Preliminary observation of the use of sodium bicarbonate solution as an adjunct in the treatment of coronavirus 2019 disease (COVID-19): prognosis improvement in patients requiring intensive care

Observação preliminar do uso de solução de bicarbonato de sódio como coadjuvante no tratamento da doença coronavírus 2019 (COVID-19): melhora do prognóstico na necessidade de terapia intensiva

DOI:10.34117/bjdv7n12-039

Recebimento dos originais: 12/11/2021
Aceitação para publicação: 02/12/2021

Carolina Pontes Soares
PhD, Physiotherapist, Research project coordinator and Adjunct Professor of the Center for Health Sciences and Sports, Federal University of Acre
E-mail: carolina.soares@ufac.br

Simone Aparecida Fernandes da Silva
Intensive care specialist, Head Physiotherapist of Intensive Care Unit COVID-19
R. Benjamin Constant, 830 - Centro, Rio Branco, Acre, Brazil
E-mail: si_fisiot@hotmail .com

Fernanda Farias Soares
MSc student, Nurse of the Center for Health Sciences and Sports, Federal University of Acre, BR-364- KM-4, Distrito Industrial, Rio Branco – Acre, Brazil
E-mail: ffernandaffarias2010@gmail.com

Edna Lopes Monteiro
Intensive care specialist, Head nurse of Intensive Care Unit COVID-19
R. Benjamin Constant, 830 - Centro, Rio Branco, Acre, Brazil.
E-mail: ednalops@hotmail.com

Socorro Elizabeth Rodrigues de Souza
MSc, Intensivist and pediatric, Head doctor of Intensive Care Unit COVID-19 and Adjunct Professor of the Center for Health Sciences and Sports, Federal University of Acre, BR-364- KM-4, Distrito Industrial, Rio Branco – Acre, Brazil
E-mail: socorro.souza@ufac.br

Andréia Fernandes Brilhante
PhD, Pharmacist and Adjunct Professor of the Center for Health Sciences and Sports, Federal University of Acre, BR-364- KM-4, Distrito Industrial, Rio Branco – Acre, Brazil
E-mail: andreia.brilhante@ufac.br

Rita de Cássia Ribeiro Pereira
MSc, Radiologist doctor and Assistant Professor of the Center for Health Sciences and Sports, Federal University of Acre, BR-364- KM-4, Distrito Industrial, Rio Branco – Acre, Brazil
E-mail: rita.pereira@ufac.br

Joicely Melo Costa
PhD, Cardiologist doctor and Assistant Professor of the Center for Health Sciences and Sports, Federal University of Acre, BR-364- KM-4, Rio Branco – Acre, Brazil
E-mail: joicely.costa@ufac.br

Leandro Cavalcante Santos
PhD student, Biomedical Scientist, Tropical Medicine and Public Health – Federal University of Goiás
R. 7 de setembro, 291, Raimundo Melo, CEP: 69921-038 , Rio Branco – Acre, Brazil
E-mail: leandrocavalcante@discente.ufg.br

Hemeson Lira de Moura
PhD student, Biologist, Tropical Medicine and Public Health – Federal University of Goiás
R. Benjamin Constant, 830 - Centro, , Rio Branco – Acre, Brazil
E-mail: hemesonlira@gmail.com

Ildercílio Mota de Souza Lima
PhD, Biomedical Scientist and Adjunct Professor of the Center for Health Sciences and Sports, Federal University of Acre (UFAC), BR-364- KM-4, Rio Branco, Acre, Brazil
E-mail: ildercilio.lima@ufac.br

Larissa Vanessa Machado Viana
PhD, Nurse and Adjunct Professor of the Center for Health Sciences and Sports, Federal University of Acre, BR-364- KM-4, Distrito Industrial, Rio Branco – Acre, Brazil
E-mail: larissa.viana@ufac.br

Cydia de Menezes Furtado
PhD, Biologist and Adjunct Professor of the Center for Health Sciences and Sports, Federal University of Acre, BR-364- KM-4, Distrito Industrial, Rio Branco – Acre, Brazil
E-mail: cydia.furtado@ufac.br

Anselmo Fortunato Ruiz Rodriguez
PhD, Physicist, Coordinator of the Bionorte Network and Professor of the Post-graduate Program in Science, Innovation and Technology for Amazonia, Federal University of Acre, BR-364- KM-4, Distrito Industrial, Rio Branco – Acre, Brazil
E-mail: anselmo.rodriguez@ufac.br

Patrícia Rezende Prado
PhD, Nurse and Adjunct Professor of the Center for Health Sciences and Sports, Federal University of Acre, BR-364- KM-4, Distrito Industrial, Rio Branco – Acre, Brazil
E-mail: patyrezendeprado@gmail.com

Cirley Maria de Oliveira Lobato
PhD, Doctor Infectologist and Adjunct Professor of the Center for Health Sciences and Sports, Federal University of Acre, BR-364- KM-4, Rio Branco – Acre, Brazil
E-mail: cirley.lobato@ufac.br

Angélica Bento de Almeida
Physiotherapist and Research project coordinator
Intensive care specialist, Criminal Forensics and Forensic Sciences
E-mail: annngel.almeida@gmail.com

ABSTRACT
Introduction*:* This study aimed to evaluate the use of sodium bicarbonate solution as an adjunct in the treatment of critically ill patients in an intensive care unit (ICU). Methods: A group of 76 patients were followed up, of which 44 received treatment with a sodium bicarbonate ($NaHCO_3$) solution along with the conventional treatment, and 32 patients used only the conventional treatment. Results: In patients treated, there was an improvement in radiological findings, a decrease in opacity and bilateral consolidations, as well as reduced length of stay in the ICU, and mortality. Conclusion: The use of $NaHCO_3$ solution as an adjunct in the treatment of COVID-19 improved prognosis compared to conventional treatment.

Keywords: Coronavirus, Bronchoalveolar lavage, Sodium bicarbonate, intensive care unit

RESUMO
Introdução: O objetivo deste estudo foi avaliar a utilização da solução de bicarbonato de sódio como coadjuvante no tratamento de pacientes críticos internados em uma unidade de terapia intensiva (UTI). Métodos: Acompanhou-se um grupo de 76 pacientes, dos quais 44 receberam tratamento com solução de bicarbonato de sódio ($NaHCO_3$) junto com o tratamento convencional e 32 pacientes utilizaram apenas o tratamento convencional. Resultados: Nos pacientes tratados, houve melhora dos achados radiológicos, diminuição da opacidade e das consolidações bilaterais, bem como redução do tempo de internação na UTI e mortalidade. Conclusão: O uso da solução de NaHCO3 como coadjuvante no tratamento da COVID-19 melhorou o prognóstico em comparação ao tratamento convencional.

Palavras-chave: Coronavírus, Lavagem broncoalveolar, bicarbonato de Sódio, Unidade de Tratamento Intensivo

1 INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was recently discovered to cause coronavirus disease 2019 (COVID-19) and has been impacting healthcare systems and the economy worldwide. According to data from August 2021, approximately 215 million COVID-19 cases and 4.5 million COVID-19 deaths were reported.[1]

When COVID-19 cases are symptomatic, they can present with varied clinical manifestations, with respiratory disorders such as dyspnea and acute respiratory failure being the most serious symptoms of the disease, necessiting treatment with non-invasive ventilatory support, intubation, and mechanical ventilation (MV).[2]

Several therapies use hypertonic solutions, bronchodilators, and antibiotics to treat respiratory disorders. Airway infections, whether bacterial or viral, tend to acidify fluids.[3] Some studies have shown that the use of sodium bicarbonate ($NaHCO_3$) in lung disorders increases the pH and improves the viscosity of airway secretions[4], including in cases of COVID-19.[5]

Since few studies are exploring such clinical applicability, this study aimed to analyze whether $NaHCO_3$ solution as an adjunct in the treatment of COVID-19 improves the prognosis in intensive care patients.

2 METHODS

The study was performed at the Hospital de Urgência e Emergência (HUERB) in Rio Branco municipality, State of Acre, Brazil, which has 10 beds in the intensive care unit (ICU) exclusively for COVID-19 cases.

During the period from December 2020 to May 2021, 76 critically ill patients of both sex aged between 20 and 79 years with positive results on real-time polymerase chain reaction (RT-PCR) for SARS-CoV-2 were separated into two groups using a single-blind draw.

1) Conventional (n=32): Use of conventional drug treatment; and

2) Experimental (n=44): Use of conventional drug treatment along with bronchoalveolar lavage using a 3% $NaHCO_3$ solution in saline (0.9% NaCl).

Bronchoalveolar lavage was performed with the instillation of 10 ml of $NaHCO_3$ solution directly into the tube (closed circuit), where we calculated 500 µl for each lung segment, followed by aspiration of the solution. This procedure was performed every 6 h for 7 days (QID).

In addition to conventional treatment, patients had a positive end-expiratory pressure (PEEP) between 12 and 15 with an inspired oxygen fraction (F_IO_2) of 100% to maintain a satisfactory peripheral oxygen saturation (SpO_2) since the patients had SpO_2 between 89% and 91%.

Patients underwent chest radiography before and 48 h after treatment with the solution and conventional treatment. Although the “gold standard” examination to assess the lungs of patients with COVID-19 is computed tomography, given that critically ill patients of COVID-19 present instability and may desaturate on the way to another floor of the hospital, it was decided to use radiographs that are performed in the ICU itself, thus

preventing it from affecting the patient's clinical condition. Radiographs were analyzed by scoring, as described by Toussie et al.[6].

Oxygen saturation was verified during the treatment (24 h, 48 h, 72 h and 96 h). Information on the length of stay and the outcome of the cases (discharge, transfer to semi-intensive, and death) was also considered.

To verify whether the groups were homogeneous, we used the chi-square test for sex and the t-test for age. For comparison of before and after data in individuals, we used the T-paired and Wilcoxon signed-ranks test for parametric data and non-parametric data, respectively. The alpha value was set at $p<0.05$. The analyses were performed using the STATA 13.

3 RESULTS

The two study groups, conventional and experimental, were statistically homogeneous in terms of sex (p=0.09) and age (p=0.31). However, results differed significantly (P = 0.00). In conventional treatment, 56.3% of deaths occurred and, in experimental treatment, most of them were transferred to the semi-intensive care unit (81.8%) (Table 1).

Regarding the days of hospitalization, there was a significant difference only in the semi-intensive outcome group (p=0.02). The median number of days in the conventional group was lower (Table 1).

By the Toussie et al.[6] analysis, it was found that the conventional treatment had an average score of 3.93 on the first day, and 4.75 (p=0.00) after seven days, showing a worsening in the clinical condition. On the other hand, for patients in the experimental treatment, the mean score decreased from 4.76 to 2.16 in one week (p=0.00), demonstrating a significant improvement in the evolution of COVID-19.

Table 1. Outcome and days of hospitalization of patients admitted to the ICU under conventional and experimental treatment (n=76).

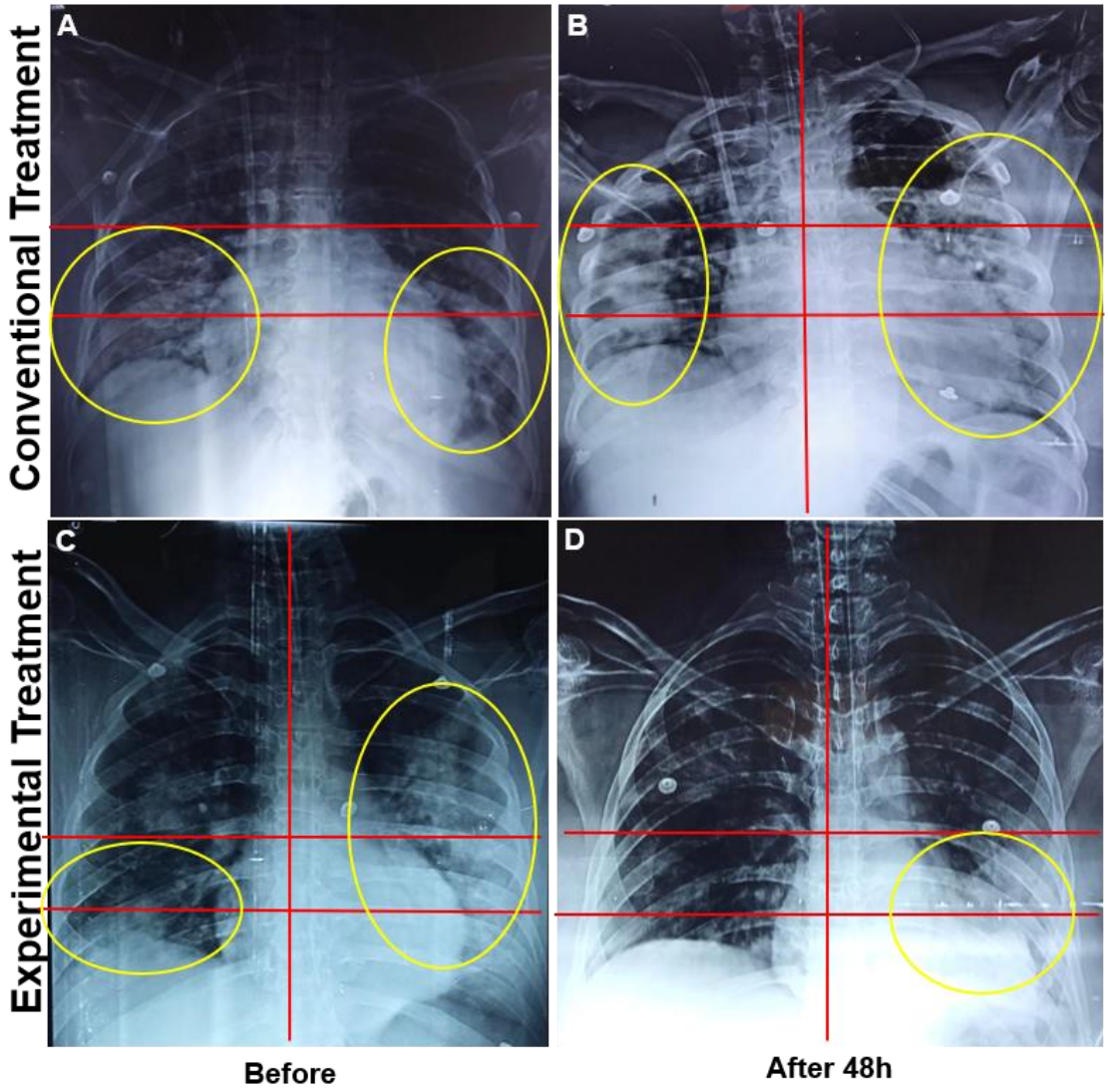
Outcomes							
Group	**Discharged**	**n**	**Semi-intensive**	**n**	**Deaths**	**n**	**p**
Conventional	9.3%	3	34.4%	11	56.3%	18	0.00
Experimental	4.6%	2	81.8%	36	13.6%	6	
Length-of-stay (days)							
Group	**Discharged**	**p**	**Semi-intensive**	**p**	**Deaths**	**p**	
Conventional	3	0.80	11	0.02	18	0.24	
Experimental	5		36		6		

Wilcoxon signed-point test, p=0.00

In the radiographs, it was observed that the patients in the experimental treatment had a decrease in opacity and bilateral consolidations (Figure 1; Figure S1), while in the control group, there was a progressive increase in pulmonary involvement, demonstrating an advance in the severity of the acute respiratory syndrome in COVID- 19.

The oxygen saturation, in the conventional treatment group, there was a significant difference at 24 h (p=0.00), 72 h (p=0.00) and 96 h (p=0.04), except at 48 h (p=0.12). In the experimental treatment group, the increase in the saturation rate was significant in all measurements from 24 h to 96 h (p=0.00).

Figure 1. Chest radiography of two intubated female patients admitted to the intensive care unit (ICU/COVID-19) with severe respiratory syndrome due to COVID-19. Yellow circles indicate regions of the lung with visible opacities. **A**: Patient's chest radiography with conventional treatment, showing bilateral involvement along with cloudy opacities in the lower and middle right lung zone, lower and middle left lung zone, with a score of 4 according to the Toussie et al.[6]. **B**: After 48 h of conventional treatment, there was an increase in bilateral involvement and lower, middle and upper lung area, right and left, scoring 6, which is the maximum score on the scale by Toussie et al.[6]. **C:** Chest radiography before experimental treatment showing bilateral involvement in the lower and middle and left upper lung zones, scoring 5. **D**: After 48 h of experimental treatment, there was a decrease in lung involvement, with only involvement of the lower and middle lung zones that progressively evolved to weaning from ventilation.



4 DISCUSSION

The chest radiography plays a considerable role in diagnosing the evolution and severity of COVID-19. Common patterns in X-ray findings, such as ground-glass opacity, are associated with clinical deterioration to a serious condition. Al-Smadi et al.[7] showed that the number of opaque lung zones was a predictor of mortality in patients with SARS. In the present study, we found less lung opacity in patients treated with sodium

bicarbonate, demonstrating regression of lung parenchyma lesions and improvement in the clinical picture.

Oxygen saturation is a considerable measure to predict complications and mortality from COVID-19, and in severe cases of respiratory diseases, low saturation and hypoxemia are expected.[8] In our results, both groups of patients showed an improvement in saturation levels in 48h, probably due to pharmacotherapy with corticosteroids and bronchodilators. But experimental treatment group, the increase in the saturation rate was significant in all measurements from 24 h to 96 h. This phenomenon can be explained by the sodium bicarbonate that potentiates the action of some antibiotics of the macrolides, aminoglycosides and fluoroquinolones classes.[9]

Some studies claim that viruses need an acid medium to invade cells and begin to multiply immediately.[10,11] In coronaviruses, a slightly acidic environment created by endosomes is required to obtain a membrane fusion and envelope viruses, followed by melting stages, release, and uncoating of the genome into the host cell cytoplasm.[12]

The $NaHCO_3$ can bring the pH level of the human body into balance, in the range of 7.35-7.45, and perform its functions, preventing viruses from invading cells and replicating. Although this pH is higher than the serum pH, using it in the form of inhalation is safe without altering blood pH.[4,13] In our treatments, the bronchoalveolar lavage did not change the blood pH, as analyzed by arterial blood gases, being a local therapy in the respiratory tract only.

Few studies have reported the clinical applicability of NaHCO3 to respiratory diseases. NaHCO3 may be a potential therapeutic agent for patients with cystic fibrosis.[4] El-Badrawy et al.[14] reported clinical and radiological improvements in patients with tuberculosis. Regarding COVID-19, to date, no studies or randomized clinical trials have demonstrated the effectiveness of sodium bicarbonate. However, we emphasize that NaHCO3 is accessible, inexpensive, and safe, and is used to treat other pathological conditions.

In a recent study, Machado et al.[15] found that hypertonic saline solution inhibits SARS-CoV-2 replication in human lung epithelial cells, shown that the concentrations used increase intracellular metabolism, using more ATP and leading to cell membrane depolarization, making virus replication unfeasible, thus, concluding that hypertonic solutions should be further investigated as a prophylactic or therapeutic measure for COVID-19. In our study, the sodium bicarbonate solution was prepared at a concentration

of 3% in saline, thereby enhancing the effect of sodium bicarbonate, which may increase endosome pH by inhibiting replication of SARS-CoV-2.[16]

5 CONCLUSION

Although definitive proof of its efficacy is not available, these findings are justifiable for a study with a larger number of patients, at different evolutionary stages of COVID-19, within randomized clinical trials.

One of the limitations of this study is the need for randomized, placebo-controlled clinical trials to elucidate its effectiveness of $NaHCO_3$ solution as an adjuvant in the treatment of COVID-19. However, this report on the use of NaHCO3 solution as an adjuvant treatment may bring some light on its effectiveness and reduction of length of stay in the ICU and death in critically ill patients.

ACKNOWLEDGMENTS

The authors thank the Universidade Federal do Acre (UFAC), Secretaria de Estado de Saúde do Acre (SESACRE), and the hospital staff from HUERB for their logistical support.

The authors declare that the procedures followed were in accordance with the Declaration of Helsinki of the World Medical Association updated in 2013. This study was approved by the National Research Ethics Commission (Comissão Nacional de Ética em Pesquisa - CONEP) under the number CAAE: 35002720.3.1001.5010. The patients provided consent from their family members to carry out the protocol through a signed term.

REFERENCES

Johns Hopkins Coronavirus Resource Center. World - COVID new cases, deaths, testing data. Available in https://coronavirus.jhu.edu/ accessed August 27, 2021.

Wunsch H. Mechanical ventilation in COVID-19: Interpreting the current epidemiology. Am J Respir Crit Care Med 2020;202:1-4.

Rossi GA, Morelli P, Galietta LJ, Colin AA. Airway microenvironment alterations and pathogen growth in cystic fibrosis. Pediatr Pneumol 2019:1-10.

Gomez CCS, Parazzi PLF, Clinckspoor KJ, et al. Safety, tolerability and effectes of sodium bicarbonate inhalation in cystic fibrosis. Clin Drug Investig 2019; 40:105-117.

Wardeh A, Conklin J, Ko M. Case reports of observed significant improvement in patients with ARDS due to COVID-19 and maximum ventilatory support after inhalation of sodium bicarbonate. J Clin. Intensive Care Med 2020; 5:016-019.

Toussie D, Voutsinas N, Finkelstein M, Cedillo MA, Manna S, Maron SZ, et al. Clinical and chest radiography features determine patient outcomes in young and middle-aged adults with COVID-19. Radiology 2020; 297(1):E197-E206.

Al-Smadi AS, Bhatnagar A, Ali R, Lewis N, Johnson S. Correlation of chest radiography findings with the severity and progression of COVID-19 pneumonia. Clin Imaging 2021; 71:17-23.

Choi KJ, Hong HL, Kim EJ. The association between mortality and the oxygen saturation and fraction of inhaled oxygen in patients requiring oxygen therapy due to COVID-19–Associated pneumonia. Tuberc Respir Dis (Seoul) 2021; 84(2):125-133.

Farha MA, French S, Stokes J, Brown ED. Bicarbonate alters bacterial susceptibility to antibiotics by targeting the proton motive force. ACS Infect Dis 2018;9:4:382-390.

Skehel JJ, Bayley PM, Brown EB, Martin SR, Waterfield MD, White JM, et al. Changes in the conformation of influenza virus hemagglutinin at the pH optimum of virus-mediated membrane fusion. Proc Nati Acad Sci 1982;79:968-972.

White JM. Viral and cellular membrane fusion proteins. Annu Rev Physiol 1990; 52:675-697.

Chu VC, McElroy LJ, Chu V, Bauman BE, Whittaker GR. The avian coronavirus infectious bronchitis virus undergoes direct low-pH-dependent fusion activation during entry into host cells. J Virol 2006;80:3180-3188.

Aslan S, Kandiş H, Akgun M, Cakir Z, Inandi T, Görgüner M. The effect of nebulized NaHCO3 treatment on “RADS” due to chlorine gas inhalation. Inhal Toxicol 2006; 18(11):895-900.

El-Badrawy MK, Arram EO, Abdalla DA, et al. Effect of adding inhalation of sodium bicarbonate 8.4% to the usual treatment on smear-positive pulmonary tuberculosis: A prospective controlled study. Egypt J Bronchol 2019; 13(4):531-538.

Machado RRG, Glaser T, Araujo DB, Petiz LL, Oliveira DBL, Durigon GS, Leal AL, Pinho JRR, Ferreira LCS, Ulrich H, Durigon EL, Guzzo CR. Inhibition of Severe Acute Respiratory Syndrome Coronavirus 2 Replication by Hypertonic Saline Solution in Lung and Kidney Epithelial Cells. ACS Pharmacol Transl Sci 2021;4, 5, 1514–1527.

Belouzard S, Millet JK, Licitra BN, Whittaker GR. Mechanisms of coronavirus cell entry mediated by the viral spike protein. Viruses. 2012;4(6):1011-33.