ORIGINAL ARTICLE

ROLE OF BCG IN PREVENTING CHILDHOOD TUBERCULOSIS

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Background: Childhood tuberculosis claims many lives and BCG vaccine is the only prevention available against its most serious forms**. Objective** was to find out protective role of BCG vaccine against childhood tuberculosis by calculating odds ratio. **Methods:** It was a case control study. The study was conducted at Paediatrics department of Ayub Teaching Hospital. A total of 308 patients were included in the study. One hundred and fifty-four patients admitted in paediatrics ward and diagnosed with pulmonary, extra pulmonary, disseminated or any other forms of tuberculosis were included as cases in the study. For the control group, 154 children free of tuberculosis were selected as age matched controls from paediatric outpatient department. BCG scar was checked over right upper deltoid in both cases and controls. Data was recorded and analysed using spss. **Results:** From a total of 308 patients 167 (54.22%) were males and 141 (45.78%) were females. BCG scar was found in 170 (55.19%) out of 308 patients and it was absent in 138 (44.81%) children. Only a slight preponderance among males was noted who were affected by tuberculosis (50.9%) as compared to females from which (48.9%) of total were affected. Odds ratio for presence or absence of BCG scar and presence or absence of tuberculosis was less than 1, i.e., 0.692 (95% CI: 0.441 to 1.086). Administration of BCG vaccine was not a potent protective factor in our study. Pearson's two tailed correlation between BCG scar and presence or absence of tuberculosis showed $p>0.05$ and was statistically not significant. **Conclusion:** There was no significant protective effect of BCG against childhood tuberculosis.

Keywords: BCG vaccine, childhood tuberculosis, EPI, Protection, Prophylaxis

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INTRODUCTION

Mycobacterium tuberculosis is one of the oldest pathogens in history that has claimed millions of lives in their most reproductive years, and still it remains a threat. Hippocrates used the term 'phthisis', or 'consumption', as it was a very widespread illness of his age but at that time neither prevention nor a cure was available, so it was always fatal.[1,2] As estimated by World Health Organization (WHO) Tuberculosis was responsible for approximately 10.7 million deaths globally in the year 2016. About a million children were diagnosed with tuberculosis in 2016, excluding missing cases. Internationally, with rise in acquired immune deficiency syndrome (AIDS), cases of tuberculosis also rose. In 2016 an estimated 10.4 million new diagnosed cases of tuberculosis were reported, of which 10% were HIV positive, 90% were adults of which 65% were males. Of the 10.4 million, 74% of TB patients were living in Africa and 64% from the total were distributed in seven countries including India, Indonesia, China, Philippines, Pakistan, Nigeria, and South Africa.[3,4] Currently, worldwide BCG vaccine is the only protection given to babies after birth as protection against serious forms of childhood tuberculosis.

Globally with more than 3 billion total doses of BCG given, still the number of children diagnosed with pulmonary and other forms of tuberculosis is rising. In Pakistan tuberculosis is endemic. Vaccination rates are low as vaccine is unavailable in remote areas like Kohistan. We are still dependent on UNICEF/WHO for provision of vaccine and during periods of shortened supply many children are denied BCG vaccine in government setup. In government-run hospitals BCG vaccination is given to all babies as the 1st vaccine after birth as part of EPI schedule and is free of cost. It is the only prevention against tuberculosis available in Pakistan as other methods such as treating latent tuberculosis and screening high risk children are not being utilized. There is no clear policy for controlling tuberculosis in KPK. Abroad, control methods used are BCG, early diagnosis of primary and secondary tuberculosis and treating latent tuberculosis infection.

An attenuated strain of the original *Mycobacterium bovis* was obtained and used in humans by trade name of BCG (Bacillus Calmette Guerin), first by WHO and then in 1948 by the UNICEF. In 1974, the WHO's Expanded Program on Immunization (EPI) included it in its agenda. After 1920 due to efforts of World Health Organization (WHO) and UNICEF worldwide adaption of BCG vaccine happened. BCG coverage reached its peak of 80% in 1990 except in some countries of Africa where it was low.[5] Most countries including Pakistan give a single dose of BCG vaccine after birth. Studies implying advantage of a second or more doses are insufficient. Some countries have adapted giving a second dose if a nodule doesn't form after 1st dose, though evidence that a 2nd dose might increase the protective efficacy of the vaccine is lacking.[6] The protective effect of single dose of BCG against tuberculosis meningitis and miliary tuberculosis

is evident, but studies of its protective effect against pulmonary tuberculosis show either no protection or protection only up to 80%. Single dose is believed to offer good protection till 15 years of life.[7] Our study was aimed at finding out its protective role against childhood TB.

MATERIAL AND METHODS

This case control study was conducted at Paediatrics Department of Ayub Teaching Hospital. A total of 308 patients were included in the study. One hundred and fifty-four (154) patients admitted in Paediatrics Ward and diagnosed with pulmonary, extra pulmonary, disseminated, and any other form of tuberculosis were included as cases in the study. (Cases were diagnosed with pulmonary or extra pulmonary forms of tuberculosis, by registering with TB DOTS and either of the following: positive findings on chest X-rays, a positive Mantoux test, presence of acid-fast bacillus (AFB) in sputum samples, CSF analysis or positive TB-ICT tests).

Age matched controls free from tuberculosis were selected from Outpatient Department of Ayub Teaching Hospital. Right upper deltoid region was examined in both groups to establish presence or absence of BCG scar. Data was recorded on proforma and analysed using SPSS-21. Results were presented as frequencies and percentages.

RESULTS

In 308 patients, 167 (54.22%) were male and 141 (45.78%) were female. Their ages ranged from 1–15 years with mean age 7.78±3.851 years. Only 170 (55.19%) children had a BCG scar and 138 (44.81%) had no BCG scar. Among the 167 males, 92 (55.1%) had a BCG scar and in 75 (44.9%) BCG scar was absent. In the 141 females, 78 (55.3 %) had BCG scar and 63 (44.7%) girls had no BCG scar. No gender preference for BCG vaccine was noticed.

From the 167 males 85 (50.9%) had tuberculosis and 82 (49.1 %) had no tuberculosis. In the 141 females 69 (48.9%) had tuberculosis and 72 (51.1%) had no tuberculosis. Pulmonary tuberculosis was the most common type of tuberculosis and was present in 70 out of 154 cases (45.45%), followed by tuberculosis meningitis that was the second leading cause of childhood tuberculosis and affected 66 (42.86%) children out of 154.

Tuberculous meningitis affected 66 children, from which 26 children had a BCG scar and in 40 children BCG scar was absent; whereas from the 70 (45.5%) children with pulmonary tuberculosis, BCG scar was present in 42 and absent in 28 (Table-1).

Correlation between presence or absence of BCG scar and presence or absence of tuberculosis showed a value of $p>0.05$ and was statistically not significant (Table-2). The odds ratio between presence or absence of BCG scar and presence or absence of tuberculosis was 0.69 (95% CI, 0.441 to 1.086), implying that BCG exposure was not a potent protective factor in our study, and the chances of having tuberculosis were 0.69 less if BCG scar was present. Also 1/OR was calculated and was 1.45 implying that there were 1.45 times more chances of having tuberculosis if BCG scar was absent. So although exposure to BCG was associated with lower chances of tuberculosis but the effect of protection offered was not significant (Table-3).

Table-1: cross tabulation between presence or absence of BCG scar and Type of tuberculosis

Type of BCG	BCG scar		Total	Percentage
	Present	Absent		
Pulmonary	42	28	70	45.45
Meningitic	26	40	66	42.85
Abdominal	4	3	7	4.55
Miliary	4	3	7	4.55
Disseminated	2	2	4	2.60
Total	78	76	154	100

Table-2: 2×2 contingency table between BCG scar and Tuberculosis for calculating odds ratio

BCG scar	Tuberculosis		Total
	Present	Absent	
Present	78	92	170
Absent	76	62	138
Total	154	154	308
***p*-value**	0.10		

Table-3: Odds ratio for BCG scar present/BCG scar absent and presence or absence of tuberculosis

	Value	95% confidence interval	
		Upper	Lower
Odds ratio for BCG (BCG scar present / BCG scar absent	0.69	0.441	1.086
For cohort tuberculosis= tuberculosis present	0.83	0.667	1.040
For cohort tuberculosis= tuberculosis absent	1.21	0.956	1.517
Number of Valid cases	308		

DISCUSSION

In our study no preference of gender regarding BCG vaccination was found among children. Only a slight preponderance among males was noted who were affected by tuberculosis as compared to females, but this preference was statistically not significant ($p>0.05$).

This male preference by *Mycobacterium tuberculosis* has been reported elsewhere also. In one study it was noted that when exposed to *Mycobacterium tuberculosis* only 5–10% people will be infected by it but out of these approximately 70% would be males. This relative resistance of females among humans might be multifactorial involving hormonal differences etc. but further studies have yet not be done regarding male preference of *Mycobacterium tuberculosis*.[8]

Our study showed that in children with no BCG scar tuberculous meningitis was more common form of TB. The relatively more effective protection of BCG against tuberculosis meningitis is also observed in other studies and is mentioned in text books as well. A meta-analysis involving BCG vaccination trials was published according to which it was noticed that BCG vaccine when given in infancy was up to 50% effective in preventing pulmonary form of tuberculosis in children but the protection against tuberculosis meningitis and disseminated tuberculosis was up to 50–80%. It was concluded that at present the best use of BCG vaccine is for prevention of serious and life threatening forms of TB in children.[9] Protective effect of BCG varies according to the potency of BCG and how it's delivered. And when given to infants decreases chances of disseminated forms of tuberculosis but is not very protective against pulmonary tuberculosis in late childhood and adolescence.[10]

The BCG scar was present in only 55% of patients included in our study. Many factors can be involved in such a low rate of BCG vaccination in our community such as lack of awareness, difficult access to vaccine centres, factors regarding storage and transport of BCG vaccine. During period of shortage many children are deprived of its beneficial effect. The low vaccination rates were also reported in Bangladesh where it was reported that only 2% of newborns get BCG vaccination in the first week after birth and only 23% in the first month of life and majority of children are deprived of beneficial effect of this vaccine.[11]

Odds ratio for BCG scar presence or absence and presence or absence of tuberculosis was 0.692 (95% CI: 0.441 to 1.086), so in our study, administration of BCG vaccine was not a potent protective factor (p>0.005), though it has been claimed that it has more protective effect against serious forms of tuberculosis as tuberculous meningitis. This reduced effectiveness may be attributed to other factors as well, e.g., if vaccine storage was up to date etc. Further studies such as performing Monteux test in children who have a BCG scar may help in a deep insight of the problem. Questions have been raised regarding the effectiveness of BCG as a protection against childhood tuberculosis. In spite of the fact that till now more than 5 billion doses of BCG have been administered, this had negligible effect on limiting the spread of or controlling tuberculosis infection globally and that still tuberculosis remains an epidemic in many regions.[12]

It was also claimed that BCG alone is insufficient to eradicate tuberculosis and there is need to develop a new vaccine against tuberculosis. The anti-tubercular drugs given to eradicate infection in diagnosed cases require administration of 4 or 5 drugs during initiation therapy and at least two drugs in the continuation phase. Most of these are hepatotoxic and resistance to these antibiotics against mycobacterium is also developing. In some studies it was claimed that this existing BCG vaccine, is only effective in preventing infection in 15–40% of children and probably is not effective at all in adults.[13] BCG remains the only tool available for prevention of severe forms of TB in HIV-uninfected children. As BCG contains attenuated organisms, it was contraindicated since 2007 and recommended not to be used in HIV positive patients. The study in Angola conducted in 2005 aimed at checking the efficacy of BCG in preventing tuberculosis in HIV infected children by calculating odds ratio. The results of the study showed no significant protective effect of BCG vaccination against TB. The odds ratio values of the study ranged from 0.79 (when adjusted for healthcare variables) to 1.14. That study suggested that BCG does not have a protective effect against tuberculosis among immunodeficient HIV-infected children.[14] In one case-control study, the odds ratio for Tuberculosis was 0.50 (95% CI= 0.39 to 0.64); it showed a 50% protective effect against tuberculosis. BCG vaccine significantly reduces the risk of tuberculosis by 50–80%. This protective effect was observed in many populations, different study designs, and forms of TB.

Age at vaccination did not have an effect on efficacy of BCG. Protection against tuberculous death, meningitis, and disseminated disease is higher than for total TB cases.[15] In spite of all the shortcomings, till a new and more effective prevention is available; at present BCG is the only vaccine that offers some protective effect against this disease of childhood.[6]

CONCLUSION & RECOMMENDATIONS

There was no significant protective effect of BCG against childhood tuberculosis especially pulmonary tuberculosis. BCG vaccination was low as only about half of the children had a BCG scar. Further studies are recommended with larger sample size and considering other contributing factors such as childhood malnutrition, poverty, overcrowding, immune compromised states etc. that might be the cause of decreased effectiveness of BCG.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Hershkovitz, I, Donoghue HD, Minnikin, DE, Besra GS, Lee OY, Gernaey AM, *et al*. Detection and molecular characterization of 9,000-year-old *Mycobacterium tuberculosis* from a Neolithic settlement in the Eastern Mediterranean. PLoS ONE 2008;3(10):e3426.
2. Herzog H. History of tuberculosis. Respiration 1998;65:5–15.
3. Global Tuberculosis Control (2017). WHO: Geneva; 2017. Available from: www.who.int/tb/publications/global_report/en/
4. Grange JM, Gibson J, Osborn TW, Collins CH, Yates MD. What is BCG? Tubercle 1983;64:129–39.

5. Starke JR, Connelly KK. Bacille Calmette-Guerin vaccine. In: Plotkin MEA, (Ed). Vaccines. Philadelphia: WB Saunders; 2004. p.456–89.
6. Barreto ML, Pereira SM, Ferreira AA. BCG vaccine: efficacy and indications for vaccination and revaccination. J Pediatr (Rio J). 2006;82(3 Suppl):S45–54.
7. World Health Organization. WHO vaccine-preventable diseases: monitoring system 2006 Global summary. WHO: Geneva; 2006.
8. Neyrolles O, Quintana-Murci L. Sexual Inequality in Tuberculosis. PLoS Med 2009;6(12):e1000199
9. Roy A, Eisenhut M, Harris RJ, Rodrigues LC, Sridhar S, Habermann S, *et al*. Effect of BCG vaccination against Mycobacterium tuberculosis infection in children: systematic review and meta-analysis. BMJ 2014;349:g4643.
10. Hay WW Jr, Levin MJ, Deterding RR, Abzug MJ, (Eds). Current Diagnosis and Treatment Pediatrics. 22nd ed. New York, NY: McGraw-Hill Education LLC; 2014. p.1336.
11. Chaity AJ. Study finds newborns rarely get TB vaccine at birth. Dhaka Tribune. November 28, 2017.
12. BCG-vaccine-to-be-boosted-to-effectively-prevent-tuberculosis. Available from: http://www.bio-medicine.org/medicine-news/BCG-vaccine-to-be-boosted-to-effectively-prevent-tuberculosis-5002-1/
13. Smith R. Eradication of tuberculosis by 2050 impossible without new vaccine. BMJ 2009;338:b1291.
14. Van-Dunem JC, Rodrigues LC, Alencar LC, Militão-Albuquerque Mde F, Ximenes RA Effectiveness of the First Dose of BCG against Tuberculosis among HIV-Infected, Predominantly Immunodeficient Children. Biomed Res Int 2015; 2015:275029.
15. Colditz GA, Brewer TF, Berkey CS, Wilson ME, Burdick E, Fineberg HV, *et al*, The efficacy of BCG in the prevention of tuberculosis: Meta-analyses. JAMA 1994;271(9):698–702.

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