Safety of intradermal Bacillus Calmette-Guerin vaccine for neonates in Eastern Saudi Arabia

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ABSTRACT

الأهداف: تقييم مدى آمان التطعيم ضد التدرن الرئوي في الرضع السعوديين، وتحديد كيفية التعامل مع تضخم الغدد اللمفاوية الناتج أحياناً عن هذا التطعيم.

الطريقة: لقد قمنا باسترجاع بيانات الرضع المصابين بالمضاعفات الناتجة عن التطعيم ضد التدرن الرئوي والذين دخلوا إلى مستشفى الأطفال والولادة، الدمام، المملكة العربية السعودية خلال الفترة من مارس 2008م إلى مارس 2011م. لقد قمنا بتحليل بيانات كافة الرضع المشاركين وذلك فيما يتعلق بالعمر، والجنس، والوزن أثناء الولادة، والمظاهر السريرية، والنتائج. لقد أعطي اللقاح ضد التردن الرئوي خلال 48 ساعة بعد الولادة، وقد حصلنا على العدد الكلي للمواليد الملقحين من سجلات المرضى.

النتائج: لقد تلقى 26000 رضيع اللقاح المضاد للتدرن الرئوي خلال 3 سنوات، عانى خلالها 81 رضيع من المضاعفات الناتجة عن التطعيم حيث كان متوسط العمر 4.8 أشهر (51 ذكر، و30 أنثى). وهكذا فقد كانت نسبة حدوث المضاعفات 3.12 لكل 1000 مولود. ولقد كانت المظاهر السريرية كالتالي: تضخم الغدد اللمفاوية عند الإبط الأيسر) العدد:62)، تضخم الغدد اللمفاوية فوق عظمة العضد (العدد:9)، وتجمع صديدي عند وضع التلقيح (العدد:6)، وإصابة رضيع واحد بتضخم الغدد العنقية اليسرى عند كلاً من الإبطين، وعند الساعد الأيسر، وتجمع عند مكان التلقيح. وأشارت نتائج الدراسة إلى أن اثنان كان لديهما نقص في المناعة، وعولجت 6 حالات من مجموعة التجمع الصديدي عند مكان التلقيح بالسحب، فيما قمنا بإزاحة الخراج من ذراع مريض واحد. وقد قمنا بمعالجة المرضى المصابين بتضخم الغدد اللمفاوية (العدد:6)، فيما قمنا باستئصال التضخم (العدد:65) من المصابين بتضخم الغدد اللمفاوية فوق عظمة العضد (العدد:68)، أو النزح والاستئصال معاً من دون العلاج بمضادات التدرن الرئوي (العدد:3).

خاتمة: يعد التطعيم ضد التدرن الرئوي آمن، ولكنه مصحوب بنسبة عالية من تقيح الغدد اللمفاوية، ومن الممكن علاج الغدد اللمفاوية المتضخمة بدون تقيح بدون جراحة، بينما تحتاج الغدد المتقيحة إلى استئصال وهذه العملية آمنه، وتمنع الإصابة بمضاعفات انفجار الغدد، وتقلل فترة العلاج بدون الحاجة إلى الأدوية المقاومة للتدرن. وهكذا أثبتت الدراسة بأن التطعيم المقاوم للتدرن بالرغم من مضاعفاته فإن المضاعفات المذكورة أفضل كثيراً من مضاعفات المرض نفسه.

Objectives: To evaluate the safety of Bacillus Calmette-Guerin (BCG) in Saudi infants and outline our management for BCG related lymphadenitis.

Methods: The records of infants who developed BCG related complications were retrospectively reviewed from March 2008 to March 2011 at the Maternity and Children Hospital, Dammam, Saudi Arabia for age, gender, birth weight, presentation, and outcome. All our patients were immunized with the BCG vaccine within 48 hours after birth, and the total number of vaccinated newborns was obtained from the vaccination registry.

Results: During a 3-year period (March 2008 to March 2011), 26,000 newborns received BCG and 81 (51 males and 30 females) developed complications. This gives an incidence of 3.12 complications/1000 newborns. Their presentations were: left axillary lymphadenitis (n=62), supraclavicular lymphadenitis (n=9), collection at immunization site (n=6), and one each (left cervical lymphadenitis, bilateral axillary lymphadenitis, left arm abscess, left axillary lymphadenitis and collection at immunization site). Two were immunocompromized and 6 with local collection were aspirated. The arm abscess had drainage. Simple lymphadenitis (n=6) were treated expectantly, while those with suppurative lymphadenitis (n=68) had excision (n=65) or incision and drainage (n=3) without anti-tuberculous treatment.

Conclusions: Bacillus Calmette-Guerin is safe but is associated with a relatively high incidence of suppurative lymphadenitis. Non-suppurative lymphadenitis can be treated conservatively, while suppurative lymphadenitis should be treated with excision. This is safe, avoids rupture, and shortens the recovery period without anti-tuberculous treatment. Although, the use of BCG vaccine may be associated with side effects, the potential morbidity and mortality from tuberculosis outweighs that from BCG related complications.

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Tuberculosis is a serious health problem in developing countries. Its main and serious complications are tuberculous meningoencephalitis and miliary tuberculosis. One important way to overcome this is to offer routine immunization to all newborns using BCG (Bacillus Calmette-Guerin) vaccine. The efficacy of currently used BCG vaccines in preventing serious tuberculosis complications is variable ranging from 60-90%.[1,2] Bacillus Calmette-Guerin vaccine is a live attenuated vaccine derived from *Mycobacterium bovis*. It was used to immunize humans in 1921 and currently more than 100 million children are given the vaccine each year. Bacillus Calmette-Guerin vaccine is considered to be safe, but it is known to be associated with a number of complications. These include local scarring, ulceration and abscess formation at the vaccination site, regional lymphadenitis, BCG osteitis and rarely disseminated infection, pulmonary tuberculosis and tuberculous meningitis, which are usually seen in immuncompromized patients.[3,-7] The incidence of regional lymphadenitis is variable ranging from as low as one in 10,000 to as high as 38 in 1000.[1,7-10] The management of this complication is still controversial and varies from no treatment, surgical incision and drainage, surgical excision, administration of anti-tuberculous drugs or a combination of these. In Saudi Arabia, a national policy for vaccination was adopted and the BCG vaccine is administered to all newborns at birth. The aim of this report was to evaluate the safety of intradermal BCG vaccine administered to neonates in Eastern Province, Saudi Arabia and outline our management strategy for BCG vaccine related lymphadenitis.

Methods. The records of infants who developed BCG related complications were retrospectively reviewed from March 2008 to March 2011 at Maternity and Children Hospital, Dammam, Saudi Arabia for age at presentation, gender, duration of symptoms, type of presentation, bacteriology, histopathology, method of treatment and outcome. All our patients were immunized with BCG vaccine (BCG vaccine SSI, Copenhagen, Denmark) within 48 hours after birth and the total number of vaccinated newborns was obtained from the vaccination registry office. All infants received 0.05 ml of the vaccine which was injected intradermally in the left arm at the deltoid insertion. All vaccines were administered during the study period by a constant group of 3 trained nurses. All patients with BCG related lymphadenitis (suppurative and non suppurative) and local complication at the site of vaccination were included.

Ethical approval for the study was obtained from the hospital's ethics committee. The BCG vaccination is a part of the national program and no consent is needed for the same and the cases that were operated were consented for the procedure and the aspiration was an out patient procedure.

The study does not involve comparisons between 2 modalities of treatment; therefore, no statistical analysis was needed.

Results. Over a period of 3 years, 26,000 newborns received BCG immunization at Maternity and Children Hospital, Dammam and during that period, 81 infants developed BCG related complications. This gives an incidence of 3.12 BCG related complications/1000 newborn. There were 51 males and 30 females. Their age at presentation ranged from 2 months to 12 months (mean 4.8 months). Their presentations were as follows: left axillary lymphadenitis (n=62), left supraclavicular lymphadenitis (n=9), local collection at the immunization site (n= 6), left cervical lymphadenitis (n=1), bilateral axillary lymphadenitis (n=1), left arm abscess (n=1) and left axillary lymphadenitis and local collection at the site of immunization (n=1) (**Figures 1-5**). All were normal immunologically except 2 who were found to be immunocompromized (severe

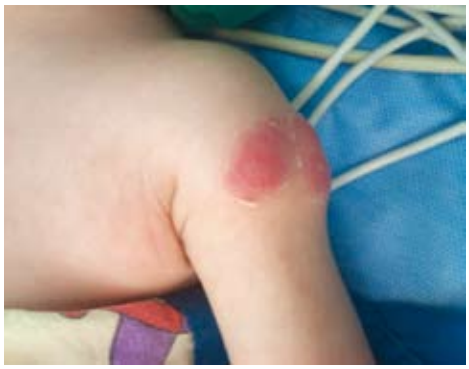

Figure 1 - Clinical photograph showing severe localized collection at the site of immunization.

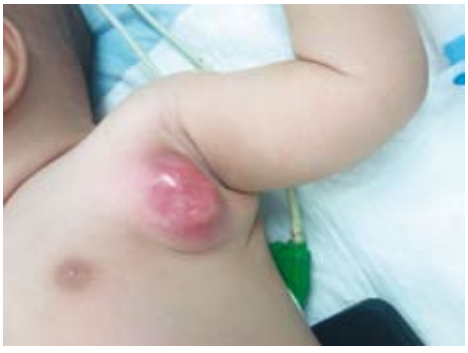

Figure 2 - Clinical photograph showing severe suppurative left axillary post Bacillus Calmette-Guerin lymphadenitis.

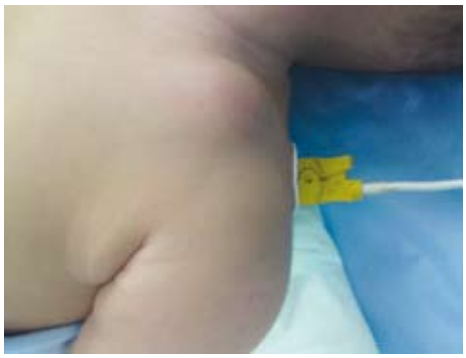

Figure 3 - Clinical photograph showing left supraclavicular post-Bacillus Calmette-Guerin lymphadenitis.

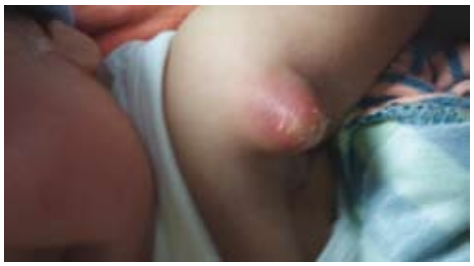

Figure 4 - Clinical photograph showing severe left arm abscess following Bacillus Calmette-Guerin vaccination.

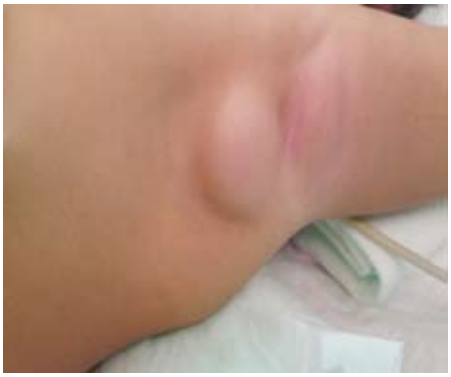

Figure 5 - Clinical photograph showing simple non-suppurative left post-Bacillus Calmette-Guerin lymphadenits.

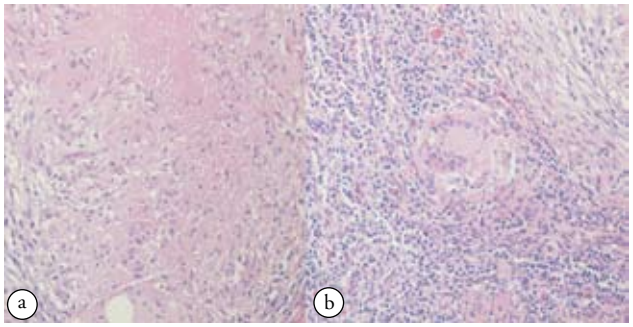

Figure 6 - Histological pictures of excised lymphnodes showing **a)** caseating necrosis, epitheliod cells, **b)** granulomas, and giant cells.

combined immundefeciency [SCID] and HIV). These 2 patients required treatment with anti-tuberculous drugs in addition to surgery. The 6 patients with localized collection at the site of immunization were treated with aspiration only while the patient with left arm abscess required incision and drainage. The remaining patients (n=74) were divided into 2 groups, those with simple lymphadenitis (n=6) and those with suppurative lymphadenitis (n=68). Those with simple lymphadenitis were treated expectantly and the enlarged nodes resolved spontaneously. The remaining patients with suppurative lymphadenitis were treated with total excision (n=65) or just incision and drainage (n=3) without anti-tuberculous treatment. Swabs for acid-fast bacilli stain and culture were taken from 25 and were positive in 9 (36%). Histology of the excised nodes was positive for granuolomatous lymphadenitis in all those who had excision (**Figure 6**). Postoperatively, all did well with no complications.

Discussion. Bacillus Calmette-Guerin is a live-attenuated vaccine derived from *Mycobacterium bovis* and it is given to neonates and infants throughout many countries of the world. The vaccine efficacy has been a source of controversy over the years but it is accepted that it is highly effective in preventing tubercuous meningitis and miliary tuberculosis.[1] Bacillus Calmette-Guerin vaccine is considered to be safe with a low incidence of serious side effects. One of the common complications of BCG vaccine is lymphadenitis. The prevalence of lymphadenitis in our study was 0.3%. This is higher than the generally accepted prevalence of 0.1% but it is lower than that reported from other parts of the world. Our prevalence was lower than that reported from Turkey (0.7%), Chile (0.7%), Canada (1%), Jamaica (1.9%), Iran (5.8%), and South Africa (0.5%).[6,8-13] A number of factors have been incriminated in the etiology of BCG vaccination related lymphadenitis. These include the age of the patient, technique of immunization, the BCG strain, the dose, potency of the vaccine, and immunogenicity of the vaccine.[1] Epidemics of BCG vaccine related lymphadenitis were reported from different parts of the world and all these reports attributed it to an exaggerated response to a more immunogenic vaccine.[1,5,6,8] This may be the case in our series also. We feel the use of SSI vaccine in our patients with its inherent potency may be the critical factor contributing to the increase in the incidence of post-BCG lymphadenitis in our patients. This is supported by the fact that this increase coincided with the change of the manufacturer of the vaccine used in our hospital. This is similar to other observations from England, South Africa and Ireland.[1,11,12,14] The vaccines manufactured by different laboratories will result in

differing immunogenicity of the vaccine. This will be reflected in different degrees of protection, different immunogenicity and varying incidence of adverse effects. Add to this inappropriate storage of the vaccine and inappropriate method of administering the vaccine. It is well known that subcutaneous administration of the vaccine instead of intradermal will lead to an increased incidence of BCG related lymphadenitis. In our hospital, the vaccine dose is well controlled as we use a syringe that can administer only 0.05 ml of the vaccine and can be used only for one patient at a time. Add to this, the fact that the vaccine is given by a limited number of well trained nurses. These factors make it unlikely that the dose of the vaccine or poor vaccination technique could account for the increase in post-BCG lymphadenitis in our patients. Tuberculosis is still a major health problem in developing countries. Although, the use of BCG vaccine may be associated with side effects, the potential morbidity and mortality from tuberculosis outweighs that from BCG related complications. Bacillus Calmette-Guerin vaccine should be administered to all newborn in developing countries where there is a high prevalence of tuberculosis. Bacillus Calmette-Guerin is contraindicated only for immuodeficient infants (symptomatic HIV-positive infants and infants born of HIV-positive mothers, and those with congenital severe combined immunodeficiency syndrome).[1,15,16] The WHO stopped recommending BCG vaccine for infants with HIV even if there is a high risk of exposure to tuberculosis as BCG can cause disseminated and life-threatening infection. Two of our patients with immunodeficiency received BCG vaccination and both of them developed severe local and regional lymphadenitis which necessitated treating them with ant-tuberculous drugs in addition to surgery. Post-BCG vaccine lymphadenitis commonly occurs on the ipsilateral side, but it can affect the supraclavicular or cervical nodes depending on the location of the injection on the arm. Interestingly, one of our patients had bilateral axillary BCG lymphadenitis. This patient had no underlying immunological disease and the reason for this bilateral axillary lymphnode involvement is not known. We recognized 2 forms of BCG lymphadenitis, simple or non-suppurative lymphadenitis and suppurative lymphadenitis which is characterized by the presence of redness, edema of the overlying skin, and fluctuation. In our study, there was a high frequency of suppurative lymphadenitis when compared to other studies. The reason for this is not known. The management of regional BCG lymphadenitis is controversial. We advocate conservative management of simple non-suppurative lymphadenitis as it follows a benign course and most cases regress spontaneously.[3,4,17,18] There is no place for antibiotics and the use of anti-tuberculous drugs was not shown to hasten the recovery.[17-20] Six of our patients with simple non-suppurative lymphadenitis were treated conservatively and the nodes regressed spontaneously. The management of suppurative BCG lymphadenitis is not well defined and most reports describe retrospective studies. Repeated needle aspiration was advocated by some authors to avoid spontaneous rupture and prolonged discharge while others advocate complete surgical drainage.[15,18,19] Repeated aspiration is an effective and less invasive method of treatment, but it takes long time for these nodes to disappear. We like others to advocate total excision of these nodes.[3,8,9,15] Total excision is not a simple procedure but definitely it shortens the recovery period. All our patients were discharged 48-72 hours postoperatively.

Study limitations. The present study is a retrospective study looking at the effectiveness of total excision of the BCG associated suppurative axillary lymph nodes Many studies have reported effectiveness of simple aspiration in the situation and a future prospective study comparing simple aspiration with complete excision in the management of post BCG suppurative lymphadenitis is important in this regard.

In conclusion, BCG vaccine is safe but associated with a relatively high incidence of suppurative lymphadenitis. Non-suppurative lymphadenitis can be treated conservatively. Suppurative lymphadenitis on the other hand should be excised. This is safe, avoids rupture and shortens the recovery period without the need for additional anti-tuberculous treatment. Although, the use of BCG vaccine may be associated with side effects, the potential morbidity and mortality from tuberculosis outweighs that from BCG vaccine related complications.[21]

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Related topics

Al-Hassan AA, Ahsanullah AM. Bacillus Calmette-Guerins vaccination at birth causing tuberculous granulomatous lymphadenitis. ***Saudi Med J*** 2011; 32: 412-414.

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