances in blood gas analysis and electrolyte imbalances. Sodium bicarbonate has seen expanded medical use in recent years. The European Resuscitation Council (ERC) Guidelines endorse sodium bicarbonate for hyperkalemia, malignant hyperthermia, and specific drug intoxications. Its potential roles in treating intracranial hypertension and symptomatic hyponatremia are also being explored. However, its application in emergency departments (ED) remains inconsistent, particularly in profound metabolic acidosis cases. We conducted a review of sodium bicarbonate's therapeutic uses. The evolving understanding of sodium bicarbonate's role in emergency medicine and intensive care highlights both its potential applications and associated risks. While not universally beneficial, especially in lactic acidosis, it may aid specific patient subgroups, such as those with acute kidney injury. Its use in hyperkalemia, intracranial hypertension and diabetic ketoacidosis (DKA) also presents mixed results, with potential benefits in particular contexts. Further large-scale, randomized controlled trials are needed to develop precise guidelines, ensuring its safe and effective use tailored to individual patient needs.

KEYWORDS: bicarbonate, lactic acidosis, hyperkalemia, diabetic ketoacidosis, intracranial hypertension

1. Introduction

Critical conditions often include disturbances in blood gas analysis or electrolyte levels. Sodium bicarbonate ($NaHCO_3$) was first used by Egyptians for skin care, wound disinfection or as an agent in mummification process [1]. In recent years its medical use has been more widely explored. European Resuscitation Council Guidelines allow the use of sodium bicarbonate only in three specific situations: hyperkalemia, malignant hyperthermia and certain drugs intoxication, e.g. tricyclic antidepressants and other sodium channel blocker overdoses [2,3]. A potential role of this substance was also explored in treating and preventing the intracranial hypertension [4]. However, the use of sodium bicarbonate in the emergency department (ED) is inconsistent and lacks clear guidance in various clinical scenarios beyond the well-established indications, especially in cases of profound metabolic acidosis.

There are three sodium bicarbonate solutions available: 7.5% and 8.4% in 50 mL ampule and 4.2% in 10 mL ampule for pediatric patients, however the 8.4% solution is most used [1,5]. It contains 84 mg per mililiter, one ampule of 20 mL contains 1.68 g sodium bicarbonate. 1 mL of this solution equals 1 mEq of $NaHCO_3$, that means 1 mmol Na^+ and 1 mmol HCO_3^-. It can be administered as a bolus or a continuous infusion [1].

It seems intuitive to treat all acidoses with an alkalotic sodium bicarbonate, however such therapeutic approach may be potentially harmful. Possible dangers include a leftward shift in the oxygen dissociation curve, alkalemia, fluid shifts or hypercarbia, if the patient's ventilation is ineffective [1,3]. All these situations can lead to further complications.

The aim of this review is to summarize the prospects of sodium bicarbonate in emergency medicine and

intensive therapy, putting the emphasis on its expanded therapeutic potential and the latest clinical evidence supporting these uses.

2. Materials and Methods

The authors carried out a narrative review of the available scientific literature of sodium bicarbonate therapeutic uses in specified fields. The literature was searched using the PubMed database for the articles written in English, published between January 2014 and May 2024 and then analyzed. Predefined search terms included: „bicarbonate", „sodium bicarbonate", „acidosis", „hyperkalemia", „hyponatremia", „intracranial pressure" in titles, abstracts and keywords and they were used to identify specific studies.

3. Mechanism of action

Sodium bicarbonate acts as a buffering agent, neutralizing excess acid in the blood and tissues. It dissociates into sodium and bicarbonate ions. The bicarbonate ions can bind to hydrogen ions to form carbonic acid, which is then converted to water and carbon dioxide. The latter is exhaled through the lungs. This buffering capacity underpins its use in states of acidosis and hyperkalemia [6]. In the hyperkalemic conditions, sodium bicarbonate can be used to shift potassium into cells by increasing blood pH, providing a temporary measure to reduce serum potassium levels [7].

Potential adverse effects of sodium bicarbonate include metabolic alkalosis, hypernatremia, hypocalcemia and fluid overload [1,6,8]. The suspicion of sodium bicarbonate as a cause of intracellular acidosis has not been confirmed in vivo [8]. Hypocalcaemia can be caused in a pH dependent manner and by direct calcium binding. As a key factor in cardiac muscle contractility, it was shown in an experimental model of lactic acidosis that when sodium bicarbonate was combined with calcium, the myocardial elastance, aortic and mesenteric vasoreactivity were improved in comparison with sodium bicarbonate alone [8].

3.1. Lactic acidosis and diabetic ketoacidosis

Lactic acidosis occurs when a serum lactate concentration rises above 4 mmol/L and pH falls below 7.35. There are two types of hyperlactatemia: type A with disoxia and decreased tissue perfusion (e.g. severe hypoxia, anemia, shock) and type B with disorders of oxidative phosphorylation within the mitochondria or sepsis [1,9,10]. Acidemia is suspected to contribute to cardiovascular instability and decreased response to catecholamines. It is also associated with increased mortality [11,12]. Most studies evaluating the sodium bicarbonate use in lactic acidosis have been retrospective or observational. Some data suggested that its administration does not improve hemodynamics in critically ill patients with lactic acidosis [1,6].

Diabetic ketoacidosis (DKA) can lead to severe metabolic acidosis because of insulin deficiency and increase in the levels of counterregulatory hormones. When the hormone-sensitive lipase is released, the lipolysis of free fatty acids into ketoacids lead to an anion gap metabolic acidosis (AGMA), with these unmeasured anions as the predominant components. Both anion and non-anion gap metabolic acidosis can be a component of DKA, because of osmolar diuresis, vomiting and acute kidney injury. The lactate production can also be observed as there is a decrease in tissue perfusion, catecholamine excess and altered glucose metabolism [1,13,14].

Several studies indicate a potential role for bicarbonate therapy during the recovery phase of DKA. Following volume resuscitation, bicarbonate is typically regenerated, but this process can be hindered by the development of hyperchloremia due to the preferential excretion of ketoacids over chloride anions. Additionally, patients with ongoing kidney injury and reduced renal bicarbonate production might theoretically benefit from bicarbonate administration to address this relative bicarbonate deficiency [1,13].

3.2. Hyperkalemia

Hyperkalemia can be defined as a serum potassium level above 5.5 mmol/L. The main threat for patients with severe hyperkalemia are lethal arrhythmias. The management involves three tasks - antagonization of any electrocardiographic changes with intravenous calcium chloride or gluconate, redistribution of potassium into the cells with insulin, salbutamol and/or the infusion of sodium bicarbonate, if there is metabolic acidosis, and removing potassium from the organism with sodium polystyrene sulfonate or hemodialysis [15]. There are reports suggesting no decrease in potassium concentration after receiving intravenous sodium bicarbonate [16,17], as well as suggesting otherwise [18,19]. The satisfactory decrease in potassium concentration was observed in patients with metabolic acidosis with pH < 7.35, significant hypobicarbonatemia (serum bicarbonate levels < 17 mmol/L), doses of sodium bicarbonate > 120 mEq, and mostly serum potassium concentrations > 6 mmol/L. The unresponsive patients had few of these features and they were all hemodialysis patients [15]. The enhanced effectiveness of sodium bicarbonate in lowering serum potassium concentration in patients with significant metabolic acidosis is attributed to increased sodium entry into acidotic skeletal muscle. Elevated extracellular bicarbonate levels stimulate sodium bicarbonate co-transport into cells, while decreased extracellular hydrogen enhances sodium entry via sodium-hydrogen exchange. The resulting higher intracellular sodium increases the activity of sodium-potassium adenosine triphosphatase, promoting cellular potassium uptake. This response to sodium bicarbonate in hyperkalemia occurs even when increased partial pressure of carbon dioxide prevents changes in arterial pH; thus, an increase in plasma bicarbonate alone appears to facilitate the intracellular movement of potassium [15,18,20].

There are few concerns regarding the efficacy of sodium bicarbonate. One of them is that it works over several hours, which reflects the usual administering over four hours [15,21]. Nevertheless, it seems likely that rapid administration could also be effective. Secondly, it should not be given to hypervolemic patients, as they have a higher risk of developing pulmonary edema [15,22]. Third concern is unpredictability of the needed amount of sodium bicarbonate [15,20,22].

3.3. Intracranial hypertension

Well established treatment for lowering the intracranial pressure (ICP) remains hypertonic saline

[23,5]. However saline solutions can cause hyperchloremic metabolic acidosis [5]. A solution that could have a similar effect on ICP reduction but with a potential advantage of avoiding this complication is an equiosmolar infusion of 8.4% sodium bicarbonate [23,4,5]. There are studies that analysed its potential on lowering ICP in patients after traumatic brain injury (TBI) and demonstrated the effectiveness of sodium bicarbonate in lowering ICP without changing the mean arterial pressure (MAP), leading to sustained rise in the cerebral perfusion pressure (CPP) [23]. The mechanism remains unclear; however, the assumption is that at least some of this effect is mediated by an osmotic mechanism. It is well known that cerebral acidosis can lead to poor outcome in TBI and cerebral ischemic condition. Whether it is just a marker of injury severity or plays a role in the pathophysiology of events leading to post-TBI cerebral edema remains unclear [4,24]. The aquaporin-4 (AQP-4) is a water channel at the blood brain barrier, primarily expressed on astrocytes. One of the theories suggests that acidosis leads to dysfunction of AQP-4, which can result in edema formation [4, 25,26].

4. Discussion

The expanded understanding of sodium bicarbonate's current role in emergency medicine or intensive care presents both promising new applications and challenges. Sodium bicarbonate has been a cornerstone in treating severe metabolic acidosis, hyperkalemia, and specific drug overdoses. However, the evolving landscape of emergency care necessitates a closer examination of its broader utility and safety.

Several studies challenged the use of sodium bicarbonate in lactic acidosis, including the Medical Information Mart for Intensive Care III database which found out that sodium bicarbonate does not improve mortality in critically ill patients with severe acidemia (pH < 7.2) or in septic patients with metabolic acidosis [1,27,28]. The only exception, both in this and in the BICAR-ICU study, were the patients with acute kidney injury - this subgroup showed a decreased mortality when the sodium bicarbonate infusion was given [1,29]. The BICAR-ICU trial used a 4.2% sodium bicarbonate infusion in critically ill patients admitted to the ICU. The target pH was above 7.3. Emergency department patients were not included in the study. Another exclusion criterion was a bicarbonate infusion in the 24 hours prior enrollment. There was no difference in 28-day mortality or single-organ failure at day 7 (primary composite outcome), however the subgroup of patients with acute kidney injury and pH < 7.2 did show a decreased mortality at 28 days; the need for renal replacement therapy was also decreased in those receiving the sodium bicarbonate infusion. The observed adverse events included hypernatremia, hypocalcemia and metabolic alkalosis [29].

In summary, while sodium bicarbonate does not show a mortality benefit or improvement in hemodynamics for lactic acidosis, emerging data suggest that patients with persistent metabolic acidosis and acute kidney injury may benefit from a bicarbonate infusion following initial resuscitation [1,29]. The primary focus should remain on addressing the underlying cause of the acidosis.

A systematic review by Chua et al. investigated the clinical and physiological outcomes of bicarbonate therapy in adult and pediatric patients with diabetic ketoacidosis (DKA). The findings revealed that sodium bicarbonate use did not provide a mortality benefit compared to conventional fluid resuscitation [13]. What is more, three pediatric studies showed an association between bicarbonate therapy and development of cerebral edema, however two of them found no association after adjusting for baseline acidosis [1,30,31,32]. Bicarbonate therapy did not result in improved neurologic recovery in adult patients with DKA [33,34]. Notably, an earlier, small-scale randomized controlled trial found that in DKA patients with a pH range of 6.90 to 7.14 bicarbonate therapy did not improve morbidity, mortality, or the time needed for DKA resolution [34]; another one discovered no difference in the length of hospital stay among the patients receiving bicarbonate therapy [35]. The inconsistency in available data is evident in the differing guidelines from various professional societies. While some recommend sodium bicarbonate administration for patients with a pH below 6.9, others do not [36,37]. Two randomized controlled trials in adults reported faster reversal of acidosis within the first 2 hours of bicarbonate therapy, but this benefit did not persist beyond that time [33,35]. These studies found no significant differences in glycemic control, insulin sensitivity, tissue oxygenation, or cerebrospinal fluid acidosis, but did observe higher rates of hypokalemia. Additionally, two studies noted a paradoxical increase in ketonemia with bicarbonate therapy, which is theorized to result from enhanced hepatic ketogenesis [35,38].

Although the evidence supporting the use of sodium bicarbonate for treating hyperkalemia is controversial, hypertonic sodium bicarbonate infusion does affect serum potassium concentration [8]. Ngugi et al. observed that bicarbonate was less effective than salbutamol and insulin-dextrose in a group of 10 patients with end-stage renal disease [39], whereas Schwarz et al. reported that infusing 144–408 mmol of sodium bicarbonate over 2–4 hours reduced serum potassium by 2–3 mmol/L in four patients with severe acidosis [40]. Jaber et al. described no difference in the primary outcome, which was composite of death from any cause by day 28 or one organ failure at day 7, between the group of critically ill patients with severe metabolic acidemia (pH < 7.2) that received 4.2% sodium bicarbonate and the control group, however the sodium bicarbonate group showed significantly lower potassium and calcium concentrations and required renal replacement therapy less frequently [29]. As Kimmoun et al. showed in an experimental model, severe hypocalcemia can lead to myocardial dysfunction, so the ionized calcium should be monitored and corrected while using sodium bicarbonate [41].

Several studies have investigated alternatives to mannitol or hypertonic saline for managing raised intracranial pressure (ICP) following traumatic brain injury (TBI). Qureshi et al. demonstrated the effectiveness of hypertonic sodium chloride/acetate in reducing elevated ICP in two studies [42,43]. Additionally, Ichai et al. found that a hypertonic sodium lactate solution was more effective than an equiosmolar dose of mannitol for ICP reduction and showed a trend toward improved outcomes [44].

Zeiler et al. reviewed 367 articles and within the randomized controlled trials (RCT) identified 20 episodes

of raised ICP, 10 of them treated with sodium bicarbonate and 10 with hypertonic saline. The mean ICP reduction at 60 minutes post infusion in the sodium bicarbonate group was slightly higher than the reduction in hypertonic saline group, without a statistically significant difference in the change of ICP over time. However, after 150 minutes the ICP was significantly higher in the hypertonic saline group. There were no reported changes neither in MAP, nor an increase in pCO2 with sodium bicarbonate administration. An increase in serum pH and sodium levels was observed, nevertheless none of the analyzed studies described any adverse events related to sodium bicarbonate administration [4].

A potential advantage of infusing hypertonic sodium bicarbonate is that it can avoid the hyperchloremic metabolic acidosis frequently resulting from repeated doses of hypertonic saline. Although the clinical significance of hyperchloremic metabolic acidosis is debated, hypertonic sodium bicarbonate might serve as a useful alternative for managing raised ICP in patients with established acidosis [23]. Further studies are necessary to assess the acid-base changes resulting from repeated doses.

Despite the potential benefits, the administration of sodium bicarbonate carries inherent risks. Metabolic alkalosis, hypernatremia, and fluid overload are significant concerns, particularly in patients with renal impairment or congestive heart failure [6,8]. These risks necessitate vigilant patient monitoring and a judicious approach to dosing. The interplay between sodium bicarbonate and other treatments, such as vasopressors and diuretics, also warrants careful consideration to avoid adverse interactions and optimize therapeutic outcomes [45].

5. Conclusions

Sodium bicarbonate's expanded roles in emergency medicine and intensive therapy offer promising avenues for improving patient care, particularly in challenging conditions like metabolic acidosis, hyperkalemia, and potentially symptomatic hyponatremia or intracranial hypertension. However, the benefits must be weighed against the risks, and further research is essential to develop precise, evidence-based guidelines. Personalized medicine approaches, considering individual patient characteristics and specific clinical contexts, will be crucial in maximizing the therapeutic potential of sodium bicarbonate while minimizing its risks. Future large-scale, randomized controlled trials will be instrumental in providing the robust evidence needed to refine and expand the clinical applications of sodium bicarbonate in critically ill patients.

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