

COMPARISON OF EFFECTIVENESS OF BCG VACCINE IN PREVENTION OF PULMONARY TUBERCULOSIS IN IMMUNIZED AND NON-IMMUNIZED PAEDIATRIC PATIENTS

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ORIGINAL ARTICLE

Background: Mycobacterium Tuberculosis (TB) is a bacterial organism responsible for causing TB in various parts of the human body, but it mainly affects the lung parenchyma. TB is one of the leading causes of morbidity and mortality globally. In the year 2015, 10.4 million adults suffered from TB and 1800,000 died while 1000,000 paediatric population suffered from TB and 170,000 passed away due to this illness. **Objective:** To find an association between pulmonary tuberculosis and BCG vaccination in the paediatric population. **Methodology:** It was an observational case-control study. The study was carried out in the departments of Pulmonology of The Children's Hospital and the Institute of Child Health, Lahore. The duration of the study was six months. A total of 122 patients fulfilling the inclusion criteria were enrolled in the study. BCG vaccination status was determined. **Results:** The mean age of the cases was 7.67 ± 4.30 years that of controls was 7.79 ± 4.13 years. Among cases, there were 32(52.2%) males and 29(47.5%) females while among controls there were 39(63.9%) males and 22(36.1%) females. In the cases group there were 27(44.3%) children with BCG Vaccination and 34(55.7%) without BCG vaccination on the other side among controls there were 33(54.1%) children with BCG vaccination and 28(45.9%) without BCG

vaccination. There was no significant association between BCG vaccination and study groups ($r=0.67$, p -value=0.27). **Conclusion:** There was no association between pulmonary TB and BCG vaccination in the paediatric population

INTRODUCTION

Mycobacterium Tuberculosis is an agent responsible for causing TB in various parts of the body but it mainly affects the lung parenchyma. TB is one of the leading causes of morbidity and mortality globally. In the year 2015, 10.4 million adults suffered from TB and 18 lacs died while 10 lacs paediatric population suffered from TB and 1,70,000 passed away due to this illness. Above 90% of the affected people belong to third world countries. It is a communicable disease that mostly spreads via droplet infection. The symptoms which alert a physician to diagnose TB are low-grade fever, cough for more than 3 weeks,

night sweats, chills, fatigue, anorexia and gradual weight loss.¹ TB is amongst the most prevalent diseases in Pakistan and it stands fifth in number in comparison with 22 TB prevalent states all over the world. In the Eastern Mediterranean Region demarcated by WHO about 61% of diseased persons are from Pakistan.² The vaccine which has been devised for prevention of TB is called Bacillus Calmette Guerin vaccine (BCG) and is widely used in developing countries for the prevention of childhood TB.³

BCG vaccine has been adopted in the national

immunization program of many countries and about 80% of children are inoculated by this vaccine soon after birth.⁴ Pakistan adopted this vaccine in its extended program of immunization in 1948 and it has been in practice since then.⁵

For many years multiple studies have been carried out regarding the protective efficacy of BCG vaccination against TB. Studies show that BCG vaccination is 60-80% effective in combating TB especially TB meningitis in the paediatric age group but efficacy against pulmonary type is extremely uncertain.^{6, 7}

The efficiency of BCG vaccine varies in different areas because of multiple factors like genetic variation, environmental differences, laboratory methodology in culturing bacteria and inoculation techniques. It has been observed that BCG has no protective value when it is given to an individual who is exposed to the causative agent.⁸⁻¹⁰ A case-control study was conducted in Birmingham to assess the role of BCG vaccine against TB. Of the cases, 57% had received BCG, and of the controls, 78% had received BCG.¹¹ Though Pakistan stands among the countries rampant with TB and despite the immense burden that it has on the economy, there is very little data available that shows the efficacy of BCG vaccination in the prevention of pulmonary TB. Parents of newborns undergoing vaccination are interested in the efficacy of the vaccine in the prevention of disease and should be provided with reliable data regarding the efficacy of a particular vaccine. The main objective of the study was to find out the protective role of BCG vaccine against pulmonary TB amongst the Pakistani paediatric population considering the hypothesis that there is an association between pulmonary TB and BCG vaccination.

MATERIALS AND METHODS

Study Design: It was an observational case-control study. **Setting:** The study was carried out in the department of Pulmonology of The Children's Hospital and the Institute of Child Health, Lahore. **Duration:** It was completed within six months i.e., 8-5-2018 to 8-11-2018. **Sampling technique:** Non-probability purposive sampling

technique was used for sample collection.

Sample size: A sample size of 122 (61 in each category) was calculated with a 5% level of significance and 80% power of the test and taking the expected frequency of cases to be 57% and control 78%.¹¹ **Sample selection criteria:** Inclusion criteria: Patients from 1 month to 14 years of age of either gender were included in the study. Those diagnosed with pulmonary TB on Kenneth Jones criteria (score of >5 was labelled as pulmonary tuberculosis) were selected as cases and those with history, clinical examination and investigations not suggestive of TB (who required medical attention in the same hospital where a case was enrolled) were taken as control group. **Exclusion criteria:** Patients with chronic lung disease other than TB. e. g. interstitial lung disease, cystic fibrosis, bronchiectasis, etc. were excluded from the study. **Data collection procedure:** A total of 122 patients (61 in the case and 61 in the control group) fulfilling the inclusion criteria were enrolled in the study. After taking informed consent from parents of children, their demographic information including name, age, sex, and vaccination status was recorded. Vaccination status was confirmed by examining the BCG scar mark on the right arm and vaccination card as well. **Data analysis plan:** Data analysis was done by software Statistical Package for the Social Sciences (SPSS) version 20. Frequency and percentage were calculated for qualitative variables like gender and vaccination status. Mean \pm Standard Deviation was calculated for a quantitative variable like age. Two groups were compared, the chi-square test was applied, Odds ratio was calculated taking a p-value < 0.05 as significant. Data was stratified for age and gender. Post-stratification chi-square test was used taking P-value < 0.05 as significant.

RESULTS

The mean age of the cases was 7.67 ± 4.30 years, the minimum age was 1 year and the maximum was 14 years whereas the mean age of the controls was 7.79 ± 4.13 years, the minimum age was 1 year and the maximum was 14 years. (Table 1) Among cases, there were 32(52.2%) males

and 29(47.5%) females while among controls there were 39(63.9%) males and 22(36.1%) females. (Table 2) In the cases group there were 27(44.3%) children with BCG Vaccination and 34(55.7%) without BCG vaccination on the other side among controls there were 33(54.1%) children with BCG vaccination and 28(45.9%) without BCG vaccination. (Table-3) There was no significant association between BCG vaccination and study groups as the p-value was not significant. (p-value=0.27). The odds ratio was 0.67 which means that among cases i.e., children who are exposed have 33% fewer chances of developing the disease as compared to the non-exposed group. (Table-4) In the age group of 1-5 years, there was a significant association between BCG vaccination and the study groups as the pvalue was significant (p-value=0.003)

while in the age groups 6-10 years and 11-15 years there was no significant association between BCG vaccination and the study groups as the pvalue was not significant (pvalues=0.86 and 0.28). The odds ratio in the age group of 1-5 years was 0.14 while that in the age groups of 6-10 years was 1.05 which means that there were 1.05 times more odds of the disease and in the age group 11-15 years the odds ratio was 1.98 meaning that there were 1.98 times more odds of disease. (Table 5) Among males and females, there was no significant association between BCG vaccination and the study groups as the p-value was not significant (p-values=0.24 and 0.60). The odds ratio was 0.57 and 0.74 which means there were 43% and 26% times fewer odds of developing the disease among males and females who are already exposed. (Table-6)

Table 1: Demographic analysis of participants

Variable	Case	Control
No. of patients (n)	61	61
Minimum Age (years)	1	14
Maximum Age (years)	1	14
Mean Age (years)	7.67	7.79
Standard Deviation	4.30	4.13

Cases: Diagnosed pulmonary TB cases

Controls: No history of TB

Table-2: Gender of the Patients Group

Gender	Group	
	Case	Control
Males	32(52.2%)	39(63.9%)

Females	29(47.5%)	22(36.1%)
Total	61(100%)	61(100%)

Table-3: BCG. Vaccination

BCG Vaccination	Frequency	Percentage
Yes	60	49.2%
No	62	50.8%
Total	122	100%

Table-4: Association between BCG. Vaccination and TB

BCG Vaccination	Group		Percentage
	Case	Control	
Yes	27(44.3%)	33(54.1%)	60(49.2%)
No	34(55.7%)	28(45.9%)	62(50.8%)
Total	61(100.0%)	61(100.0%)	122(100.0%)

Odds Ratio = 0.67 (95% CI: 0.33-1.37)

Chi-square = 1.18

P-value = 0.27

Table-5: Association between BCG. Vaccination and TB Stratified for Age Groups

Age Group	BCG Vaccination	Group		P-value	OR (CI = 95%)
		Case	Control		
1-5 years	Yes	5(21.7%)	15(65.2%)	0.003	0.14 (0.040-0.54)
	No	18(78.3%)	8(34.8%)		

	Total	23(100%)	23(100%)		
6-10 years	Yes	9(52.9%)	9(50%)	0.86	1.059 (0.556-2.015)
	No	8(47.1%)	9(50%)		
	Total	17(100%)	18(100%)		
11-15 years	Yes	13(61.9%)	9(45%)	0.28	1.986 (0.571-6.902)
	No	8(38.1%)	11(55%)		
	Total	21(100%)	20(100%)		

Table-6: Association between BCG. Vaccination and TB Stratified for Gender

Gender	BCG Vaccination	Group		P-value	OR (CI = 95%)
		Case	Control		
Male	Yes	12(37.5%)	20(51.3%)	0.24	0.57 (0.22-1.47)
	No	20(62.5%)	19(48.7%)		
	Total	32(100%)	39(100%)		
Female	Yes	15(51.7%)	13(59.1%)	0.60	0.742 (0.24-2.27)
	No	14(48.3%)	9(40.9%)		
	Total	29(100%)	22(100%)		

DISCUSSION

Pulmonary tuberculosis is a rampant disease in the subcontinent and there is very little data showing the efficacy of BCG vaccination in protecting against TB, especially in the Asian subjects. Rennie et al showed from their results that 2

percent (7/425) of contacts who were vaccinated developed active TB while four per-cent (57/1479) of contacts who were unvaccinated developed active TB.¹² Lanckriet C et al, deduced from their results that the chances of developing

tuberculosis in vaccinated children were 7.3% compared to 25% in unvaccinated children, corresponding to 71% efficacy of BCG vaccine.¹³ This was in similarity to the findings of Hanekom WA, showing a positive result in favour of vaccination in newborns¹⁴ but when Briassoulis G et al conducted studies in the adolescent population then contrasting results were obtained.¹⁵ Childhood TB is because of direct contact with an infected adult individual, at majority of times. It is still not certain if all individuals develop immunity/protection against TB after BCG vaccination. Grindulis H et al, from their study in Birmingham showed that only 46 (69/149) percent of children who were inoculated with BCG vaccine were Mantoux positive after 22 months of age.¹⁶ It could have been due to reduced cellular immune response in the neonatal age group. Similarly, Tameris MD et al, conducted their study in Bradford which showed that 45 percent (59/131) of children who were vaccinated with BCG vaccine in the first three months of infantile age were having a negative reaction when checked later on before 2 years of age.¹⁷ Multiple factors (like age of inoculation, method of injecting, cold chain maintenance) could be responsible when it comes to the efficacy of BCG vaccination as conflicting results are seen in different studies. Hadfield J et al disclosed that 98 percent (353/361) of neonates in the UK showed a positive response to the tuberculin test when tested after three months of vaccination.¹⁸ Alessia et al, don't identify gender to be a risk factor for acquiring TB¹⁹ which is similar to the results obtained in our study though males were relatively more infected (52 percent) as compared to females. While Teo S et al in a different but related study showed that females were more prone to developing TB as compared to males (56 percent) and even in this study there was no significant difference in acquiring disease between vaccinated and unvaccinated individuals.²⁰ Chandra P, has concluded from his data that being vaccinated with BCG doesn't guarantee protection against pulmonary TB.²¹ Gupta et al recorded the same results as ours that there was no significant difference in terms of disease protection when unvaccinated individuals were compared with

vaccinated ones, also no relationship was established between gender and BCG vaccination.²² Pulmonary involvement by mycobacterium tuberculosis is commonly seen as compared to extrapulmonary TB. Though the protection provided by BCG vaccine against pulmonary TB is still not clear, it is also unclear if the disease severity is lower in vaccinated individuals.²³ Pulmonary tuberculosis can occur at any age and children are prone to acquire the disease from close contact. Other factors like poor socio-economic conditions, overcrowded houses, malnutrition and poor ventilation also play their part in the spread of TB. Our study shows the age group of 11-15 years to be the most vulnerable to acquiring pulmonary TB while in the study conducted by Gupta et al the age group of 0-4 years was having the highest prevalence of TB.²² Narain et al, and Chakraborty et al, in two different studies showed the prevalence of tuberculous disease in children below 4 years to be 38.9 and 54.3 percent respectively.²⁴ Hence there was no association between pulmonary TB and BCG vaccination in the paediatric population. Overall, the data of this study suggest that BCG vaccination may protect against more severe forms of TB.

CONCLUSION

According to the findings of the study, there was no association between pulmonary TB and BCG vaccination in the paediatric population. Overall, the data of this study suggest that BCG vaccination may protect against more severe forms of TB.

Author's Contributions

SF: Conceptualization, Methodology, Investigation, Analysis, Validation

MAAB: Writing, Analysis, Validation, Review & Editing

MMA: Writing, Resources, Validation, Review & Editing

SK: Resources, Validation, Review & Editing

SS: Resources, Validation, Review

SM: Supervision, Validation, Resources, Review

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