Tuberculin Conversion after BCG Vaccination

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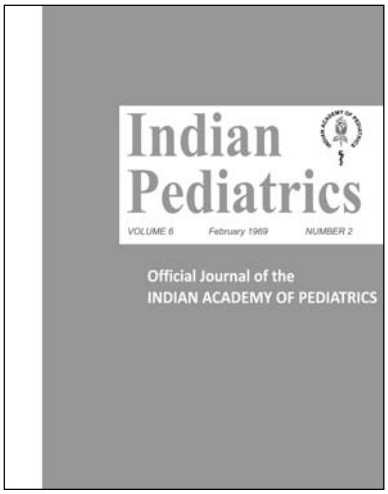
BCG vaccination remains an essential part of tuberculosis (TB) prevention strategy, especially in children. BCG is generally considered to protect against tuberculous meningitis and military and disseminated forms of TB among infants and young children. The efficacy against non-serious forms of TB has been a matter of debate with various studies showing it to be in range from 0 to 80%. Protective efficacy of BCG has been assessed by various methods, including tuberculin sensitivity. Positive tuberculin response after BCG vaccination has been considered to be an important marker of successful vaccination.



THE PAST

This study [1], published in *Indian Pediatrics* 50 years ago, was one of the first few studies to assess tuberculin conversion after BCG vaccination in neonatal period. This was a prospective study in which out of 1000 infants who received BCG in first 7 days of life, 510 (all weighing >2.2 kg) were administered Mantoux test at 2-3 months of life. Of 510 infants, 390 were observed for tuberculin reaction after 72 hours of injecting purified protein derivative (PPD). Among these infants, 125 were tested with 1 test unit (TU) PPD (RT23 with Tween 80) after 2 months; 160 were tested with 1 TU PPD after 3 months; 69 were tested with 2 TU PPD after 3 months; and 36 were tested with 5 TU PPD after 3 months of BCG vaccine. All these infants were simultaneously examined for weight gain and sign of any infection. For the purpose of comparison and efficacy of technique, 370 schoolchildren aged between 6-12 years who were initially tuberculin negative were vaccinated with BCG, and tuberculin reaction was studied after 3 months in 318 of these children. Induration ≥6 mm in infants and ≥8 mm in schoolchildren was considered as positive. The results showed that 16% of infants who received BCG at birth had positive induration with 1 TU tuberculin given 8 weeks after BCG vaccination. After 12 weeks, the same increased to 21.3%. The proportion of positive conversion with 2 TU PPD was 37.7% after 12 weeks of BCG vaccination, and those who received 5 TU PPD showed positive conversion in 66.7%. Of 318 schoolchildren considered as controls, 82.9% had an induration of ≥8 mm to tuberculin test performed 3 months after BCG vaccine. The authors concluded that newborns exhibit poorer response to BCG as compared to older children, and tuberculin positivity is 3-fold higher with 5 TU PPD as compared to 1 TU PPD.

Historical background and past knowledge: BCG vaccine was named after two famous French scientists – Albert Calmette and Camille Guérin. The history of BCG vaccine dates back to 1900 when Calmette and Guerin started their research at Pasteur Institute, Lille. In next 20 years, they successfully completed the trials in animals. In 1921, BCG was given first time to a human. It was delivered by Dr Weil Hale to a baby whose mother died of tuberculosis few hours later. The vaccine was given orally and baby grew to a healthy boy with no signs of tuberculosis. From 1921-1924, 317 more infants were vaccinated. By 1928, Calmette released multiple reports showing BCG to be effective; although, the medical media had lot of criticism on the figures displayed in the reports. BCG got a major setback after the Lübeck disaster where 72 of 252 children died of tuberculosis within one year of vaccine. Though later, the cause was found to be contamination with a virulent strain at the local laboratory where the vaccine was made ready for administration [2].

The controversies kept persisting till BCG vaccine once again came into use after resurgence of tuberculosis after Second World War. Since then multiple studies were conducted across the world to assess the efficacy of BCG vaccine and found to be varying between no benefit to as high as 80% protection. The cause of this large variation is still not understood. Simultaneously, multiple countries

started producing its own supply maintaining same stringent conditions as at the Pasteur institute [2].

Robert Koch, in 1890, first time described the tuberculin hypersensitivity at the site of injection of heat-killed tubercle bacilli. The work was further expanded by Von Pirquet in 1909. Tuberculin sensitivity test, further known by Mantoux test, first came into use in 1912 after the intradermal technique introduced by Charles Mantoux, a French physician who developed on the work of Von Pirquet. Further in 1939, Seibert prepared a large lot of PPD (lot 49608), which then became the reference standard for the US Public Health Service's Bureau of Biologics Standards. It was further renamed as PPD-S (standard), and was adopted as International standard by WHO. By convention, 5 TU is the bioassayable skin test activity contained in 0.0001 mg of PPD. RT-23, another PPD prepared by Statens Serum Institute was introduced by WHO in 1958 [3].

The tuberculin reaction is read after 48 hours and needs an incubation period of 2-12 weeks after infection by *M. tuberculosis* to develop sensitivity. The reaction to intradermally injected tuberculin is the classic example of a delayed (cellular) hypersensitivity reaction. T-cells sensitized by prior infection are recruited to the skin site where they release lymphokines. These lymphokines induce induration through local vasodilatation, edema, fibrin deposition and recruitment of other inflammatory cells to the area.

THE PRESENT

Multiple studies have been conducted in last 50 years to assess the efficacy of BCG vaccine. One of the most recent similar study [4] assessed scar formation and tuberculin conversion at 3 months of age after BCG vaccination. Seventy babies were followed up for positive induration (≥5 mm) after tuberculin test with 5 TU PPD done 3 months after BCG vaccine. They found that 71.4% babies had a positive conversion at 3 months of age. These results were much higher than the initial study [1] that we discussed. Similar results were noted in many other studies [5,6] conducted over last 50 years, though some of the studies had a relatively lower tuberculin skin test positivity varying between 44-68% [7,8]. The vast variation in these results has been attributed to multiple factors such as strength and quality of PPD, age group, timing of the test, quality dose and method of administration of BCG, nutritional status of children, and co-administration of other vaccines/drugs.

Though tuberculin test has been considered as one of the criteria to show successful response to BCG, the wide variation in response has made it less dependable. A study by Faridi, *et al.* [9] shwed leucocyte migration inhibition test to be positive in 84.1% of babies who received BCG vaccine within 7 days of birth and found to have negative Mantoux at 3 months of age.

Regarding efficacy of BCG, in a recent systematic review and meta-analysis, Roy, *et al*. [10] reviewed all studies done to compare the infection rates with *M. tuberculosis* in vaccinated and unvaccinated children (age <16 y) with recent exposure to patients with pulmonary tuberculosis. The analysis included 14 studies with 3855 participants. Interferon gamma release assays were used for assessing the infection. They found that the overall risk ratio was 0.81 with protective efficacy of 19% against infection among vaccinated children after exposure compared with unvaccinated children.

In the nutshell, the diagnostic accuracy of tuberculin skin test for BCG uptake, as well as the efficacy of BCG for protection of tuberculosis, still remain controversial; however, both of these continue to be used widely in absence of better alternatives.

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