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Title page

Sodium Bicarbonate Nebulized Therapy in Patients with Confirmed COVID-19

Jalil Rashedi[1] https://orcid.org/0000-0002-9627-1491, Behroz Mahdavi Poor[1]* https://orcid.org/0000-0002-8856-3750, Mohammad Asgharzadeh[2] https://orcid.org/0000-0003-3386-4342

[1]*Department of Laboratory Sciences, School of Paramedicine, Tabriz University of Medical Sciences, Tabriz, Iran.*

[2]*Biotechnology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.*

***Corresponding author:** Behroz Mahdavi Poor

Email: Behroz.mahdavi@gmail.com

Complete Postal Address: Faculty of Paramedicine, Tabriz University of medical sciences, Golgasht Ave, Azadi St, Tabriz, I.R.Iran. Tel: +9841-33392633, +989144021126

Fax: +9841-33371971

Sodium Bicarbonate Nebulized Therapy

In Patients with Confirmed COVID-19

Dear Editor,

A global outbreak of severe acute respiratory syndrome (SARS) caused by a new coronavirus (CoV-2) began in December 2019. It induced a novel identified sickness named coronavirus disease 2019 (COVID-19). The rapid emergence of COVID-19 along with the considerable illness and mortality of the disease made it a major public health issue. Due to the lack of effective treatments, an extensive attempt is under way to provide and examine antiviral drugs.

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Coronaviruses are enveloped positive-stranded RNA viruses that replicate in the host cell cytoplasm. To release their nucleocapsid into the cell, they rely on the binding to the cellular receptors, angiotensin converting enzyme 2 (ACE2) for SARS-CoV-2, by major conformational changes of the virus spike glycoprotein (S) and entry into the cells by endocytosis. [1, 2] The created endosome, where a slightly acidic environment is required for optimum fusion of its membrane and virus envelope, followed by the stages of fusion, uncoating and release of the genome into the host cell cytoplasm. [3, 4] The protonation of critical residues on a viral envelope glycoprotein alters its conformation and exposes a hydrophobic "fusion peptide" domain to facilitate the fusion.[5] Infection of SARS-CoV-2 may be prevented by treatment of cells with inhibitors of endosome acidification.

Sodium bicarbonate ($NaHCO_3$), like endosomotropic weak bases ammonium chloride (NH_4Cl), chloroquine (CLQ)/ hydroxychloroquine (CLQ-OH) as well as bafilomycin A (BAF), may raise the pH in vesicle/endosomes and would be expected to inhibit nucleocapsid release of a SARS-CoV-2 which required an acidic endosomal environment for uncoating (as shown in the figure below).[1, 4, 6, 7]

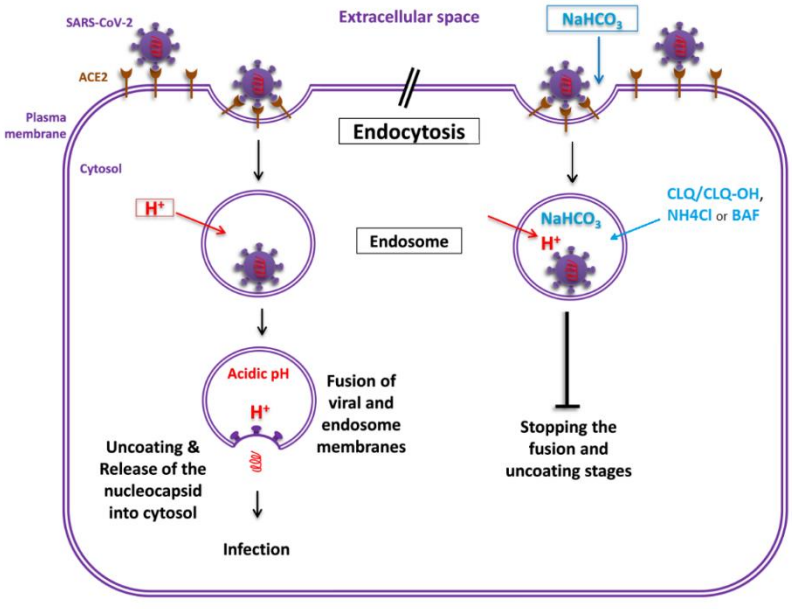

Figure. Assumed pathway of endocytosis of SARS-CoV-2 into the target cells with Sodium bicarbonate (right pathway) and without it (left one). Binding of the virus S-protein to ACE2 promotes internalization into endosomes, where the low pH environment triggers fusion activity in the S-protein. Inhibitors of acidification, such as $NaHCO_3$, CLQ/CLQ-OH, NH_4Cl or BAF can be used to dissect the pathway because they specifically block pH-dependent membrane fusion.

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Therefore, inhalation of the nebulized sodium bicarbonate solution (<5%) by the patients with confirmed COVID-19, several times during the day, probably able to stop the fusion and uncoating stages. In this case, the replication phase will also remain barren and eventually the respiratory infection will be controlled. Prospective controlled trials are needed to evaluate this method efficacy.

Conflict of interest statement

The authors declare that there is no conflict of interests.

References

1. Hofmann H, Pöhlmann S. Cellular entry of the SARS coronavirus. *Trends microbiol* 2004;12(10):466-72. doi: 10.1016/j.tim.2004.08.008

2. 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. doi: 10.3390/v4061011. Epub 2012 Jun 20

3. 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(7):3180-8. doi: 10.1128/JVI.80.7.3180-3188.2006

4. Li D, Cavanagh D. Role of pH in syncytium induction and genome uncoating of avian infectious bronchitis coronavirus (IBV). *Adv Exp Med Biol* 1990;276:33-6. doi: 10.1007/978-1-4684-5823-7_5

5. Gallagher TM, Escarmis C, Buchmeier MJ. Alteration of the pH dependence of coronavirus-induced cell fusion: effect of mutations in the spike glycoprotein. *J Virol* 1991;65(4):1916-28. doi: 10.1128/JVI.65.4.1916-1928.1991

6. Yang ZY, Huang Y, Ganesh L, Leung K, Kong WP, Schwartz O, et al. pH-dependent entry of severe acute respiratory syndrome coronavirus is mediated by the spike glycoprotein and enhanced by dendritic cell transfer through DC-SIGN. *J Virol* 2004;78(11):5642-50. doi: 10.1128/JVI.78.11.5642-5650.2004

7. Fantini J, Di Scala C, Chahinian H, Yahi N. Structural and molecular modelling studies reveal a new mechanism of action of chloroquine and hydroxychloroquine against SARS-CoV-2 infection. *Int J Antimicrob Agents* 2020:105960. doi: 10.1016/j.ijantimicag.2020.105960