Original Article

Scar formation and tuberculin conversion following BCG vaccination in infants: A prospective cohort study

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Abstract

Background: There is considerable variation in BCG scar failure rate on available data and correlation between BCG scar and tuberculin conversion remains controversial. Through this study we aimed to determine the scar failure rate and tuberculin conversion in term infants vaccinated with BCG within the first month. **Materials and Methods:** A prospective cohort study was conducted among 85 consecutive infants weighing >2 kg attending the immunization clinic of a medical college hospital. Fifteen subjects who could not complete the follow up were excluded. Total of 70 cases were analyzed. All babies were administered 0.1 ml of BCG and examined at 3 months (+1 week) for scar. Tuberculin test was done with 5TU PPD. An induration of >5 mm was considered positive. Statistical analysis was done using Microsoft Excel and SPSS-22. **Results:** Out of the 70 infants, 41 (58.6%) were males. Although majority (72.9%) of infants were vaccinated within 7 days, only 18 (25.7%) received BCG within 48 hours of birth. Sixty-four (91.4%) had a visible scar at 12 weeks post vaccination representing a scar failure rate of 8.6%. Tuberculin test was positive in 50 (71.4%). The mean ± s.d. for scar and tuberculin skin test (TST) reaction size was 4.93 ± 2.01 mm and 6.01 ± 3.22 mm, respectively. The association between scar formation and tuberculin positivity was highly significant ($P < 0.001$). There was significant correlation between scar size and TST size ($r = 0.401$, $P = 0.001$) **Conclusions:** Less than 10% of infants fail to develop a scar following BCG vaccination. There is good correlation between scar positivity and tuberculin conversion.

Keywords: BCG, scar failure, tuberculin test

Introduction

Tuberculosis (TB) is a serious public health problem and BCG vaccination remains an essential part of TB prevention strategy especially in children. BCG scar is a surrogate marker of vaccination and an important index in the vaccination program. However scar failure is a well-known phenomenon with prevalence varying from 1% to 20%[1-4] in term infants in different studies worldwide. There is also wide variation in tuberculin conversion following BCG in various studies. Apart from protection against severe forms of TB, BCG also has a non-TB-related beneficial effect on child survival. Studies suggesting association of BCG scar with decreased childhood mortality in developing countries have rekindled the interest on BCG scar.[5,6] The true magnitude of scar failure and whether the scar negative infants need to be monitored remains unclear. This study was undertaken to determine the scar failure rate and tuberculin conversion in infants vaccinated with BCG within the first month of life.

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Materials and Methods

This prospective cohort study was carried out at the immunization clinic of a medical college hospital after obtaining permission from the Institutional Ethics Committee. Our cohort was the infants recruited for study from July 2010 to December 2010 and the study period was from July 2010 to March 2011. Only those infants whose parents consented to participate in the study were recruited. Total 85 cases were included by the method of purposive sampling. Preterms, babies weighing less than 2 kg, HIV-exposed infants and those with family history of TB or suffering from any acute illness were excluded from the study. All study subjects were administered 0.1 ml of BCG by a single trained staff nurse on the left arm just above the insertion of deltoid muscle intradermally with a 26-gauge needle and tuberculin syringe. BCG vaccine containing Moscow BCG-I (Russian) strain manufactured at the Serum Institute of India, Pune was used. This vaccine was licensed in India in 2001 and subsequently

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prequalified by WHO in 2003 for use in developing countries. The freeze-dried vaccine was reconstituted with normal saline and was used within 3 hours. All cold chain precautions were maintained. All vaccinated babies were inspected for the presence of a wheal by one of the investigators. Simultaneously, oral polio vaccine and hepatitis B vaccines were also administered as per the national immunization schedule. The parents were given a follow up date 3 months (+1 week) from the date of vaccination. On follow up, infants were examined for the presence of scar or local reaction at the vaccination site. BCG scar size was measured both across and along the arm in millimeter using a plastic ruler and the average was calculated. Tuberculin skin test was done with purified protein derivative (PPD) solution (5TU PPD/0.1 ml, SPAN diagnostic limited, Surat) 0.1 ml injected intradermally with a 26-Gauge needle on the flexor aspect of left forearm 2 to 3 inches below the elbow. Tuberculin skin test was read after 48 to 72 hours by a ball point pen technique. Infants showing a transverse diameter of >5 mm were considered tuberculin converted following BCG vaccination.

Statistical analysis

Continuous variables were summarized using means and standard deviations, while categorical variables were summarized using percentages. The Chi-square test was used to determine the association between BCG scar and tuberculin skin test as well as the association of BCG scar with age at vaccination and sex. A *P* value of less than 0.05 was considered statistically significant.

An unpaired *t*-test was used to determine the significant difference between mean BCG scar size and TST reaction size of subjects vaccinated within 7 days and after 7 days as well as males and females. Pearson's correlation coefficient was obtained between scar size and TST reaction size. Statistical analysis was done using Microsoft Excel and Statistical Software SPSS-22.

Results

Of the 85 term neonates recruited, 2 died at home before completion of the study due to unrelated causes and 13 could not complete the follow up as per protocol. Hence, a total of 70 infants were included in the final analysis. There were 41 (58.6%) males and 29 (41.4%) females. Mean ± s.d. of age at vaccination was 6.31 ± 5.385 (range 1–23 days). Only 18 (25.7%) babies received vaccination within 48 hours of birth, which was significantly low (t = 5.510, P = 0.000). Majority (72.9%) of infants were vaccinated within 7 days of life, while 15.7% were vaccinated between 8 to 14 days and 11.4% after 14 days of age. Sixty-four (91.4%) out of 70 infants exhibited a visible scar after 12 weeks of vaccination representing a scar failure rate of 8.6%. The mean ± s.d. of scar size was 4.93 ± 2.01 (range: 0–10 mm; 95% C.I: 0.91, 8.95). The presence of BCG scar was not significantly affected by age at vaccination (≤7 days or >7 days) or gender. Similarly, TST positivity was also not affected by age or sex [Table 1]. Tuberculin test was positive (>5 mm) in 50 (71.4%) infants. Mean ± s.d. of TST reaction size at 12 weeks was 6.01 ± 3.224 (95% C.I: –0.43, 12.46). No infant had TST reaction size more than 10 mm. The association between scar formation and tuberculin positivity was highly significant ($P < 0.001$). One infant had a positive tuberculin test without a BCG scar [Table 2]. There was no significant difference in the scar or TST reaction size in the different age groups or sexes [Table 3].

There was moderate positive but highly significant correlation between scar size and TST reaction size (r = Karl Pearson correlation coefficient = 0.401, P = 0.001). No adverse reactions to BCG were found in the study subjects.

To check dependency of tuberculin positivity, parameters like age at vaccination, sex and presence of scar were considered in multivariate analysis. Enter method was used to find out the

Table 1: Association of BCG scar and TST with sex and age at vaccination

	Sex		Age		Total
	Female	Male	≤7 days	>7 days	
Scar –ve	3	3	4	2	6
	50.00%	50.00%	66.70%	33.30%	100.00%
Scar +ve	26	38	47	17	64
	40.60%	59.40%	73.40%	26.60%	100.00%
	Chi-square=0.199, *P*=0.656		Chi-square=0.127, *P*=0.721		
TST –ve	10	10	14	6	20
	50.00%	50.00%	70.00%	30.00%	100.00%
TST +ve	19	31	37	13	50
	38.00%	62.00%	74.00%	26.00%	100.00%
	Chi-square=0.848, *P*=0.357		Chi-square=0.127, *P*=0.721		

TST: Tuberculin skin test

Table 2: Association of BCG scar and TST

	Scar –ve	Scar +ve	Total
TST –ve	5	15	20
	25.00%	75.00%	100.00%
TST +ve	1	49	50
	2.00%	98.00%	100.00%
Total	6	64	70
	8.60%	91.40%	100.00%

Chi-square=9.643, *P*=0.006. TST: Tuberculin skin test

Table 3: Comparison of scar and TST reaction size according to sex and age at vaccination

	Mean	Std. Deviation	Std. Error Mean	*t*	*P* value
Scar					
Female (*n*=29)	4.83	1.983	0.368	−0.353	0.725
Male (*n*=41)	5	2.049	0.32		
≤7 days (*n*=51)	5.14	2.069	0.29	1.541	0.132
>7 days (*n*=19)	4.37	1.77	0.406		
TST					
Female (*n*=29)	5.83	3.475	0.645	−0.396	0.693
Male (*n*=41)	6.15	3.071	0.48		
≤7 days (*n*=51)	6.16	3.24	0.454	0.604	0.55
>7 days (*n*=19)	5.63	3.235	0.742		

TST: Tuberculin skin test

most significant predictors. Binary logistic regression showed that scar is the best and significant predictor of TST positivity ($P = 0.014$) [Table 4].

Discussion

The burden of TB is high in developing countries and BCG vaccination continues to remain an important armamentarium in the prevention of serious childhood TB. It is one of the oldest and most commonly used vaccines despite the controversies surrounding it. BCG is generally considered to protect against tuberculous meningitis and miliary TB among infants and young children. As per WHO recommendation, BCG vaccine should be administered as soon as possible after birth and before 1 month of age for maximum protection. In this study, although majority (72.9%) of infants were vaccinated within 7 days only 25.7% were vaccinated within 48 hours which was significantly low ($P < 0.05$). This may be because BCG is given only 2 days a week in our clinic as a measure to prevent wastage. Nevertheless, it is important that due care is taken to vaccinate infants at the earliest and create better awareness regarding the timing of vaccination especially countries where TB is endemic. In the present study, scar failure rate was 8.6%. This was comparable to other Indian studies on term infants by Rani (10%)[2] and Lakhar (6.1%).[7] Higher scar failure rate (55%) has been reported in low birth weight babies from India.[8] A study from Pakistan reported scar failure rate of 19.6%,[3] whereas the studies from LIMA Peru,[1] Nigeria,[4] and Brazil[9] showed much lower scar failure rate of 1.4%, 3.7% and 3.1%, respectively. This difference could be accounted for by variability in the study design and differences in the demographic characteristics of subjects. Development of BCG scar depends on the strain, injected dose and technique of administration.[5,10] Other factors like quality of vaccine, proper transport, storage and undiagnosed underlying immune disorder in infants are also responsible for the absence of scar formation.[8,11] We did not find any association between age and scar positivity unlike Surekha *et al*'s study where scar failure was more common in infants vaccinated within 48 hours.[2]

The presence of BCG scar is the only simple and successful way of determining previous vaccination in clinical settings as well as in health surveys to assess vaccine uptake in spite of studies indicating that scar development is not a reliable indicator of the immunological response to BCG.[2] The mean scar size in this study was 4.93 mm which was quite similar to that observed by Aggarwal *et al.* The scar size is usually related to the dose and strain of BCG vaccine and has no relation to induced immunity. In Aggarwal *et al*'s study on timing and dose of vaccination in infants, subjects were divided into three groups: Group A: Newborns vaccinated with 0.05 ml of BCG, group B: Newborns vaccinated with 0.1 ml BCG, group C: Infants vaccinated at 4–6 weeks with 0.1 ml BCG. They observed scar positivity in 93.8%, 100% and 97.1% in groups A, B and C, respectively. They found a significant difference in scar size in group A as compared to groups B and C. The mean TST reaction also was significantly higher in infants who received 0.1 ml of BCG as compared to those who received 0.05 ml of BCG. The authors therefore concluded that dose of BCG in neonates should be 0.1 ml.[12] A mean scar size of 3.4 mm and 3.3 mm at 6 months following 0.1 ml BCG was observed by the study form Peru in average weight and low birth weight babies, respectively.[1]

Table 4: Binary logistic regression

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
Age	0.019	0.055	0.125	1	0.724	1.02	0.916	1.135
Sex (female)	–0.487	0.578	0.71	1	0.4	0.615	0.198	1.907
Scar (+ve)	2.796	1.141	6.005	1	0.014	16.387	1.75	153.404
Constant	–1.52	1.183	1.65	1	0.199	0.219		

B: Regression coefficient; S.E.: Standard error; Wald: Wald statistic; df: Degrees of freedom; Sig: Significance (*P* value); Exp(B): Odds ratio

Tuberculin skin test positivity at 12 weeks following BCG was 71.4%. Higher tuberculin conversion rates (80–93%) were observed in other studies.[9,13-15] Thayyil Sudhin reported tuberculin conversion to be 80% in term infants and 80.7% in preterms.[16] On the contrary, a low TST positivity (44–68%) was observed by many investigators.[17-19] Our finding is similar to Aggarwal *et al.*, who reported tuberculin conversion in 74.7% term newborns vaccinated with 0.1 ml BCG.[12] The wide variations in tuberculin conversion following BCG between different studies is attributable to factors like difference in vaccine strain, potency, strength of TU used, age groups examined, time of TST after BCG, environmental mycobacteria etc. It has been shown that tuberculin positivity increased significantly when repeated at 1 year in infants who were tuberculin negative at 3 months post vaccination.[13]

Correlation between BCG scar and TST is controversial. Many investigators[2,18,20] have found poor correlation between BCG scar and TST. Faridi m (2009) in their study concluded that TST is not a reliable indicator to assess BCG response either at 12 weeks or 6 months although they demonstrated a higher positivity at 6 month as compared to 12 weeks.[21] In variance we found good correlation between BCG scar and TST. Similar observations were made by Gupta *et al.*, in their study on twin newborns.[22] Another recent study from Taiwan found good correlation between abscess formation at BCG site and tuberculin positivity but failed to show any correlation between scarring and tuberculin positivity.[19] Despite its drawbacks, TST following BCG vaccination has been used as a measure of post vaccine allergy in a number of studies. Although *in vitro* assays like leukocyte migration inhibition test (LMIT) is more sensitive than TST in assessing the CMI response to BCG, it is not easily available or feasible and in its absence TST remains the best surrogate of efficacy of BCG. TST and LMIT have been shown to have good correlation.[16]

The absence of scar should not remain a mere observation of parents but should be part of health surveys. Presently there is no universal recommendation for BCG vaccination in scar negative infants. Infants who fail to develop a scar is a matter of concern and whether these infants need to be followed and

evaluated remain unresolved. Recent studies[5,6] have suggested that BCG scar and positive tuberculin tests are associated with better survival in early childhood in countries with high child hood mortality. The beneficial effect of BCG is attributed to the non-specific enhancement of both antibody and cellular immune responses.[23,24] Considering these studies it seems prudent to revaccinate children without a BCG scar in developing countries with high under 5 mortality. There is a need for proper evaluation and monitoring of the BCG vaccination programs.

Small sample size is a key limitation of the study. Moreover, we have followed up the infants up to 12 weeks only and done a single tuberculin test. It is possible that positivity of scar as well as TST might have increased if we had longer follow up at least for 6 months.

Conclusion

Majority of infants (91.4%) developed a scar at 12 weeks post vaccination. The association between BCG scar and TST positivity was highly significant. BCG scar formation was not affected by age or gender. There was moderate positive but highly significant correlation between scar size and TST reaction size. Larger studies to reveal the true magnitude of the problem and regular evaluation of BCG vaccination programs are recommended. The finding of BCG scar associated with reduced childhood mortality need to be evaluated in further research in developing countries.

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