



REVIEWED ARTICLE

Association between BCG vaccine and COVID-19: A possible alternative treatment strategy

Muhammad Ibrar¹, Muhammad Hassan^{*2} and Dil Noor¹

¹Department of Allied Health Sciences, Iqra National University, Swat Campus, Peshawar, **Pakistan**

²Department of Pharmacy, Bacha Khan University, Charsadda, Kpk, **Pakistan**

COVID-19, a highly contagious disease caused by 2019nCoV, still lacks effective treatment modalities. Researchers are in struggle to find suitable medications for its treatment and produce. Vaccines for prevention against COVID-19 to save lives, however, developing vaccines for COVID-19 will take a long time. So currently the scientists are repurposing the existing vaccines as additional tool which can induce non-specific immune benefits. Bacillus Calmette–Guérin [1], vaccine, primarily used against tuberculosis, is currently getting attention for effective treatment of COVID-19. This review article summarizes the current status of research on association of BCG with COVID-19 for possible effective treatment and future prevention of COVID-19.

Keywords: COVID-19, Current treatment, BCG vaccine, Re-purposing, Clinical studies

INTRODUCTION

During last days of December 2019, multiple human cases of respiratory infections were reported in Wuhan city of China that spread rapidly throughout the world. After the identification and isolation of the infectious virus, the disease was named as coronavirus disease-2019 (COVID-19) and the virus was named as novel corona virus (2019nCoV) [2]. Till date, this disease has infected more than 3 million people in which more than 2 lac died. The virus has stronger transmission capacity and the rapid increase in COVID-19 confirmed cases makes the control and prevention extremely serious.

2019nCoV is a β -coronavirus belonging to the family of enveloped viruses having single-stranded RNA [3]. The sub groups of this family consists of alpha, beta, gamma and delta corona virus and beta corona virus is reported be most dangerous among all. Earlier it was believed that it can only infect animals. Recent studies confirms that it cause acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) which leads to pulmonary failure and result in fatality in humans [3]. The interaction of viral particles and specific proteins present on the host cell surface initiate the infection by delivering their nucleocapsid to the target cells. The spike proteins play an important role in fusion process. The spike protein of 2019nCoV specifically binds to human cell-surface protein known as Angiotensin-converting enzyme 2 (ACE2) [4]. These receptors play a pivotal role in Renin-angiotensin system activating physiological pathways in different systems via different mechanisms: kidney, liver, respiratory, cardiovascular (CVs) and central nervous system (CNS). Activation of AT1 receptors is responsible for regulation of some key events including fluid and sodium balance, arterial pressure, cellular growth and migration and fibrosis [4]. Overactivation of AT1 receptors may result in damaging events like fibrosis in liver, lungs and other organs [5]. Moreover, the prevention and control of COVID-19 is made extremely serious by the high contagiousness nature of disease and the rapid increase in infectious cases. Novel infectious diseases caused by RNA viruses subject to genetic recombination, mutation and cross-species transmission, will continue to present a serious global health threat, as exemplified by COVID-19. A large number of drugs are used or suggested for COVID-19 patients treatment including lopinavir/ritonavir, hydroxychloroquine, chloroquine phosphate, methylprednisolone, angiotensin receptor 2 blockers, ribavirin, IL-1 or IL-1R suppressors, azithromycin, rapamycin, quercetin, doxycycline, phosphodiesterase inhibitors, nifedipine, acetazolamide, tocilizumab, zinc supplements, convalescent plasma transfusions, statins, traditional Chinese medicine and monoclonal antibodies [6].

Edited by:

Farhat Yasmeen

Peer Review policy:

Double-blind

***Correspondence:**

meet_ibrar@yahoo.com

Specialty section:

This article was submitted to *Infectious Diseases*, a section of the journal "Innovators in Medical and Health Sciences"

Received: 09 Sep., 2022

Accepted: 03 Feb., 2023

Published: 25 Feb., 2023

Citation:

Ibrar, 2023, Association between BCG vaccine and COVID-19: A possible alternative treatment strategy *Innt. Med. Health Sci.* 3(1):01-04. Uoi: 01-04-03(1)2023MHS22-135

Peer-reviewed

Open access

Journal by Innovative Scientific Information & Services Network

Available online at

www.isisn.org

Researchers are in struggle to produce and investigate the preventive effects of vaccines against COVID-19 but it will take a long time. So currently the scientists are repurposing the existing vaccines as additional tool which can induce non-specific immune benefits [7]. The studies provide strong evidences of decreased mortality rates by using live attenuated vaccines. For example Bacillus Calmette–Guérin vaccine (BCG) that is primarily used worldwide against tuberculosis, reduces 38-45% mortality rates [8-9]. Currently studies has been published which states the correlation between Bacillus Calmette–Guérin vaccine policy in different regions of the world and decrease in morbidity and mortality in 2019nCOV infected patients [10]. These studies provide a ray of hope for countries with low resources affected with global pandemic COVID-19. Research is in progress whether BCG vaccination can provide protection against COVID or not. Mechanistic evidence exists to suggest that BCG vaccination possess protective effects against many viral infections. An experimental TB vaccine called VPM1002, closely related to BCG will soon be tested in healthcare workers and elderly patients in German hospitals against COVID-19.

Similarly another vaccine of Mycobacterium tuberculosis (MTBVAC), developed by University of Zaragoza (Spain) will be tested soon in SARS-CoV-2 in animal models and will be screened for future trial in human beings[11]. Researchers are now scientifically investigating the hypothesis that heterologous protection caused by BCG may provide protection against severe COVID-19 infection. This review article summarizes the current status of research on association of BCG with COVID-19 for possible effective treatment and future prevention of COVID-19.

BCG vaccines and COVID-19:

The BCG vaccines were introduced for the first time in 1921 against tuberculosis. Many studies revealed that the BCG vaccines are not only effective against tuberculosis but it also provides

Protection against many other disease like allergy, malignancies, asthma and non mycobacterial infections [12-13]. The BCG was found to provide protection in mice against DNA and RNA viruses including herpes and influenza viruses and had a quick and stronger antibody response against influenza A vaccine strain in human volunteers [14-15]. Moreover a limited study carried out in Gunie Bissau shown that girl children administered with BCG vaccines had a lower incidence of pneumonia [16]. The mechanism through which the BCG vaccine provides nonspecific protection against various infections is the focus of current research. This non specific or cross protection against pathogens has been attributed to trained immunity. It is also referred to as innate immune memory involves cells of the immune system such as Natural Killer (NK) cells, cytokines, innate lymphoid cells and pattern recognition proteins The stronger response

exhibited by innate immune memory to secondary stimuli is not specific to particular infectious agent (in this case SARS Cov2) and involves transcriptional and epigenetic reprogramming [17]. BCG vaccines are reported to produce a genome-wide epigenetic reprogramming of human monocytes which has a protective role against many viral infections.. Evidences are available that peoples with a history of BCG vaccination shown higher amount of cytokines (IL-1 β , IL-6, IFN γ and TNF) in response to infection of different pathogens in comparison with monocytes of individuals who did not receive BCG vaccination [18]. So infection of COVID-19 in patients with history of BCG vaccination results in rapid expansion and activation of natural killer cell leading to production of cytokines providing T-cells independent protection [19]. It is believed that BCG vaccine mainly affects the trained or innate immune memory which cause epigenetic modulation of macrophages and monocytes, induces the secretion of pro inflammatory cytokine IL-1 β . Current studies reported the promotion of TH1 and TH17 response due to BCG vaccination. Considering that BCG has been shown to increase titers of polysaccharide-specific IgG in bacterial infections, it is possible that the same might be true in the case of SARS-CoV2 spike glycoprotein, which is used by 2019nCOV to bind to cells expressing ACE2[20-21]. It is beyond doubt that BCG vaccines possess prophylactic and therapeutic effect in both bacterial and viral infection. The countries having the policy of BCG vaccination have decreased mortality and morbidity rates due to COVID-19 as compared to other countries [22]. A study carried by Miller et al statistically compared countries having universal BCG policy with countries having no BCG vaccination policy [10]. The countries were classified according to their GNI per capita in 2018. The countries that had BCG vaccination policy had a little COVID-19 mortalities in comparison with those countries having no BCG coverage or started BCG vaccines late. Iran adopted BCG vaccination policy in 1984, has more cases of mortalities in comparison with Japan, whose universal BCG was introduced in 1947. Middle high and high income countries (55) having universal BCG policy had 0.78 \pm 0.40 (mean \pm SEM) deaths per million people while other 5 countries having middle high and high income with no universal BCG vaccination had an elevated mortality rates of 16.40 \pm 7.32 deaths per million people. Another report also uncovered the fact that the number of mortalities and cases per one million people were significantly associated with BCG policy of the country. The amount of variance in deaths and cases conferred by BCG vaccination policy ranged between 12.5% and 38%. The study was carried out in 199 countries by using linear regression modeling [22]. Another study found that mandatory BCG vaccination can effectively provides protection against COVID-19 [23]. Similarly a study performed on association of BCG vaccine with COVID 19, the fatality rates were compared between countries having high number of COVID-19

cases and countries that adopted BCG vaccination policies in the past. An elevated death rate found in high burden countries with 5.29 % as compared to countries having BCG vaccination practice with a death rate of 0.61% [1]. Hegarty PK et al, performed an analysis with the aim whether BCG vaccine protects against COVID-19 and plays role in reduced rate of mortality. In this study 131 countries having BCG vaccination program were compared with 21 countries having no program on BCG vaccination. COVID-19 cases reported in countries with BCG vaccination Policy in 15 days were 38.4/million while 358.4/million cases were recorded in countries having no BCG policy. The death rate recorded between two groups was 4.28 per million with comparison of 40 per million people. So the data support the similar conclusion that countries having no BCG program appear to have high death ratio as compared to other countries having BCG vaccination program [24]. Currently Murdoch Children Research Institute, Australia is performing controlled trial in healthcare workers (n=4170) in Australian hospital sites to determine the effect of BCG vaccines in reducing the infection and severity of COVID-19 which will be followed for 12 months (NCT04327206) [25].

CONCLUSION

The lack of specific active drugs against 2019nCoV has resulted in COVID-19 related increased mortalities and morbidities. This has led the scientists to use existing vaccines in order to find effective current treatment and future prevention of COVID-19. This review was undertaken to examine current research status of repurposing BCG vaccine for the treatment to COVID-19. Studies have found that countries with universal BCG policy have low rate of COVID-19 related mortalities as compared to those with no universal BCG policy. Similarly, deaths rate was found low in countries having BCG vaccination policy as compared to those without BCG vaccination policy. Another study with 12-months follow up is currently investigating the effects of COVID-19 in healthcare workers with and without BCG vaccination. Though, no clinical study has reported the protective potential of BCG vaccine in patients with COVID-19 however, information support the idea that universal BCG vaccine is an effective tool against COVID-19 probably reducing the progression and severity of disease. Therefore, BCG vaccine clinical trials are intensely required to establish its key role in COVID-19 especially in countries without a universal BCG vaccination policy.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

AUTHOR CONTRIBUTIONS

Muhammad Ibrar planned the current study, collected the literature & wrote up the text. Muhammad Hassan and Dil Noor Designed and reviewed the manuscript. All authors

read and approved the final version.

Copyrights: © 2023@ author (s).

This is an open access article distributed under the terms of the [Creative Commons Attribution License \(CC BY 4.0\)](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author(s) and source are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

REFERENCES

- Lillie, P.J., et al., *Novel coronavirus disease (Covid-19): the first two patients in the UK with person to person transmission*. Journal of Infection, 2020.
- Xu, H., et al., *High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa*. International Journal of Oral Science, 2020. **12**(1): p. 1-5.
- Wevers, B.A. and L.v.d. Hoek, *Renin-angiotensin system in human coronavirus pathogenesis*. Future Virology, 2010. **5**(2): p. 145-161.
- Zeinalian, M., et al., *A potential protective role of losartan against coronavirus-induced lung damage*. Infection Control & Hospital Epidemiology, 2020: p. 1-2.
- Zhou, M., X. Zhang, and J. Qu, *Coronavirus disease 2019 (COVID-19): a clinical update*. Frontiers of medicine, 2020: p. 1-10.
- de Vrieze, J., *Can a century-old TB vaccine steel the immune system against the new coronavirus?* Science, 2020.
- Biering-Sørensen, S., et al., *Early BCG-Denmark and neonatal mortality among infants weighing < 2500 g: a randomized controlled trial*. Clinical Infectious Diseases, 2017. **65**(7): p. 1183-1190.
- Garly, M.-L., et al., *BCG scar and positive tuberculin reaction associated with reduced child mortality in West Africa: a non-specific beneficial effect of BCG?* Vaccine, 2003. **21**(21-22): p. 2782-2790.
- Miller, A., et al., *Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study*. medRxiv, 2020.
- Sharquie, I., *BCG is a Good Immunotherapeutic Agent for Viral and Autoimmune Diseases: Is it a New Weapon against Coronavirus (COVID-19)?*. Electron J Gen Med. 2020; **17** (6): em229. 2020.
- Barlan, I.B., et al., *Role of bacillus Calmette-Guérin as an immunomodulator for the prevention and treatment of allergy and asthma*. Current opinion in allergy and clinical immunology, 2005. **5**(6): p. 552-557.
- Netea, M.G. and R. van Crevel. *BCG-induced protection: effects on innate immune memory*. in

- Seminars in immunology*. 2014. Elsevier.
13. Leentjens, J., et al., *BCG vaccination enhances the immunogenicity of subsequent influenza vaccination in healthy volunteers: a randomized, placebo-controlled pilot study*. *The Journal of infectious diseases*, 2015. **212**(12): p. 1930-1938.
 14. Moorlag, S., et al., *Non-specific effects of BCG vaccine on viral infections*. *Clinical Microbiology and Infection*, 2019. **25**(12): p. 1473-1478.
 15. Stensballe, L.G., et al., *Acute lower respiratory tract infections and respiratory syncytial virus in infants in Guinea-Bissau: a beneficial effect of BCG vaccination for girls: community based case-control study*. *Vaccine*, 2005. **23**(10): p. 1251-1257.
 16. Netea, M.G., et al., *Trained immunity: a program of innate immune memory in health and disease*. *Science*, 2016. **352**(6284): p. aaf1098.
 17. Arts, R.J., et al., *BCG vaccination protects against experimental viral infection in humans through the induction of cytokines associated with trained immunity*. *Cell host & microbe*, 2018. **23**(1): p. 89-100. e5.
 18. Sun, J.C., J.N. Beilke, and L.L. Lanier, *Adaptive immune features of natural killer cells*. *Nature*, 2009. **457**(7229): p. 557-561.
 19. Walls, A.C., et al., *Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein*. *Cell*, 2020.
 20. Ritz, N., et al., *Non-specific effect of Bacille Calmette-Guérin vaccine on the immune response to routine immunisations*. *Vaccine*, 2013. **31**(30): p. 3098-3103.
 21. Sala, G. and T. Miyakawa, *Association of BCG vaccination policy with prevalence and mortality of COVID-19*. medRxiv, 2020.
 22. Berg, M.K., et al., *Mandated Bacillus Calmette-Guérin (BCG) vaccination predicts flattened curves for the spread of COVID-19*. medRxiv, 2020.
 23. Dayal, D. and S. Gupta, *Connecting BCG Vaccination and COVID-19: Additional Data*. medRxiv, 2020.
 24. Hegarty, P.K., et al., *BCG vaccination may be protective against Covid-19*. preprint, 2020.
 25. <https://clinicaltrials.gov/ct2/show/NCT00396370>