Journal of Medical Sciences

ISSN 1682-4474

science alert

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Research Paper

J. Med. Sci., 13 (8): 797-802
15th November, 2013
DOI: 10.3923/jms.2013.797.802

Immunogenicity of Neonatal BCG Vaccination in Children Aged 6 Years in Egypt, Is Booster Dose Needed?

[1]Mohamed Mohamed El-Mazahi, [1]Magdy Mohamed Ashmawy Sakr, [1]Hany Abd El-Hady El-Khaleegy and [2]Mahfauze Awad El-Nagar

Presence of BCG scar is used as an indicator of vaccination but its significance is still the subject of controversy. The aim of the study was evaluate the immunogenicity of neonatal BCG vaccination in children age 6 years to detect if a booster dose is necessary or not. Two hundred children, selected from primary schools in Damietta by stratified random sampling, from March to December 2010. They divided into two groups, study group (150) with BCG scar, second group (50) lack BCG scar. A questionnaire including personal data, vaccination, disease and drug intake history was completed. Then BCG scar was checked and measured in mm and PPD test was done. Examination for anemia, jaundice, organomegaly and assessment of nutritional status was done. Male to female ratio of 1.27: 1; no significant difference between both groups as regard anthropometric measurement while there was significant increase in BCG diameter in study in comparison to control group (4.66±1.88 vs. 0.0±0.0 mm, respectively). PPD test results revealed that 182 (91.0%) were non-reactive while 18 (9.0%) were suspicious and there was significant difference between groups. Finally, there was powerful, positive, significant correlation between BCG scar and PPD test results. Conclusion of this study revealed that children at the age of school entry better to receive booster dose of BCG vaccination to lengthen and increase the efficacy of the immunity.

Key words: Tuberculosis, BCG vaccination, children, disease, drug intake history

JMS (ISSN 1682-4474) is an International, peer-reviewed scientific journal that publishes original article in experimental & clinical medicine and related disciplines such as molecular biology, biochemistry, genetics, biophysics, bio-and medical technology. JMS is issued eight times per year on paper and in electronic format.

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Mohamed Mohamed El-Mazahi
Department of Pediatric,
Al-Azhar Faculty of Medicine,
Egypt

ANSInet
Asian Network for Scientific Information

[1]Department of Pediatric, Al-Azhar Faculty of Medicine, Egypt
[2]Resident of Pediatrics, Egypt

INTRODUCTION

Tuberculosis (TB) is a common health problem that had higher mortality rate. Mycobacterium tuberculosis is the causative organism especially in human beings. It usually presented as a pulmonary disease but tuberculosis can affect other parts of the body. Pulmonary tuberculosis discovered accidently in routine examination, as the organism transmitted through air causing asymptomatic, latent infection. Active disease developed in about one of ten latent infections (Konstantinos, 2010). Control of tuberculosis by chemotherapy and vaccination is an important achievement for public health. Immunization with Bacillus of Calmette-Guerin (BCG) vaccine is done in 64 countries in the world and has been suggested to others. BCG vaccination is done at birth in some countries including Egypt but in some others, it is administered at primary school entry or at puberty. World Health Organization (WHO, 1998) has recommended BCG vaccination at the age of 3 months, as a part of expanded program of immunization (Briassoulis *et al*., 2005). BCG vaccination results in a delayed type hypersensitivity to tuberculin which can be measured by intradermal injection of Purified Protein Derivative (PPD). This reaction is used in evaluating the immune status of previously administered BCG (Rowland *et al*., 2006). Different studies with a very long follow up period (50-60 years) revealed that, vaccination at neonatal period had been 52% more effective than placebo (Aronson *et al*., 2004). According to the assumption that, BCG protection is decreased with time, some countries, (e.g., Russia, Portugal, Chile and Hungary), use repeated doses of BCG vaccine (Barreto *et al*., 2006).

Aim of the work: This study has been designed to evaluate the immunogenicity of BCG vaccination (taken in early infancy) in children at the age of 6 years (age of school entry) to detect the necessity of a booster dose of BCG vaccine at this age.

MATERIALS AND METHODS

This study is a prospective controlled study. Stratified random sample was used for sampling: The Damietta governorate was selected as the study site. As it is impossible to study every child in the governorate, Faraskur city was randomly chosen to represent the governorate. Furthermore, 5 large villages were chosen randomly as representative samples and then, one school from each village was used to collect the sample of the study. The present study included 200 children, at school age, selected from primary schools, at the period from March to December 2010. They were from different socioeconomic classes and 150 children have BCG scar while 50 children don't have the scar.

Inclusion criteria: All children with history of BCG vaccination, with or without BCG scar; provided that, they had not any of exclusion criteria.

Exclusion criteria: Children with malnutrition or chronic disease, immune-compromised states, positive history of any vaccination or acute febrile illness during last month prior to study.

The included children were divided into two groups according to the presence or absence of BCG scar. The first group (study group): Included 150 cases with positive BCG scar. The second group (Control group): Included 50 cases with negative BCG scar.

A questionnaire was completed by the child himself or his/her guardian. It included sociodemogrpahic data, vaccination history, history of acute or chronic diseases, drug intake, blood transfusion and history of contact with TB cases or patients with Anti-TB drugs. Examination was done to search for presence of BCG scar, scar of any surgical interventions, signs of anemia, presence of jaundice, lymph node enlargement and organomegaly. Nutritional status was assessed by anthropometric measurements. At first, the largest diameter of BCG scar was measured in millimeters and recorded for every selected child. Then 0.1 mL of 6 unit PPD solution was injected interdermally at volar surface of left forearm in such a manner that small papule about 6-10 mm in diameter appear at injection site. Forty eight to seventy two hours later, the largest diameter of indurated area generated by PPD injection, measured in millimeters and recorded. When the induration area is less than 5 mm, the test is considered negative (non-reactive). The test is positive if the diameter is 10 mm or more. The results equal to 5 through 9 mm are suspicious (Sakha and Behbahan, 2008).

Statistical analysis of data: The collected data was organized, tabulated and statistically analyzed using Statistical Package for Social Science (SPSS), version 13 (SPSS Inc. USA). For qualitative data, frequency and percent distribution were calculated; for comparison between groups, Chi square test was used. For quantitative data, Mean and Standard Deviation (SD) were calculated and for comparison between two means, the students (t) test was used. For interpretation of results, p-value ≤ 0.05 was considered significant.

RESULTS

The present study included 200 children, 112 of them (56.0%) were males and 88 (44.0%) were females with male to female ratio of 1.27: 1 and there was statistically insignificant difference between study and control groups (males represent 54% of the study group compared to 62% of the control group).

Table 1: Comparison between study and control groups as regard to gender weight and height for age percentiles BMI (kg m^{-2})

Variable	Study group (n = 150)	Control (n = 50)	Test	p-value
Male gender (n, %)	81(54.0%)	31(62.0%)	0.97	0.32(NS)
Weight for age	74.86±23.09	90.70±26.29	1.01	0.31(NS)
Height for age	65.26±19.85	67.60±17.17	0.74	0.45(NS)
BMI	17.34±20.24	16.72±02.74	1.59	0.11(NS)

NS: Not significant

Table 2: Comparison between study and control groups as regard to BCG scar size (mm)

	Study group		Control group		Total			
Size	No.	%	No.	%	No.	%	Test	p-value
Absent	0	0.0	50	100.0	50	25.0		
1-3	42	28.0	0	0.0	42	21.0	200.00	<0.001(S)
4-6	83	55.3	0	0.0	83	41.5		
7-9	23	15.3	0	0.0	23	11.5		
≥10	2	1.3	0	0.0	2	1.0		
Mean±SD	4.66±1.88		0.0±0.0		3.49±2.59		17.44	<0.001(S)

This was done according protocol of Sakha and Aghaee (2003), S: Significant

Table 3: Comparison between study and control groups as regard to PPD test results

	Study group		Control group		Total			
Size	No.	%	No.	%	No.	%	Test	p-value
<5	132	88.0	50	100.00	182	91.0	3.65	0.047(S)
≥5 mm	18	12.0	0	0.00	18	9.0		
Mean±SD	2.95±1.53		1.52±0.88		2.59±1.53		6.24	<0.001(S)

S: Significant

Weight for age ranged from 25 to 95 percentile with a mean of 73.87±23.93 while height for age ranged from 25-90 with a mean of 65.85±19.20 and there was statistically insignificant difference between study and control groups as regard weight for age and height for age distribution. Body mass index ranged from 11.42-23.15 with a mean of 17.18±2.38 kg m^{-2} and there was statistically insignificant decrease in BMI of control group in comparison to BMI of study group (16.72±2.74 vs. 17.34±2.24 kg m^{-2}, respectively) (Table 1).

BCG scar ranged from 0-10 mm with a mean of 3.49±2.59 mm and there was statistically highly significant increase in BCG diameter in study group in comparison to control group (4.66±1.88 vs. 0.0±0.0 mm, respectively). In addition, BCG scar was 1-3 mm in 28% of cases, 4-6 mm in 55.3%, 7-9 mm in 15.3% and ≥10 mm in 1.3% and there was statistically significant difference between study and control groups as regard BCG scar distributions (Table 2). In addition, PPD indurated area ranged from 0-7 mm in largest diameter with a mean of 2.59±1.53 mm and there was statistically significant increase in indurated area in study group in comparison to control group (2.95±1.53 vs. 1.52±0.88 mm, respectively). In the study group, the size of PPD-test indurated area was <5 in 88.0% compared to 100.0% of the control group; while it was ≥5 mm in 12% in study group compared to 0% in control group with statistically significant difference between groups (Table 3). PPD test results revealed that 182 cases out of 200 cases (91.0%) were non-reactive while 18 cases (9.0%) were suspicious and there was statistically significant difference between study and control groups. In addition, there was powerful ($r>0.7$), positive, statistically significant ($p<0.05$) correlation between BCG scar and PPD test results (data not presented).

DISCUSSION

Indeed, the immunogenicity of BCG vaccine is under question, its efficacy is known to be dependent on the quality of its production, transport and injection techniques. The preventive effects of BCG vaccine has been repetitively studied in the world, its rate of immunogenicity in older children and adults has been shown to be 77% in United Kingdom while 14% in South of USA but ineffective at all in Madras-India (Briassoulis *et al*., 2005).

A meta-analysis study by Colditz *et al*. (1994) in Boston-USA showed that BCG vaccination decreases the risk of tuberculosis up to 50%. Study on PPD test in New York showed that tuberculosis was rare in children entering primary schools despite of its tripled incidence in general population between 1978 and 1992. Besides, in everyone whose test became positive, it was found to be due to vaccination (Scholten *et al*., 1999). A study in Barcelona-Spain showed that two BCG vaccinations in neonatal period and school age sustain the tuberculin test, positive for 20-25 years. They found that an

indurated area larger than 15 mm in diameter cannot rule out its vaccinal origin and recommended that a booster dose of BCG vaccine should be injected in those children whose PPD test has become negative after previous vaccination (Miret-Cuadras *et al*., 1996).

The present study was designed to evaluate the immunogenicity of neonatal BCG vaccination in children at the age of 6 years (age of school entry) to detect the necessity of a booster dose of BCG vaccine at this age to increase and lengthen the efficacy of neonatal BCG vaccination. It included 200 children, 112 of them (56.0%) were males and 88 (44.0%) were females with male to female ratio of 1.27: 1 and there was statistically insignificant difference between study and control groups (males represent 54% of the study group compared to 62% of the control group). Sakha and Behbahan (2008) reported that, 150 children were included in their study; 94 males (62.7%) and 56 females (37.3%). This percentage is slightly different than that reported in the present study, although it follows the same distribution of increased males in comparison to females.

In the present study, anthropometric measurements revealed no statistically significant difference between study and control groups and all studied children were in normal range for their age. These results are anticipated, as exclusion criteria aiming to choose normal children, to avoid possible effects of nutritional status (e.g., deficiency) on the result of PPD test results. In the present study, 150 children were included in the study group; all of them have the BCG scar with different sizes. The BCG scar was 1-3 mm in 28% of cases, 4-6 mm in 55.3%, 7-9 mm in 15.3% and was >10 mm 1.3%. While 50 children were included in the present study as a control group, they have no BCG scar inspite of history of administration of the BCG vaccine. Thus, BCG scar sizes in control group of the present study are 0 mm. So, there was statistically significant difference between study and control groups as regard BCG scar distribution. In their work, Sakha and Aghaee (2003) reported that, all studied children had a BCG scar, from 1-11 mm in the largest diameter and the largest BCG-scar (11 mm) in diameter was seen only in one girl. In general, there were BCG-scar with size of 8 mm or more in 34 girls (60.7%) and 14 boys (15.95%), this difference is statistically meaningful and shows that BCG-scars are larger in girls than in boys ($p = 0.007$). The average size of BCG scar was 7.03 mm in girls and 5.45 mm in boys and 6.05 mm for all cases. These results are contradicted to those reported in the present work, as the average diameter of BCG-scar was less in the present study than that of Sakha and Behbahan (2008). Unfortunately, they do not include a control group like that of the present study. Instead, they reported a statistically significant difference between males and females, the entity that can not be elucidated in the present study.

In the present study, PPD indurated area ranged from 0-7 mm in largest diameter with a mean of 2.59±1.53 mm and there was statistically significant increase in indurated area in study group in comparison to control group (2.95±1.53 vs. 1.52±0.88 mm, respectively). In the study group, the size of PPD-test indurated area was 0 in 9.3% of cases, 1-4 mm in 78.7%, 5 mm in 6.7% and >5 mm in 5.3% of cases while the size of PPD test indurated area was 0 in 12% of cases and 1-4 in 88% of cases (4 mm is the largest diameter of PPD test indurated area) in the control group and there was statistically significant difference between study and control group. So, control group has weak reaction to tuberculin test than reaction in study group. In their study, Sakha and Behbahan (2008) reported that, unless for one boy who had an induration area at PPD-injection site with a diameter of 8 mm, all other children had a PPD induration of 5 mm. Therefore, they found that PPD-test reaction is less than 5 mm in 95.33% and 5 mm or more in 4.66% of all 150 studied cases. Positive PPD-test reaction which defined as an induration area with a diameter of 10 mm or more was not seen in any child. The average size of induration reaction to PPD test was 2.3 mm in girls, 1.8 mm in boys and 1.99 mm for all cases. These results are comparable to the results of the present study. In a study carried out on the size of induration area resulted from PPD-test in 150 infants, 3 months after neonatal BCG vaccination, PPD-test reaction was less than 5 mm in 45.33% and 5 mm or more in 54.66% of infants (Sakha and Behbahan, 2008). In addition, Leung *et al*. (2005) study in Hong Kong tried to determine the need for BCG vaccination in school-age children which showed that PPD-test reaction was 10 mm or more in 1.93% of girls and 1.41% of boys in this age group. Furthermore, a study by Ildirim *et al*. (1995) in Turkey on children between 6 and 12 years of age, showed that the average diameter of PPD-test induration area was 14.8±-4.3 mm in children who possess 3 scars of BCG vaccination but it was 6.3±7.8 in children who possess one. Therefore, they recommended more than one BCG vaccination in those developing countries where tuberculosis is highly prevalent.

In the present study, PPD test results revealed that 182 cases out of 200 cases (91.0%) were non-reactive while 18 cases (9.0%) were suspicious and there was statistically significant difference between study and control groups. In study group, 132 cases (88.0%) were non-reactive and 18 cases (12.0%) were suspicious.

Some studies on Native American and Eskimos of Alaska which included a follow up period of

50-60 years showed that a single dose of BCG vaccine in neonatal period has been 52% more effective than placebo (Aronson *et al*., 2004). Sakha and Behbahan (2008) reported that, PPD test resulted in induration area sized less than 5 mm in 95.33% (no induration in 12%) and 5 mm or more in 4.66%. These results are slightly different than that reported in the present work. It may be due to the fact that, they included older children (7-8 years) than the present study.

In the present study, there was powerful, positive, statistically significant correlation between BCG scar and PPD test results. These results are supported by those reported by Sakha and Behbahan (2008) who reported that, their study revealed that, during primary school age, the larger the size of neonatal BCG-scar, the more frequent the PPD test reaction size. They added, the statistical tests showed that, there is a meaningful direct correlation between sizes of BCG scar and PPD test reaction ($r = 0.21$, $p = 0.008$). They added, comparing the frequency of different sizes of PPD-test results in two age groups after neonatal BCG vaccination shows a significant statistical difference ($p<0.001$).This means that positive PPD (tuberculin) reaction induced by BCG vaccination decreases with increasing age and finally disappears (no induration in 12% of cases).

One study in Saudi Arabia on 5 years old children showed that there was no difference in results of PPD test between BCG-vaccinated children (during neonatal period) and unvaccinated ones (Al-Kassimi *et al*., 1991). In USA, some studies showed that there is no difference in PPD (Mantoux) test reaction between BCG vaccinated and unvaccinated persons (Ballew and Becker, 1995). Another study carried out in Montreal-Canada, on persons between 10 and 25 years of age, revealed that result of PPD test was positive in 7.9, 18 and 25.4% among who has been vaccinated at infancy, 1-5 and 7 years of age, respectively. Therefore these Canadian researchers believe that the final effect of neonatal BCG vaccination looks like no vaccination (Menzies and Vissandjee, 1992). Furthermore, studies by Botswana (1996) on children between 3 and 60 months of age, who has been vaccinated during neonatal period, cleared that those children who showed induration reaction larger than 10 mm to Mantoux test, had tuberculosis (Centers for Disease Control and Prevention (CDC), 1997).

CONCLUSION

Based on results of the present study, children at the age of school entry better to receive booster dose of BCG vaccination.

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