Tuberculin skin reactivity after neonatal BCG vaccination in preterm infants in Minas Gerais, Brazil, 2001–2002

Paulo Camargos, Yara Ribeiro, Artur Teixeira, and Luciana Menezes

Objectives. The efficacy of BCG vaccination in preterm babies is unknown, and available data on conversion rates to tuberculin in this age group are scarce and controversial. This study assessed the tuberculin response in preterm infants after BCG vaccination.

Methods. This randomized cohort study was carried out at the Neonatal Department, University Hospital, Federal University of Minas Gerais in Brazil during 2001 and 2002. The BCG vaccine was administered at birth to 65 full-term (control) and 40 preterm newborns. All of them were tested with 5 tuberculin units of purified protein derivative-S approximately 3 months after vaccination.

Results. A typical BCG scar was verified in 96.9% of the control group and in 90.0% of the preterm infants ($P = 0.19$). Indurations $\geq 5$ mm in diameter were recorded in 87.7% of the full-term and 67.5% of the preterm infants ($P = 0.02$). Indurations $\geq 10$ mm were recorded in 70.8% of the full-term and 42.5% of the preterm infants ($P = 0.007$). For indurations $\geq 5$ mm the upper and the lower limits of the 95% confidence interval for the difference between proportions were 8.5% to 31.8%, and for indurations $\geq 10$ mm these limits were 18.0% to 38.4%. No adverse reactions were observed in the study population.

Conclusion. BCG vaccination could be recommended for preterm infants upon discharge from the neonatal unit to reduce morbidity and mortality in infants at risk for tuberculous infection, and to increase BCG vaccination coverage rates, especially in countries with high prevalence rates of tuberculosis.

Key words BCG vaccination, prematurity, tuberculin response, Brazil.
are scarce and controversial, these infants are usually not included in this routine practice.

Difficulties in carrying out clinical trials and case-control studies to assess the efficacy of BCG vaccination in this age group have led to the tuberculin test being used as a surrogate marker of efficacy. Our literature review identified several studies on this subject, and overall, conversion rates ranged from 31.0% to 83.0% (1–5). These conflicting results have led authors to recommend vaccination variously at birth (1, 4, 5) or later (2), or only after 33 weeks of postconceptional age (3).

The present cohort study was carried out to assess the percentage of tuberculin conversion in vaccinated preterm infants and the implications of conversion rates with regard to the appropriate timing of BCG vaccination in this age group.

MATERIALS AND METHODS

Two hundred and fifty-two neonates born at the Neonatal Department, University Hospital, Federal University of Minas Gerais in Belo Horizonte, Brazil, were recruited and vaccinated with BCG from April 2001 to June 2002 in this randomized concurrent cohort study.

Postconceptional age (in weeks) for both full-term and preterm groups was estimated with Ballard scoring (6) or ultrasonography. Gestational age between 37 and 41 weeks was the inclusion criterion for full-term infants, and the inclusion criterion for preterm infants was gestational age lower than 37 weeks. Critical illness (neonatal sepsis, assisted ventilation, hemodynamic instability), fever (of known or unknown etiology), congenital malformations, and skin lesions near the lateral aspect of the right arm were criteria for exclusion, and babies who had received steroids, blood or blood component transfusions were also excluded.

The Ethics in Research Committee of the Federal University of Minas Gerais approved the study protocol, which included informed consent signed by the infant's parents or legal guardians.

BCG vaccination

The Moureau-Rio de Janeiro strain, manufactured at Ataulpho de Paiva Foundation Laboratories (Rio de Janeiro, Brazil) in accordance with World Health Organization recommendations, was injected intradermally in the right deltoid area. Both groups received a conventional dose of 0.1 mL, and vaccinations took place from April 2001 to June 2002.

Full-term infants were vaccinated upon discharge from the neonatal unit. To avoid side effects and due to ethical constraints and technical considerations, preterm babies were vaccinated when their body weight reached ≥ 1,900 g, the usual criterion for discharge from neonatal units.

An appropriate scar was defined as a scar of typical appearance that measured ≥ 3 mm in transverse diameter.

Tuberculin skin test

Tuberculin skin tests were performed by intradermal injection, on the anterior aspect of the left forearm, of a conventional dose of 0.1 mL PPD-S (Tubersol, Connaught Laboratories, Toronto, Canada) within 3 months of postnatal age. Skin tests were examined 48–72 h after the injection, and observers were blinded as to the baby’s gestational age at birth.

Statistical analysis

Full-term and preterm babies were randomly allocated to receive BCG according to the date and time of birth. If a patient met one or more exclusion criteria, the next infant to be born at our center on the appropriate day was considered for inclusion instead. Data were recorded from April 2001 to June 2002 and analyzed from November 2002 to May 2003. Chi-squared and Fisher’s exact tests were used to analyze the difference between proportions, and Student’s t test was used to compare differences between mean values. The 95% confidence interval was calculated for the proportion of each group that showed tuberculin reactivity, as well as for the difference between proportions. The level of statistical significance was P = 0.05.

RESULTS

Two hundred and fifty-three patients were vaccinated: 182 full-term and 71 preterm newborns. Among the subjects vaccinated upon discharge from the neonatal unit, 117 (46.2%) full-term and 31 (43.6%) preterm newborns did not return for tuberculin test reading, so the results of this analysis are based on 65 control infants and 40 preterm infants.

There was no statistically significant difference between full-term and preterm babies included and babies lost to follow-up in sex distribution (P = 0.19 and P = 0.79, respectively) or gestational age (P = 0.10 and P = 0.26, respectively). Regarding birth weight, there was no statistically significant difference (P = 0.22) between preterm newborns included in the study and those who did not undergo the tuberculin test. This statistical difference was marginal (P = 0.048) for full-term neonates, demonstrating a reasonable similarity between subjects lost to follow-up and participants included in the final analysis.

Table 1 shows the descriptive statistics for the 65 full-term and 40 preterm infants. The two groups did not differ significantly in sex distribution (P = 0.34) or intrauterine growth (P = 0.36). The high proportion of infants in which a BCG vaccination scar was seen, i.e., 99 out of 105 vaccinated neonates (93.5%), implies that the technique for administering the test was appropriate. The scar was not checked in only 2 full-term and 4 preterm infants.

As expected, the difference between mean gestational age (P < 0.000) and mean birth weight (P < 0.000) was statistically significant between full-term and preterm neonates. There was no statistically significant difference between BCG scar diameter (P = 0.30), demonstrating good comparability between the two groups regarding the technical quality of vaccination.
Table 2 shows the distribution of full-term and preterm neonates by gestational age. The gestational age of preterm neonates ranged from 32 to 36 weeks, and in 90.0% of these infants, gestational age was 33 to 36 weeks. Full-term neonate gestational age ranged from 37 to 41 weeks, and in 69.2% of this group gestational age was 39 to 41 weeks.

Table 3 shows the tuberculin conversion rate following BCG vaccination in both groups. Data are given for two different groups of cut-off values for induration size: group 1, 0–4 mm and 5 mm; group 2, 0–9 mm and 10 mm.

Indurations ≥ 5 mm were observed in 87.7% (95% CI: 77.1%–94.5%) of full-term neonates and 67.5% (95% CI: 50.8%–81.4%) of preterm neonates. The 20.2% difference between the two groups was statistically significant (95% CI: 8.5%–31.8%; P = 0.02).

For indurations ≥ 10 mm as the cut-off point, the difference between groups was even greater, with a conversion rate of 70.8% (95% CI: 58.1%–81.3%) for full-term neonates and 42.5% (95% CI: 27.0%–59.1%) for preterm infants. The difference was 28.2%, which was also statistically significant (95% CI: 18.0%–38.4%; P = 0.007). Mean diameter of the tuberculin test scar was 6.8 mm (SD 4.70) in the preterm group and 10.2 mm (SD 4.53) in full-term neonates (P < 0.000).

No adverse reactions were observed in either group.

**DISCUSSION**

The 87.7% rate of tuberculin reactivity in full-term neonates in the present study is consistent with figures reported in earlier studies (7–11), including a Brazilian study that used the same BCG strain (11) and studies with preterm babies in which full-term neonates were the comparison group (1–3). The similarity between earlier figures and the tuberculin conversion rate in full-term neonates in our study suggests that methodological variations related to immunogenicity of the BCG strain, the technical quality of vaccination, and possible differences in PPD administration and reading were controlled satisfactorily in the present study, and that the conversion rate observed in preterm babies can be considered reliable.

Despite published studies, BCG vaccination in preterm infants remains controversial (1–5). Previous studies reported the frequency of indurations greater than 5 to 6 mm as 27% (5), 31% (2), 67% (3), 80% (4) and 83% (1). The variations in these numbers may be explained by methodological differences between studies in the BCG strain, inclusion and exclusion criteria,
Thayyil-Sudhan et al. (4). The proportion of infants in the study by Sedaghatian and Kardouni (2), and 32.0% of the patients in the study by Tun and coworkers (5), were found in 27% of the patients (42.5%). However, Dawodu (1) reported indurations in 27 (90%) preterm babies studied by Thayyil-Sudhan et al. (4). The low vaccination scar rate found by Sedaghatian and Kardouni (2) and by Tun and coworkers (5) suggests problems in the vaccine administration technique or a change in bioavailability and potency.

In our study, fewer preterm than full-term infants presented indurations ≥ 5 mm (67.5%) and ≥ 10 mm (42.5%). However, Dawodu (1) reported indurations ≥ 6 mm in 83.0% of infants, whereas indurations ≥ 5 mm were found in 27% of the patients studied by Tun and coworkers (5), 32.0% of the patients in the study by Sedaghatian and Kardouni (2), and 80.0% of the infants in the study by Thayyil-Sudhan et al. (4). The proportions of positive tuberculin tests in our study with indurations ≥ 5 mm (67.5% of preterm babies) and indurations ≥ 10 mm (42.5% of preterm babies) represent intermediate values in comparison to these earlier studies.

Calculating the 95% confidence interval point estimates allowed us to perform another type of comparison, which showed that for indurations ≥ 5 mm, the proportion reported by Dawodu (83.0%) (1) was close to the upper limit (81.4%) of variation estimated in the present study, while the proportion found by Sedaghatian and Kardouni (32.0%) (2) was well below the lower limit of our confidence interval (50.8%).

The wide variation in tuberculin reactivity rates may be due to methodological differences as noted above, and indicates different levels of immunologic maturity for each gestational age. In other words, the younger the gestational age, the smaller the immune response, especially that related to cell immunity. The lower response to tuberculin in preterm infants might be related to the test itself and to a likely change in cellular immunity, as described by Yoder and Polin (12).

However, prematurity and tuberculosis are major public health concerns in low-income countries. Although preterm infants showed a significantly lower tuberculin conversion rate in the present study, it seems reasonable to consider these differences as less relevant in clinical terms, and to recommend BCG vaccination upon discharge from the neonatal unit with the intention of reducing morbidity and mortality in infants at risk for tuberculosis, and increasing BCG vaccination coverage rates. Our results suggest that preterm babies could be vaccinated after 32–33 weeks of postconceptional age if their body weight is ≥ 1900 g. On the basis of available knowledge, it is unclear how long the protective effect of BCG in preterm infants would last, and further research on this topic should be encouraged.

**Acknowledgments.** Supported in part by a grant from the National Scientific and Technologic Development Council (Conselho Nacional de Desenvolvimento Científico e Tecnológico-CNPq) of the Ministry of Science and Technology, Brazil.

**REFERENCES**


Manuscript received on 21 October 2005. Revised version accepted for publication on 1 June 2006.
Objetivos. Se desconoce la eficacia de la vacunación con Bacilo de Calmette-Guérin (BCG) en neonatos prematuros, y los datos que existen acerca de la proporción de casos de conversión tuberculínica en este grupo de edad son pocos y cuestionables. En este estudio se evaluó la respuesta a la prueba de tuberculina de neonatos prematuros tras la vacunación con BCG.

Métodos. Este estudio de cohorte aleatorizado se llevó a cabo en el Departamento de Neonatología del Hospital Universitario de la Universidad Federal de Minas Gerais, Brasil, en 2001 y 2002. Se administró la vacuna BCG en el momento de nacer a 65 lactantes nacidos a término (Grupo testigo) y a 40 neonatos prematuros. Todos los niños recibieron 5 unidades tuberculínicas de derivado proteínico purificado (PPD) alrededor de 3 meses después de la vacunación.

Resultados. La típica cicatriz que deja la BCG se verificó en 96,9% del grupo testigo y en 90,0% de los neonatos prematuros (P = 0,19). Induraciones de ≥ 5 mm de diámetro se documentaron en 87,7% de los neonatos nacidos a término y en 67,5% de los nacidos prematuramente (P = 0,02). Induraciones de ≥ 10 mm se documentaron en 70,8% de los neonatos nacidos a término y en 42,5% de los prematuros (P = 0,007). En el caso de induraciones de ≥ 5 mm, los límites inferior y superior del intervalo de 95% de la diferencia entre proporciones fueron 8,5% y 31,8%, y en el caso de induraciones de ≥ 10 mm, estos límites fueron 18,0% y 38,4%. No se observaron reacciones adversas en la población estudiada.

Conclusión. La vacunación con BCG se podría recomendar para neonatos prematuros al darles de alta de la unidad de cuidados neonatales, con la finalidad de reducir la morbilidad y mortalidad de los que están en riesgo de contraer una infección tuberculosa y de aumentar las tasas de cobertura de la vacunación con BCG, sobre todo en países con una alta prevalencia de tuberculosis.

Palabras clave BCG vaccine, prematuro, test de tuberculina, Brasil.