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Internal Medicine

Role of BCG Vaccination in prevention of COVID-19 infection amongst the health care workers

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ABSTRACT **Objective** : To find out the role of additional dose of BCG vaccination in health care workers in prevention of COVID-19 infection **Study design** : A prospective study to find out the incidence of COVID 19 infection in healthcare worker exposed to COVID-19 indoor patients by doing RT- PCR testing at the end of 15 days of COVID duty. **Setting** : The study was conducted at Noida COVID Hospital, Noida District Hospital and Superspecialilty PG Teaching institute (SSPGTI) hospital, Noida **Result** : No Health care worker who received additional dose dose of BCG vaccination contracted COVID infection as confirmed by RT-PCR at the end of 15 days of indoor COVID duty (Nil out of 80 healthcare workers) whereas in controls i.e. those who were not vaccinated 28 out of 130 controls contracted COVID-19 infection. **Conclusion** :Additional dose of BCG vaccination after the age of 20 year in healthcare workers engaged in care of admitted COVID-19 patients has a protective role since the COVID status of the patients attending hospitals for any other ailments is not known routine BCG immunization of the medical staff is recommended

KEYWORDS : BCG, vaccination , COVID-19,Healthcare workers

INTRODUCTION

The incidence of COVID-19 infection and subsequent mortality is much less in countries with limited healthcare services having universal BCG vaccination programme. BCG vaccine was first given to humans in early 1920's.A review of evidence in early 1990's concluded that BCG vaccine was unreliable in protecting against lung based tuberculosis,the most common and infectious form of the disease. This lead to several countries discontinuing its inclusion in universal immunization programme. Even so the vaccine is very effective in protecting the most severe form of TB such as TB Meningitis and miliary tuberculosis in pediatric age group. So countries with high rate of TB infection such as India ,Nepal, Netherland, Japan etc continued BCG vaccination. A single dose of immunization is given to new born babies. The effect of immunization reduced markedly after the age of 20 years[1]. It has been observed that countries which discontinued BCG vaccination policy such as European countries and USA have very high mortality rate. Italy which never had a BCG vaccination programme has been hit very hard,very high infectivity rate in present pandemic with large number of deaths.

It is a known fact that BCG vaccination has a large number of non-specific non-target effects on various bacterial, viral and parasitic infections[2,3] .There is a strong evidence that BCG vaccination has strong immunomodulatory effects and is being used intravesically for bladder cancer[4].Its routine use in universal immunization programme has resulted in reduced upper and lower respiratory tract infections.

Severity in upper and lower respiratory tract infections, reduction in mortality from pneumonia, reduction in hospitalization related to respiratory tract infections[5], reduction in leprosy rates, reduction in child mortality due to malaria at Guinea Bissau. Reduction in viremia in Yellow fever vaccination in prevaccinated children with BCG. In Severe Combined Immunodeficiency Syndrome, BCG vaccination protects against systemic Candida infection.

It reduces acute lower respiratory tract infection (ALRI) by Respiratory Syncitial Virus[6]. There is also enhanced response to H1N1 influenza vaccine if the person is already received BCG vaccination[7].

Goodridge et al have suggested harnessing of beneficial heterologous immunity of BCG vaccination[8].Hegarty et al concluded tha BCG vaccine is protective against COVID-19 infection.

The underlying mechanism for off-target effects and heterologous protective effects of BCG is not clearly understood. Evidenes suggest that induction of memory in innate(inborn) immune cells like monocytes,macrophages and natural killer cells independent of any T(thymus) and B(bone marrow) dependent cell response.These respmses of boosting innate memory response is termes as trained immunity[9]. This makes these mononuclear cells alert and avid for invading pathogens thus reducing the infection rate, viremia, morbidity and mortality .This is achieved by two processes namely Chromatin Remodelling and Histone Modification through epigenetic acetylation and methylation which in turn increase accessibility of RNA polymerase to gene encoding the proinflammatory molecules.

Thus it upregulates expression interleukin 1 beta ,Tumour Necrosis Factor-alpha,IL-16,TLR4 in mononuclear cells. This in turn enhances the expression of pattern recognition receptors(PPRs) like TLRs and NOD receptors .

Apart from epigenetic reprogramming ,altered cellular metabolism also contributes to trained immunity of innate memory response in monocytes, macrophages and NK-cells.In these cells metabolism switches from oxidative phosphorylation to glycosis in these activated cells. Since glycolysis is very essential for epigenetic changes for histone modification.

Innate immune cells like monocytes and dendritic cells have half life of 5-7 days.However the off –targeted effects persist for prolonged periods. This explains the induction of trained immunity due to changes in bone marrow, progenitor cells along with the circulating monocytes and macrophages[10,11]. WHO has not recommended the use of BCG vaccination for prevention of COVID-19 infection in general population as it may lead to scarcity of the vaccine for proven specific indication in Universal Immunization Programme. According to WHO, there is no on-date evidence of its efficacy. Hence may lead to false security and at times may lead to hypersensitivity reaction leading to aggravation of COVID infection . Its beneficial factors may have confounding factors.

As the effect of BCG vaccination wanes out in 15-20 years , there is a urgent need for further study to understand the protective role of additional dose of BCG vaccination to the vulnerable healthcare worker beyond the age of 20. Till date 11 clinical trials using BCG vaccination and three trials using recombinant BCG vaccination, VPM-1002 have been initiated with aim to study BCG mediated protective effects in healthcare workers handling COVID patient and elderly population .

MATERIAL AND METHODS

Two BCG vaccination drives to vaccinate the exposed healthcare workers were launched first between 1st to 7th May in which 30 medical and paramedical staff working at Noida District Hospital in Emergency Ward were administered 0.1ml of BCG vaccine(Danish 1331 strain) in the left upper deltoid region.50 healthcare workers who didn't consented for vaccination but were put on COVID duty were considered as control .The cases as well as control were followed by RT-PCR testing at the end of their COVID duty.

During second immunization drive 50 healthcare workers including medical and paramedical staff working at Noida COVID Hospital were administer BCG vaccination in left upper deltoid region between 24th to 26th August after taking written informed consent. 80 medical and paramedical staff who could not be vaccinated but doing duty in COVID Hospital were taken as control. The cases as well as control were followed up with RT-PCR testing at the end of their duty and symptomatic suggestive of COVID infection like dry cough,coryza,fever,respiratory distress ,loss of smell and taste, diarrhea etc . were noted.

INCLUSION CRITERIAS

Medical and paramedical staff between age group 21-60 who had consented for BCG vaccination after reading the informed consent explaining the risks of vaccination. A few of these persons were having comorbidities like diabetes and hypertension as well,

EXCLUSIONCRITERIAS

The healthcare workers who had not consented for vaccination persons above the age of 60 years as they have retired,persons already infected with COVID infection,pregnant women

OBSERVATIONS AND RESULTS

Table 1 Age wise distribution of the individual in years

	Stage - 1	Stage - 2		
Age Group (year)	No of individual in study group	No of individual in control group	No of individual in study group	No of individual in control group
21-30	2	4	8	20
31-40	4	4	22	44
41-50	2	4	12	6
51-60	22	38	8	10

Table-1 indicate that maximum no ofindividual in study group belong age group 31-60

Table 2 Sex wise distribution of the individual

	Stage - 1	Stage - 2		
Age Group (year)	No of individual in study group	No of individual in control group	No of individual in study group	No of individual in control group
Male	16	22	26	42
Female	14	28	24	38

Table-2 indicate thatmale & female are equally distributed due to increase in no of male nurses during last few years.

Table 3 Symptoms wise distribution of the individual in first drive of immunisation

	Cases (who were vaccinated)		Controls(who were not vaccinated)		
Age Group (year)	No. of individual Showing Symptoms in study group	No. of individual with positive RT-PCR	No. of individual Showing Symptoms in control group	No. of individual with positive RT-PCR	No. of asymptomatic found positive by RT-PCR
21-30	0	0	1	1	0
31-40	0	0	4	4	0
41-50	0	0	2	1	0
51-60	1	0	1	1	0

Table 3 shows 8 healthcare worker out of 50 control (who didn't receive BCG vaccination) were found to be RT-PCR positive for COVID-19 in the first phase of at the end of 15 days of COVID duty.

A matron of the OT had severe symptoms of upper respiratory tract infection ,high grade fever ,throat pain and cough .But to our surprise she came out to be negative for COVID-19 on rapid as well as RT-PCR testing. The peripheral smear didn't show malaria and could be easily managed with anti-histaminics, anti-pyretics and antibiotics. Probably she having acute viral pharyngitis . It was discovered that she also received additional dose of BCG vaccine unlike other OT staff.

Table-4

Phase-2 of immunization drive

	Cases (who were vaccinated)	Controls(who were not vaccinated)			
Age Group (year)	No of individual Showing Symptoms in study group	No of individual with positive RT-PCR	No of individual Showing Symptoms in control group	No of individual with positive RT-PCR	asymptomatic found positive by RT-PCR
21-30	0	0	4	4	0
31-40	4	0	8	7	1
41-50	0	0	2	2	0
51-60	0	0	6	6	0

In 2nd phase of immunization drive. No case(vaccinated) was found to be COVID-19 positive as shown by Negative RT-PCR.

In controls(non vaccinated) 20 out of 80 contracted the COVID 19 infection, which is much higher than general population. May be due to more than general exposure of the healthcare staff to the disease . Out of them 19 were symptomatic and one was asymptomatic. The main age group infected was 31-40 years as most staff belonged to this age group and second age group involved was 51-60 years clearly showing more vulnerability to aged population to the disease.

CONCLUSION

A number of studies have shown that BCG vaccine has a protective role in prevention against COVID-19 infection12.In our study no heathcareworker who was vaccinated with BCG and exposed to COVID-19 admitted patients had COVID-19 infection .The vaccination site showed erythema, induration and ulceration only in 7 cases. No major complication was observed in the study group. Even the patients with respiratory distress and palpitations didn't show any arrthymia or prolongation of QT interval on ECG examination.(However Hydroxychloroquine which was recommended for prevention of COVID-19 did cause such complications .)

It is concluded that additional dose of BCG vaccination must be given to healthcare workers involved in the care of indoor COVID patients.Further all medical and paramedical staff should also be vaccinated with BCG as the status of other patients visiting the hospitals for other ailments is not known.theresults of BCG vaccination are very optimistic, in present limited study. A larger study including large number will be more significant but seeing the result many healthcare workers who have already refused BCG vaccination and coming forward for the vaccination. The size will further grow as now medical and paramedical staff is being recruited. Immunization to the whole population is not recommended as it may lead to scarcity of the vaccine for well established indication under universal immunization programme and it will lead to massive economic burden on the national health services. Motivated by the promising result in the above study a bigger study may establish the exact role of BCG vaccination in COVID-19 infection .

BCG induced trained innate(inborn) immunity provide non specific protection may be used a bridge the gap before disease specific COVID-19 vaccine is developed ,specially in vulnerable healthcare workers engaged in the care of COVID-19 patients. The survival of COVID-19 infection develops Immunoglobulins (IgG and IgM) which is being exploited as plasma therapy to severe COVID-19 cases. But it has been found that reinfection with COVID-19 who had earlier COVID-19 infection are creeping up. In theory they are consisered to be having COVID-19 Immunoglobulins and second attack should not have occurred. Being a RNA virus , its genome is unstable due to presence of hydroxyl group(-OH) in ribose sugar which makes its genome reactive . Additionally replacement of Thymine by Uracil in RNA molecules makes the RNA molecule unstable and prone to mutation. In view of re-infection of already COVID-19 positive cases who have subsequently recovered and become RT-PCR negative casts serious doubts regarding the efficacy of COVID-19 vaccine to be engineered .This gives fuel to the thinking that improved overall innate immunity indeuced by BCG vaccination may play a important role in containing the spread,morbidity and mortality of COVID-19 infection especially to the healthcare workers and use for general population need increased production of BCG vaccine .

FINANCIAL SUPPLIES AND SPONSHERSHIP
Nil. All the participants who volunteered for the BCG vaccination have paid for the vaccine vials themselves.

CONFLICT OF INTEREST
Nil

NOTE : All the participants volunteered themselves and provided us with written consents , having explained to them all the possible Ethical issues and probable complications .

Motivated by the promising results in the above study, we are now organizing a bigger study with a experimental group of doctors working in NOIDA COVID HOSPITAL, with a control group of doctors.

REFERENCE

1. Biering-Sorensen S, Aaby P, Lund N, et al. Early BCG-Denmark and neonatal mortality among infants weighing <2500 g: a randomized controlled trial. Clin Infect Dis 2017; 65: 1183–90.
2. Pollard AJ, Finn A, Curtis N. Non-specific effects of vaccines: plausible and potentially important, but implications uncertain.Arch Dis Child 2017; 102: 1077–81.
3. R.J.W. Arts, S. Moorlag, B. Novakovic, Y. Li, S.Y. Wang, M. Oosting, V. Kumar, R.J. Xavier, C. Wijmenga, L.A.B. Joosten, C. Reusken, C.S. Benn, P. Aaby, M.P. Koopmans, H.G. Stunnenberg, R. van Crevel, M.G. Netea, BCG vaccination protects against experimental viral infection in humans through the induction of cytokines associated with trained immunity, Cell Host Microbe 23 (2018) 89–100 e105.
4. A. Roth, P. Gustafson, A. Nhaga, Q. Djana, A. Poulsen, M.L. Garly, H. Jensen,M. Sodemann, A. Rodriques, P. Aaby, BCG vaccination scar associated with better childhood survival in Guinea-Bissau, Int. J. Epidemiol. 34 (2005) 540–547.
5. P. Aaby, A. Roth, H. Ravn, B.M. Napirna, A. Rodrigues, I.M. Lisse, L. Stensballe, B.R. Diness, K.R. Lausch, N. Lund, S. Biering-Sørensen, H. Whittle, C.S. Benn, Randomized trial of BCG vaccination at birth to low-birth-weight children: beneficial nonspecific effects in the neonatal period? J. Infect. Dis. 204 (2011) 245–252.
6. L.G. Stensballe, E. Nante, I.P. Jensen, P.E. Kofoed, A. Poulsen, H. Jensen,M. Newport, A. Marchant, P. Aaby, 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 23 (2005) 1251–1257.
7. J. Leentjens, M. Kox, R. Stokman, J. Gerretsen, D.A. Diavatopoulos, R. van Crevel, G.F. Rimmelzwaan, P. Pickkers, M.G. Netea, BCG vaccination enhances the immunogenicity of subsequent influenza vaccination in healthy volunteers: A randomized,placebo-controlled pilot study, J. Infect. Dis. 212 (2015) 1930–1938.
8. Goodridge HS, Ahmed SS, Curtis N, et al. Harnessing the beneficial heterologous effects of vaccination. Nat Rev Immunol 2016; 16: 392–400
9. Netea MG, Dominguez-Andres J, Barreiro LB, et al. Defining trained immunity and its role in health and disease. Nat Rev Immunol 2020; published online March 4. DOI:10.1038/ s41577-020-0285-6.
10. Chavakis, I. Mitroulis, G. Hajishengallis, Hematopoietic progenitor cells as integrative hubs for adaptation to and fine-tuning of inflammation, Nat. Immunol. 20(2019) 802–811.
11. I. Mitroulis, K. Ruppova, B. Wang, L.S. Chen, M. Grzybek, T. Grinenko, A. Eugster, M. Troullinaki, A. Palladini, I. Kourtzelis, A. Chatzigeorgiou, A. Schlitzer, M. Beyer, L.A.B. Joosten, B. Isermann, M. Lesche, A. Petzold, K. Simons, I. Henry, A. Dahl, J.L. Schultze, B. Wielockx, N. Zamboni, P. Mirtschink, U. Coskun, G. Hajishengallis, M.G. Netea, T. Chavakis, Modulation of myelopoiesis progenitors is an integral component of trained immunity, Cell, 172 (2018) 147–161 e112.
12. Miller A, Reandelar MJ, Fasciglione K, Roumenova V, Li Y, Otazu GH. Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. J Chem Inf Model 2020;53(9):1689–99