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# EVALUATION OF THE EFFECT OF VACCINATION TECHNIQUE ON BCG VACCINE REACTION

## *BCG AŞI TEKNİĞİNİN BCG AŞI REAKSİYONUNA OLAN ETKİSİNİN DEĞERLENDİRİLMESİ*

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**ABSTRACT**
**Objective:** To evaluate the effect of BCG vaccination technique to post BCG reactions and scarring.
**Material and Methods:** Eighty four children were enrolled in this descriptive, observational study. All of them received 0.05 ml of BCG of Serum Institute of India Ltd at 2 months of age, in the upper left deltoid region. A detailed questionnaire was completed. The vaccines were implemented by 9 different pediatricians who were trained for intradermal injection and working consecutively at the Unit between December 2011 and Mai 2012. The vaccination technique was monitored by direct observation of post-vaccination wheal and route of administration. One investigator evaluated the BCG reaction by measuring immediately the longest diameter of wheal after injection. The technique was classified as Technique 1(intradermal) if the diameter is 5-6 mm, Technique 2 if the diameter is less then 5 mm. BCG reaction was evaluated at 3 months of age and scar formation was evaluated at 12 months of age. A scar formation with a diameter more than 2 mm was accepted as present. During this follow-up period, the local reaction is noted as exaggerated if the longest diameter of the reaction was more than 6 mm.
**Results:** Technique 1 (Intradermal) was applied on 44 (52,4%) infants. . The white wheal was not formed in 10% of the infants. All infants had vaccination reaction during the follow-up but BCG reaction at 3 months of age was earlier in Technique 1 (intradermal) group. During the follow-up period we observed exaggerated local reaction in 22 (27.2 %) infants. Exaggerated local reactions were less in the intradermal technique. 0f the 81 infants assessed for scar formation only one patient had no scar at 12 months of age and his reaction was abortive.
**Conclusions:** This study showed that the vaccination technique had no impact on scar formation but exaggerated local reactions occur less with intradermal vaccination. Further randomized studies relating vaccination technique to vaccine effectiveness are needed.
***Key words:*** BCG vaccine; vaccination technique; intradermal; scar

**ÖZET**
**Amaç:** BCG aşısı yapılmış olan çocuklarda aşı tekniğinin skar oluşumuna etkisinin değerlendirilmesi amaçlanmaktadır.
**Gereç ve Yöntem:** Aralık 2011- Mayıs 2012 yılları arasında İstanbul Üniversitesi İstanbul Tıp Fakültesi Sosyal Pediatri Poliklinik'ne BCG aşısını olmak için başvurmuş 2 aylık bebeklere bu süreçte poliklinikte çalışan 9 tane farklı hekim tarafından sol üst deltoid bölgeye yapılan 0.05 ml BCG aşısının tekniği incelenmiş ve aşının nasıl yapıldığı bu dönemde kaydedilmiştir. Aynı araştırıcı tarafından yapılan aşı sonrası oluşan beyaz makül 5 mm ve daha büyük ise Teknik 1(intradermal), 5 mm'den küçük ise Teknik 2 olarak tanımlanmıştır. BCG reaksiyonu 3.ayda ve skar formasyonu 12. ayda değerlendirilmiştir. Skar oluşumu ≥ 2 mm ise pozitif olarak kabul edilmiştir. İzlem süresinde en uzun çapı 6 mm'den fazla olan reaksiyonlar abartılı reaksiyon olarak tanımlanmıştır.
**Bulgular:** Çalışmaya alınan 84 hastanın 52,3%'ü Teknik 1 ile aşılanırken, diğerleri Teknik 2 ile aşılanmıştır. Hastaların 10%'nunda aşı sonrası beyaz iz oluşmamıştır. 1 ay sonrasında BCG aşısına bağlı reaksiyon Teknik 1 grubunda Teknik 2 grubuna göre daha erken oluşmuştur. İzlem sırasında 22 hastada abartılı reaksiyon gelişmiş olup, teknik 2 ile aşılananlarda daha fazla görülmüştür. 12. ayda BCG skarı açısından değerlendirilen 81 hastanın bir tanesi hariç hepsinde BCG skarı oluşmuştur.

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**Sonuç:** Çalışmamızda BCG aşı tekniğinin BCG skarı üzerine etkisi gösterilememiş olup abartılı reaksiyon Teknik 2'de daha fazla görülmüştür. BCG aşı tekniğini ve aşının koruyuculuğuna olan etkisini inceleyen daha fazla sayıda çalışmaya ihtiyaç vardır.
***Anahtar kelimeler:*** BCG aşısı; aşı tekniği; intradermal; skar

## INTRODUCTION

The route of BCG vaccination is accepted as one of the factors influencing the scar formation (10). Post-BCG vaccination scar formation has been used as an index for the effectiveness of the BCG vaccination programmes (2).

Some studies in the past showed that percutanous route was less effective in the induction of immune responses (5) but a recent study from South Africa with a larger group showed that both routes were equivalent for efficacy and safety (3). Nevertheless the intradermal method remains widely used throughout the world and is recommended by the World Health Organization (11). There are few studies about the evaluation of vaccination technique and BCG scar formation (1,3-6,8,9) . Intradermal technique is not easy to perform (1,8). In this study, we aimed to evaluate the effect of BCG vaccination technique to post BCG reactions and scarring.

## MATERIAL AND METHODS

This was a descriptive, prospective, observational study conducted at the Istanbul University, Istanbul School of Medicine, Department of Social Pediatrics, Healthy Child Unit. Children born at the Maternity Clinic of the University Hospital constitute the majority of the infants and children followed at the Clinic. At discharge from the Maternity Clinic, each mother receives a pamphlet with information about the Healthy Child Clinic. Families attending the Clinic are relatively homogeneous regarding socio-economic and cultural level. All families are well above the poverty lines as assessed by their ability to bring their baby to the center. All parents are literate. The majority of the mothers have had at least 5 years of schooling. The majority of the fathers are high school graduates.

Eighty four children attending the Unit between December 2011 and May 2012 received 0.05 ml of BCG at 2 months of age, on the upper left deltoid region as recommended in the Turkish Childhood Vaccination Programme. BCG vaccines of Serum Institute of India Ltd were used. A questionnaire regarding the child's medical history, family's BCG history and demographic information was completed. The vaccines were implemented by 9 pediatric residents who were trained for intradermal injection and working consecutively at the Unit during the study period. The vaccination technique was monitored by direct observation of post-vaccination wheal and route of administration. One investigator evaluated the BCG reaction by measuring the longest diameter of the white wheal immediately after injection. The technique was classified as Technique 1(intradermal) if the diameter was $\geq$ 5 mm, Technique 2 if the diameter was <5 mm. The parents were routinely informed about the BCG vaccine reactions. BCG reaction within the first 2 weeks was defined as early and reaction later than 2 weeks as normal. The local reaction was noted as exaggerated if the longest diameter of the reaction was more than > 6 mm. Routine visits were made monthly during first 6 months and every 2 month until 12 months of age. Macule formation was evaluated at 3 months of age and scar formation was evaluated at 12 months of age. A scar formation with a diameter more than 2 mm was accepted as present. The BCG scar formation was examined and noted as present and not present at every visit of well-child follow-up by different pediatric residents who were informed about BCG scar status.

An approval was obtained from the Ethical Committee of Istanbul University and a verbal consent was obtained from each parent. The data were analyzed using SPSS (Statistical Package for the Social Sciences) 21.0, (Chicago, IL, USA). Statistical significance was assessed by $\chi^2$ test for nonparametric variables and by the independent Samples T test and the Mann-Whitney U test for parametric variables. The last two tests were used to compare differences between two independent groups. In all statistical analyses, two-tailed tests and a 5% level of significance were applied.

## RESULTS

The study enrolled all 2 month-old infants who consecutively applied to our clinic between December 2011 and May 2012. Of the 84 infants who accepted to participate, 47 (56%) were males. Main characteristics of the infants were given in Table 1.

**Table 1. Main characteristics of the infants**

| | | | ( n: / %) |
|---|---|---|---|
| **Gender** | **Male** | 47 | 56 % |
| | **Female** | 37 | 44 % |
| **Type of delivery** | **Vaginal Birth** | 24 | 28.6% |
| | **C/S** | 60 | 71.4 % |
| **Gestational age** | **Preterm (34-36 6/7 Weeks)** | 12 | 14.3 % |
| | **Term (≥ 37 Weeks)** | 72 | 85.7 % |
| **Birth Weight** | **SGA** | 8 | 9.5 % |
| | **AGA** | 69 | 82.2 % |
| | **LGA** | 7 | 8.3 % |

The maximum diameter of the wheal after the BCG vaccination was measured to be 6 mm (median: 5 mm). Technique 1 (Intradermal) was applied on 44 (52,3%) infants. The rest of the infants (n:40, 45,7%) who had post-vaccination white wheal less than 5 mm were accepted to be vaccinated by Technique 2. The white wheal was not formed in 10% of the infants. There was no statistically significant difference in wheal formation

**Table 2. BCG reaction at 3 months of age**

| | | BCG reaction (+) n:61 | BCG reaction (-) n:19 | P |
|---|---|---|---|---|
| **Gender** | **Male** | 32 (74.4 %) | 11 (25.6 %) | 0.794 |
| | **Female** | 29 (78.4 %) | 8 (21.6 %) | |
| **Birth** | **Vaginal birth** | 15 (65.2 %) | 8 (34.8 %) | 0.141 |
| | **C/S** | 46 (80.7 %) | 11(19.3 %) | |
| **Gestational age** | **Preterm (34-36 6/7 Weeks)** | 12 (100 %) | 0 (0 %) | 0.06 |
| | **Term (≥37 Weeks)** | 49 (72.1 %) | 19 (27,9 %) | |
| **Technique** | **Technique 1(intradermal)** | 40 (95.2 %) | 2 (4.8 %) | **0.0001** |
| | **Technique 2** | 21 (55.3 %) | 17 (44.7 %) | |

**Table 3. Exaggerated local reactions**

| | | Exaggerated local reaction (+) n:22 | Exaggerated local reaction (-) n:59 | p |
|---|---|---|---|---|
| **Gender** | **Male** | 14 (31.1 %) | 31 (68,9 %) | 0.371 |
| | **Female** | 8 (22.2 %) | 28 (77.8 %) | |
| **Birth** | **Vaginal birth** | 6 (28.6 %) | 15 (71,4 %) | 0.866 |
| | **C/S** | 16 (26.7 %) | 44 (73.3 %) | |
| **Gestational age** | **Preterm (34-36 6/7 Weeks)** | 1 (8.3 %) | 11 (91.7 %) | 0.165 |
| | **Term (≥37 Weeks)** | 21 (30.4 %) | 48 (69.6 %) | |
| **Technique** | **Technique 1(intradermal)** | 7 (17.1 %) | 34 (82.9 %) | **0.039** |
| | **Technique 2** | 15 (37.5 %) | 25 (62.5 %) | |

regarding gender, type of delivery, birth weight and gestational age. No parent reported a reaction during the first 2 weeks after vaccination. At 3 months of age, 80 infants were assessed for BCG reaction. Of all infants 76% had BCG reaction at 3 months of age and there was no statistically significant difference regarding gender, way of delivery and gestational age (Table 2). All infants had vaccination reaction during the follow-up but BCG reaction was earlier in Technique 1 (intradermal) group (Table 2 ). This difference was statistically significant.

During the follow-up period we observed exaggerated local reaction in 22 (27.2 %) infants (Table 3). There was no statistically significant difference regarding gender, way of delivery or gestational age. But we observed less exaggerated local reactions in the intradermal technique (Table 3).

0f the 81 infants assessed for scar formation at 12 months of age only one infant with the diagnosis of Down syndrome had no scar. His reaction was abortive, there was a BCG reaction until 7 months of age but the reaction became negative after 10 months of age.

## DISCUSSION

Our study on a cohort of 84 infants vaccinated at 2 months of age had significant findings about BCG scar formation until 12 months of age. BCG scars were noted in 98 % of the infants at 12 months of age in our study. Our result is similar to some findings reported in the literature (4,6), however there are studies reporting higher rates of scar formation failure (6-8). This difference may be attributed to the definition of BCG scar, vaccination technique or BCG strain in the vaccine. Esqueda et al defined a BCG scar with a diameter more than 5mm as positive and reported the scar failure as 20 %. In a study of Santiago et al the definition of BCG scar was a reaction with a diameter >2 mm and reported scar failure as %1,4(7). In a cohort of 2225 children at 6 months of age, Roth et al reported association between BCG scarring and vaccine strains. They reported also that intradermal vaccination was associated with better scarring. In our study we did not observe any difference on scar presence between the two vaccination techniques (8).

A local reaction with the longest diameter > 6 mm was defined as exaggerated in our study and of all infants 27.2 % had such a reaction. Dommergues et al followed 2435 children for 1 year after vaccination and reported local adverse reactions with a diameter larger than 10 mm as 17.8 % and the rate of abscess formation as 2,5 %. We did not observe any abscess formation but our study sample was small (1).

Subcutaneous technique was not recommended especially due to adverse reactions like abscess and intractable scar formation (10). We did not observe any abscess formation in both groups but the rate of local exaggerated reactions was higher in the subcutaneous technique group. There was also a delay of macule reaction after 4 weeks of vaccination in this group in our study. This finding led us to think that macule formation

may develop later in deeper injections than those in intradermal injections.

Even the technique was well known by the physicians, some of them (45,7 %) failed to perform intradermal injection (5-6 cm white papule) perfectly in our study. In a prospective, descriptive study with a larger sample group, Dommergues et al found that the lack of visible papule after vaccination was 14 % (1). The technique was performed by general practitioners and paediatricians in the study. We did not observe any leakage of vaccine fluid but the proportion of children with lack of visible papule formation was similar (10 %) in our study.

In our study, one infant with Down syndrome had an abortive reaction. The disappearance of papule and pustule reaction without scar formation is termed as abortive reaction and abortive reactions are reported in literature (2). The reason of abortive reaction can be various e.g ineffective vaccine, leakage of vaccine fluid during vaccination (1). There is still no conclusive evidence answering the question of what to do after abortive BCG reaction.

Our study had some limitations. The sample size was small. The diameter of wheal after vaccination was measured by one of the investigators but different physicians evaluated the scar shape and size at each visit. For this reason we included only the data showing scar positivity and local exaggerated reactions and we were not able to compare the scar size and shape between the two vaccination groups.

## CONCLUSION

The intradermal vaccination technique may fail at first attempt of an unexperienced staff or when the child is agitated. Our study showed that there was no difference between two vaccination technique groups in scar formation at one year of age. Studies evaluating and comparing the effect of subcutaneous technique on protection against tuberculosis and the protection of BCG vaccine after an abortive reaction are needed.

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**Conflict of Interest:** None.

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