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Short Communication

Does effect of BCG vaccine decrease with time since vaccination and increase tuberculin skin test reaction?

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ABSTRACT

The protective efficacy of BCG was studied for over 15 years, from 1968, in South India. A secondary analysis of data was performed to investigate the relationship between Bacille Calmette-Guérin (BCG) and tuberculosis (TB) disease and between BCG and positive tuberculin skin test for different time periods among children aged less than 10 years. A randomized controlled trial was conducted, where 281,161 persons were allocated to receive BCG 0.1 mg, BCG 0.01 mg or placebo. Tuberculin skin test was performed at baseline and at 4 years after BCG vaccination. Surveys were conducted every 2.5 years to detect all new cases of culture-positive/smear-positive TB occurring in the community over a 15-year period. Relative risk (RR) was obtained from the ratio of incidence among the vaccinated and the placebo groups. Among those children vaccinated with 0.1 mg of BCG, the RR for TB was 0.56 (95% CI: 0.32–0.87, $P = 0.01$) at 12.5 years but increased to 0.73 later. Similar pattern was seen with 0.01 mg. The increase in the number of skin test positives with 0.1 mg of BCG was 57.8%, 49.4% and 34% for cut-off points at ≥10 mm, ≥12 mm and ≥15 mm, respectively. The study suggests that the effect of BCG may decrease since vaccination and the tuberculin positive was higher at post-vaccination test period due to BCG.

1. Introduction

The 2014 WHO Global Tuberculosis (TB) Report showed that there were 9 million people who developed TB in 2013. India alone accounted for 24% of the total cases in the world in that year.[1] It is a well known fact that the efficacy of presently available Bacille Calmette-Guérin (BCG) vaccine varies widely with geographical latitude.[2,3] It was proved that the use of BCG vaccination did not offer any protection against pulmonary TB disease especially among the adult population, and only a low level of overall protection of 27% in children aged <10 years based on the Chingleput BCG trial.[4] TB still remains a major problem worldwide and especially for India. Prevention will be

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greatly facilitated by the development of a new vaccine that would show consistent protection. The cut-off point of 12 mm was defined for tuberculin positive for the BCG trial data as the antimode of the distribution of reaction sizes was at 12 mm.[5] BCG given in childhood or at an older age results in a positive tuberculin reaction.[6] Studies have shown that the protective efficacy of BCG against TB may decrease with time since vaccination.[7] We presented a secondary analysis of data from the BCG trial to investigate the relationship between BCG and TB disease, and between BCG and positive tuberculin skin test.

2. Methods and materials

A double-blind, randomized controlled trial was initiated in 1968 in a large rural community in Chingleput district in south India, to assess the protective efficacy of BCG vaccination, employing a 0.01 mg of BCG and a 0.1 mg of BCG. A total of 281,161 individuals were allocated randomly to receive vaccine or placebo. They were tested with 3 international units (IU) of PPD-S and 10 units of PPD-B at baseline. Also, a post-vaccination allergy was tested with 3 IU of PPD-S at a different site than used for the first two tests at baseline at 4 years on a selected sample of population. Case finding for TB was continuous in this area with resurveys, selective case finding and an activated passive case finding.[5] Relative risk (RR) was obtained from the ratio of incidence among the vaccination and the placebo groups.

The full study details have been published earlier.[4,5] The Institutional Ethics Committee of the National Institute for Research in Tuberculosis, Indian Council of Medical Research, approved the trial.

3. Statistical methods

Logistic regression model was employed to assess the RR for TB for two BCG vaccinated groups. The relationship between BCG vaccinated groups and tuberculin skin test was evaluated using chi-square test. A *P*-value of less than 0.05 was considered as statistically significant.

4. Results

This analysis considers children aged <10 years with the tuberculin skin test reaction of 0–7 mm to PPD-S and normal radiograph in three groups, i.e., 0.01 mg of BCG, 0.1 mg of BCG and placebo. At baseline, the study subjects were 20,265, 20,372 and 20,344, respectively. The same cohort of children was investigated over six follow-up periods (0–2.5, 0–5.0, 0–7.5, 0–10.0, 0–12.5 and 0–15.0 years) to estimate the RR due to BCG vaccination. For 0.01 mg of BCG vaccination group, in 0–2.5 years, the RR was estimated to be 2.01, and increased to 2.51 in 0–5.0 years and decreased steadily to 1.00, 0.93 and 0.69 at subsequent follow-up periods, and later increased to 0.79 in 0–15 years. Similar pattern (RRs: 1.66, 2.00, 0.83, 0.81, 0.53 and 0.73) was also seen for 0.1 mg of BCG group (Table 1). BCG was not significantly effective at any point except for 0.1 mg of BCG at 12.5 years. In terms of BCG efficacy, higher level of protection was estimated to be 31% (95% CI: −9 to 56%) and 47% (95% CI: 13–68%) due to 0.01 mg of BCG and 0.1 mg of BCG vaccination, respectively, in 0–12.5 years.

The cohort of children aged <10 years at baseline, who were also given post-vaccination tuberculin test at 4 years, was 11,741, 11,610 and 11,641 in placebo, 0.01 mg of BCG and 0.1 mg of BCG groups, and their data were analyzed to confirm whether the BCG vaccination increases the tuberculin skin test reaction size at post-vaccination test period. The cut-off point of 12 mm was defined for tuberculin positive for the BCG trial data as the antimode of the distribution of reaction sizes was at 12 mm. However, the tuberculin positive subjects were classified according to different cut-offs, ≥10 mm, ≥12 mm and ≥15 mm at baseline and post-vaccination test periods. BCG vaccination time point was significant. The positive skin test in all the cut-off points was more than twice at post-vaccination testing period when compared by baseline survey and thus BCG vaccination was significantly associated with tuberculin skin test results.

The proportions of tuberculin positive in cut-offs ≥10 mm, ≥12 mm and ≥15 mm increased to 41.5%, 33.9% and 23.4%, respectively, in 0.01 mg of BCG group at post-vaccination testing period. Similarly, in 0.1 mg of BCG group, the tuberculin

Table 1 – Effect of BCG vaccine over study duration among children aged <10 years with 0–7 mm PPD-S and normal radiograph at baseline.

Follow-up duration (years)	Placebo		0.01 mg of BCG				0.1 mg of BCG			
	TB cases, *n*	Person-years, *n*	TB cases, *n*	Person-years, *n*	Relative risk (95% CI)	*P*-Value	TB cases, *n*	Person-years, *n*	Relative risk (95% CI)	*P*-Value
0–2.5	3	50,853	6	50,648	2.01 (0.50–8.03)	0.32	5	50,918	1.66 (0.40–6.96)	0.49
0–5.0	6	101,698	15	101,273	2.51 (0.97–6.47)	0.06	12	101,818	2.00 (0.75–5.32)	0.17
0–7.5	18	152,513	18	151,890	1.00 (0.52–1.93)	0.98	15	152,710	0.83 (0.42–1.65)	0.60
0–10.0	26	203,308	24	202,493	0.93 (0.53–1.61)	0.79	21	203,588	0.81 (0.45–1.43)	0.47
0–12.5	45	254,055	31	253,078	0.69 (0.44–1.09)	0.11	24	254,458	0.53 (0.32–0.87)	0.01[a]
0–15.0	60	304,765	47	303,623	0.79 (0.54–1.15)	0.21	44	305,278	0.73 (0.50–1.08)	0.12

CI, confidence interval.
[a] Statistically significant.

positive increased to 57.8%, 49.4% and 34.0%, respectively. To investigate the relationship between tuberculin positive and BCG vaccinated groups related to placebo, the RRs were estimated for the above cut-off points. The RR of positive test of 1.04 (95% CI: 0.97–1.11) in 0.01 mg of BCG group at baseline increased to 1.39 (95% CI: 1.35–1.44) at post-vaccination testing period, and also in 0.1 mg of BCG group the RR increased to 1.94 (95% CI: 1.88–2.00) from 1.0 (95% CI: 0.94–1.09) for cut-off ≥10 mm. Similar increase in RR of tuberculin positive was seen for other cut-off points and BCG vaccinated groups (not tabulated).

5. Discussion

In the larger study conducted, it was shown that the BCG did not protect the adults from TB and only a low level of overall protection of 27% in children aged <10 years over a 15-year period. Also, the protective efficacies seen among non-reactors to PPD-B did not differ significantly from those seen among reactors to PPD-B.[4] On the other hand, we had an opportunity to re-analyze the data to investigate the level of BCG protection since with vaccinated time point at different follow-up durations, and the increase in tuberculin positive due to BCG vaccination in children below 10 years at baseline. It is seen that the effect of BCG over different study periods varied. The RRs in 0.01 mg of BCG measured varied from 2.01 at 0–2.5 years to 0.69 at 0–12.5 years follow-up and later increased to 0.79 at 0–15.0 years. In the first 5 years, the children appear to be at a higher risk of developing TB. Similarly, the RR in 0.1 mg of BCG measured was 0.53 ($P = 0.01$) at 0–12.5 years follow-up and later increased to 0.73 at 0–15.0 years. This shows that the protective efficacy decreases with time since vaccination. A significant protective effect of BCG was seen only at 12.5 years after vaccination in 0.1 mg of BCG in our study. In a meta-analysis that addressed whether the efficacy of BCG changes with time, using 10 randomized controlled trials of BCG against TB in which data for separate time periods after vaccination were available and reported, there was no good evidence that BCG provided protection for more than 10 years after vaccination.[7] A retrospective follow-up study among American Indians and Alaska Natives who participated in a placebo-controlled BCG vaccine trial during 1935–1938 reported an effective BCG vaccine can have a long duration of protection for 50–60 years.[8] Many controlled trials have followed efficacy for 10–15 years and have shown some decline with time and could only be expressed as an efficacy lasting up to 15 years.[9]

Some children who were not infected might had a reaction due to infection with other mycobacterial species or to BCG vaccine, and it was evident from our study due to BCG that the children with positive results increased to 41.5% (RR = 1.39, $P < 0.0001$) at post-vaccination testing from 11.6% (RR = 1.05) at baseline in 0.01 mg of BCG group with cut-off ≥10 mm, and similarly, the proportion increased to 57.8% (RR = 1.94, $P < 0.0001$) from 11.3% (RR = 1.01) in 0.1 mg of BCG. Similar pattern was observed in other cut-off points also for BCG groups. Thus, our study confirms with a study conducted elsewhere, which shows that those with a prior history of BCG vaccination were more likely to boost their reaction.[10] Therefore, the children who were recently vaccinated are more likely to be tuberculin skin test positive due to BCG vaccination.

6. Limitations

We have assumed that the fairly large number of children included in the post-vaccination tuberculin test only comprised about half of the initial baseline of children and would not have affected the results. We do not have few more survey results beyond 15 years follow-up to confirm whether the BCG vaccine efficacy wanes steadily with time.

7. Conclusion

Our study finding suggests that BCG efficacy may decrease with time since vaccination and increase the positive tuberculin skin test reactions. A new vaccine would take these into account to protect against TB infection and disease.

Conflicts of interest

The authors have none to declare.

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