Tuberculin response in preterm infants after BCG vaccination at birth

M R Sedaghatian, K Kardouni

Abstract
A total of 101 preterm infants between 26 and 37 weeks gestation who received BCG vaccination at birth were evaluated between two and four months after vaccination. Altogether 32% of these infants had no visible BCG scar. All infants were then tested with tuberculin purified protein derivative (PPD) but only 70 returned for the test to be read 48–72 hours later. The test was negative in 22 (31%) and there was an induration of ≤5 mm in another 26 (37%) of the infants. Of 22 infants with no BCG scar, 19 (86%) had an induration of ≤5 mm. In infants with a positive BCG scar a significantly higher number had an induration of PPD >5 mm. There were no significant differences between the rate of scarring and tuberculin conversion in the infants born before or after 32 weeks’ gestation. It is considered that routine BCG vaccination at birth on preterm infants is not indicated until a much larger study has been performed.

Results
Of the 101 preterm infants who returned to the hospital for evaluation of the vaccination site no scar was found in 32, a papule of 1–2 mm in five, 3–4 mm in 16, 4–5 mm in 31, and >5 mm in 17 (table 1). The range of scar was 1–18 mm (mean 3·2 mm). All these infants were tuberculin PPD tested but only 70 returned for the test to be read. Of these 70 infants no BCG scar was found in 22 and a scar found in 48 on initial evaluation of the vaccination site. The PPD test was negative in 22 (31%), an induration of 2–5 mm was found in 26 (37%), 6–9 mm in 16 (23%), and ≥10 mm in six (9%). The range of induration was 0–15 mm (mean 4·1 mm) (see fig 1). Of the 22 with no scar and 48 with a scar, 13 (59%) and nine (19%) respectively had a non-reactive tuberculin PPD test (fig 2). There was a significantly higher reactive PPD test among those with a visible scar (χ²=9·5967, p=0·0019). An induration of >5 mm on PPD test was found in 19 (39%) infants with a visible scar in contrast to three (14%) with no scar (p=0·0583) (fig 2). Table 1 compares the BCG scar in infants ≤32 or >32 weeks’ gestation and table 2 the tuberculin PPD induration; there was no statistically significant difference. When the rate of BCG scar and tuberculin conversion were compared between our previous study in full term infants and the present...
The absence of scar has been found to be between 3–25% in different studies in term infants.\textsuperscript{9,10} and less than 10% in preterm infants.\textsuperscript{5} In this study 32% of the infants had no BCG scar and there was a significant difference for tuberculin conversion between infants with and without a BCG scar. When we compared the numbers of those with a scar and the numbers of those with a reactive PPD test between the present study and our previous study in term infants,\textsuperscript{1} the full term infants had a significantly higher number of BCG scars and tuberculin conversion (table 3). Although the size of the tuberculin reaction after vaccination is not generally thought to influence the degree of protection offered by BCG, the non-reactive tuberculin test should be tested by a higher concentration of PPD (100 IU). We did not observe any complications of the vaccine such as lymphadenopathy or sterile abscess in the preterm infants. This could be due to the low response of preterm infants to BCG vaccination. Our study indicates that giving BCG vaccination to preterm infants at birth results in a relatively high percentage of infants with no BCG scar (32%) and a non-reactive tuberculin PPD test (31%). We did not exclude our sick infants from the study, as most preterm infants of less than 32 weeks’ gestation need ventilatory assistance and antibiotics; this study in preterm infants (table 3), both were significantly higher in term infants (p<0.001).

**Discussion**

In many developing countries tuberculosis is still a major public health problem. The use of vaccine at birth in full term infants has been shown to protect against the haematogenous spread of primary tuberculosis.\textsuperscript{7,8} The efficacy and safety of vaccination in preterm infants has not been well established. To the best of our knowledge there is only one study on 12 preterm infants of more than 32 weeks’ gestation that was carried out in Nigeria.\textsuperscript{5} There was 83% tuberculin conversion with an induration >5 mm after BCG vaccination at birth. This study excluded all infants who were small for gestational age and who had sepsis, jaundice, respiratory distress syndrome, apnoea, or congenital malformation. The rate of tuberculin conversion with an induration of >5 mm in our study was only 31%. This was 18% for preterm infants between 26–32 weeks’ gestation and 38% for those between 33–36 weeks. We did not exclude any babies because of respiratory distress syndrome, ventilatory support, jaundice, or apnoea; the only exclusions were for major congenital anomalies. The presence of a BCG scar has been used as one of the criteria to assess the coverage of vaccination. The absence of scar has been found to be between 3–25% in different studies in term infants.\textsuperscript{9,10} and less than 10% in preterm infants.\textsuperscript{5} In this study 32% of the infants had no BCG scar and there was a significant difference for tuberculin conversion between infants with and without a BCG scar. When we compared the numbers of those with a scar and the numbers of those with a reactive PPD test between the present study and our previous study in term infants,\textsuperscript{1} the full term infants had a significantly higher number of BCG scars and tuberculin conversion (table 3). Although the size of the tuberculin reaction after vaccination is not generally thought to influence the degree of protection offered by BCG, the non-reactive tuberculin test should be tested by a higher concentration of PPD (100 IU). We did not observe any complications of the vaccine such as lymphadenopathy or sterile abscess in the preterm infants. This could be due to the low response of preterm infants to BCG vaccination. Our study indicates that giving BCG vaccination to preterm infants at birth results in a relatively high percentage of infants with no BCG scar (32%) and a non-reactive tuberculin PPD test (31%). We did not exclude our sick infants from the study, as most preterm infants of less than 32 weeks’ gestation need ventilatory assistance and antibiotics; this study in preterm infants (table 3), both were significantly higher in term infants (p<0.001).

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Tuberculin response in preterm infants after BCG vaccination at birth may have partly influenced our results. The numbers of infants in our study, as well as in our previous study, are not large enough to draw any firm conclusions. Therefore a control study with a large number of infants should be performed to establish whether routine administration of BCG vaccine in preterm infants at birth is warranted.

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