Research Article

Adverse effects of BCG vaccine 1173 P2 in Iran: A meta-analysis

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Abstract

Although in the last two decades the World Health Organization (WHO) has introduced tuberculosis as "a threat to global", the vaccination with the *Mycobacterium bovis* Bacillus Calmette-Guerin (BCG) is the only way for the prevention of this fatal infectious disease. Despite of the efficacy of BCG vaccine especially against infants' meningitis, it has still some limitations due to a variety of adverse effects. Many studies have evaluated the side effects of different strains of BCG vaccines in different countries. In Iran, some studies have been done so far to evaluate the adverse effects of 1173 P2 strain which is used for BCG vaccination. Each of these studies have used different standardization and sampling methods. This review will survey all studies that have been published about adverse effects of 1173 P2 strain of BCG vaccine in Iran using data mining methods.

Key Words: Bacillus calmette-guerin, side effects, safety, 1173P2

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INTRODUCTION

Tuberculosis is caused by an aerobic bacillus called *Mycobacterium tuberculosis* (M.tb). It is noteworthy that significant percentage of the disease and death statistics is related to the two regions including Africa and Southeast Asia.[1] It is about 17 years that the World Health Organization announced the tuberculosis disease as "a threat to global".[2] On the other hand, the rise of multidrug-resistant (MDR) strains, intensify the risk of disease.[3]

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Current vaccine dealing with tuberculosis is live-attenuated *Mycobacterium bovis*, Calmette–Güerin (BCG). This vaccine is able to prevent infants' meningitis but not so powerful to fully prevent the pulmonary tuberculosis. The original strain of *M. bovis* was derived from multiple passages of wild-type *M. bovis*.[3] All existing strains of BCG have been obtained in early twentieth century, 1173 P2 is one of them, which is obtained in 1961. At least 60 countries received BCG from the Pasteur Institute in Paris between 1924 and 1927. Since then, BCG vaccine producers attempted to prepare BCG with their needs. For example in Japan, BCG vaccine manufacturer created a BCG with different morphology and higher heat resistance than other vaccines.[4]

Dr. Weill-Halle was the first physician who used the BCG orally to vaccinate infants against tuberculosis.

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Later, other methods especially intradermal route of injection was used.[5] The BCG vaccine is considered to be safe; however, some complications may occur, including:

- Abscesses at the site of inoculation and localized lesions such as osteitis.
- Disseminated disease, which is suggested as a consequence of impaired immunity such as severe combined immunodeficiency, cellular immune defect, chronic granulomatous disease and impaired IL12- and IFNγ-mediated immunity.
- Severe disease in healthy children with no obvious immunodeficiency.[6]
- Adenitis

In Iran, BCG substrain 1173 P2 vaccine is administered to children at birth. Therefore, as the infants with immunodeficiency in whom BCG vaccination is contraindicated are vaccinated prior to diagnosis, their immunodeficiency may be diagnosed after the development of BCG complications.[6]

Here, we will review all case reports, evidences, reports and papers which have been published after use of BCG vaccine in Iran.

METHODS

Data mining via databases such as Scirus, Pubmed for all available articles was published in English or Persian about side effects of BCG 1173P2 in Iran. In addition, data mining by Endnote software using different keywords to find all papers in this regard.

RESULTS

- Dr. Karimi et al. have reported eight cases of disseminated BCG during 1997–2001 following BCG vaccination. All of the cases had deficiencies in their immune system.[7]
- In 2003, Dr. Seif Hashemi et al. examined 557 infants in Semnan province of Iran vaccinated with BCG and reported less than 3% total side effects.[8]
- In the same year, Fatemeh Emami Ghoreishi reported a case of BCGitis, which affected the right muscle of abdomen.[9]
- Dr. Mamishi et al. studied 17 cases with disseminated BCG disease (9 female and 8 male) during 1995–2004, who complied with inclusion criteria of the study including: positive history of the inoculation of BCG vaccine, two or more signs and symptoms of a systemic syndrome compatible with mycobacterial disease and evidence of BCG infection. The study showed that clinical signs and symptoms had begun before 1 year of age in 82.35% of cases. They also detected impaired immunity in 10 cases (58.82%) including severe combined immunodeficiency (8/10), chronic granulomatous disease (1/10) and cell-mediated immune defect (1/10). The most common sites of acid-fast bacilli were lymph nodes (70.58%).[6]
- In 2005, Dr. Mansouri et al. reported two cases of disseminated BCG infection. The first child was two years old and suffered from complete interferon gamma (IFN-g) receptor 2 deficiency. The other, a 28-year-old adult, suffered from IL-12p40 deficiency.[10]
- In 2006, Dr. Zadie et al. reported a post BCG vaccination Juvenile Xanthogranuloma case in a 3-year-old girl in Kermanshah, Iran.[11]
- In the same year, Dr. Hematyar et al. showed a 6% prevalence of BCG adenitis among 500 infants vaccinated in Tehran, Iran. She also demonstrated a positive correlation between occurrence of BCG adenitis and both the neonate birth weight and gestational age.[12]
- In 2007, Dr. Alborzi reported a 28-month-old girl with the retroperitoneal abscess after BCG vaccination.[13]
- In the same year, Dr. Ghadiri et al. reported two cases of disseminated BCG in Kermanshah, Iran.[14]
- Isfahan University of Medical Sciences started a project in 2007 for master thesis evaluating 486 cases resulted to adverse effect rate of 3% (Data Not Published).
- Dr. Mamishi et al. studied 15 children less than 72 months who were admitted with systemic syndrome compatible with disseminated mycobacterial disease during 2004–2007. Disseminated BCG disease occurred in eight children younger than 6 months and 12 patients younger than 12 months old. Twelve patients were male. Nine of the 15 patients had well-known primary immune deficiency disorders including severe combined immunodeficiency, chronic granulomatous disease, cell-mediated immune defect and HIV infection. Nine (60%) cases had good response to four anti-mycobacterial drug therapy and IFN-g.[15]
- In 2008, Dr. Behjati reported his study in 2003. He studied a total of 480 (240 females and 240 males) consecutive newborns who received 0.05 ml of BCG vaccine intradermally on the right arm within the first week in Yazd province of Iran. He reported 26 (5.8%) cases of lymphadenitis that mostly (24/26) occurred in ipsilateral axillary nodes (92.3%). The two others had lymphadenitis in supraclavicular nodes (1/26), and supraclavicular in association with axillary nodes (1/26). Infants developed lymphadenitis during four weeks of life in one case (3.84%), between first and fourth

month of life in 14 cases (53.8%), and between fourth and sixth month of life in 11 cases (42.3%). All 26 cases of lymphadenitis were followed up for 9 months. Twenty-two cases (84.6%) had simple or non-suppurative and four cases (15.4%) had suppurative lymphadenitis. Half of the cases with non-suppurative lymphadenitis showed a spontaneous resolution and half of them had partial regression without progression or drainage. The cases with suppurative lymphadenitis developed suppuration, one of them ended with fistulation and drainage.[16]

- In 2009, Dr. Shanbestari reported a 6-month-old child with severe combined immunodeficiency who had gotten BCGitis after vaccination.[17]
- In 2011, Dr. Mamishi reported a 3.5-year-old girl with CGD who had gotten BCGitis after BCG vaccination.[18]
- In 2011, Dr. Shojaei et al. reported his study. Between 2006 and 2008, 32 cases, including 30 children with suspected BCG-related complications and two adults with local skin infections, were studied. Molecular microbiological results confirmed the presence of infection due to M. bovis BCG in 11 patients, of whom 9 were aged 2 months to 6 years and 2 were aged > 40 years. Molecular fingerprinting revealed that all isolates were genetically related to each other and to M. bovis BCG Pasteur 1173P2.

DISCUSSION

Since 1948, over 3 billion doses of BCG, considered as safe vaccines, have been administered all over the world.[19] On the basis of WHO recommendation, developing countries should give BCG at birth to every newborn. In Iran it is administered as WHO recommend to every newborn at birth. While there are some adverse effects for almost every biological products, BCG vaccine have some adverse effects as mentioned above, but still there is no substitute to fight against tuberculosis and also some of adverse effects is due to lack of knowledge and can be avoided. Some of them are listed below.

In 1997, Dr. Farshchian *et al*. by evaluation of 1240 vaccinated children have shown that administration of BCG in right arm can increase the risk of adenitis up to three times versus administration in left arm.[20] They have concluded that to decrease the risk of adverse effects of BCG vaccine, it is preferred to administer it in left arm.

While there is a positive correlation between occurrence of BCG adenitis and both the neonate birth weight and gestational age (less than 37 weeks result to up to 6 times increase of risk of adenitis), adverse effects of these newborns should not be counted as BCG vaccine adverse effects.

Administration in upper 1/3 of arm is not recommended, because of increasing risk of adenitis.[12] Administrators should avoidadministration in this site.

Administration of BCG in more than recommended dose can lead to more side effect risk,[12] which is due to influencing the inflammatory pathway. So administration of exact dose is too important to avoid increasing risk.

Administration of vaccine in subcutaneous route versus intradermal route of injection can lead to more side-effect risk. So having the fully trained administrators[12] at birth is too important.

Administration of BCG vaccine with less live bacteria and more killed bacteria can lead to more side effects risk. It may occur in cases of old cultures of manufacturers, not to consider the cold chain, not to follow the administration instruction, because of 20 doses vaccines and many others. Less live bacteria influence the inflammatory pathway leading to more adverse effects and less protection.

BCG vaccine strain plays an important role in adverse effect risks. 1173 P2 Pasteur strain, which is used in Iran, is potent than the other strains. While there is a theory that potent strains have more side effects, some of the adverse effects may be because of the strain.

Administration time especially in first week after birth and also first day after birth can increase the risk of adverse effects. Some percents of adverse effects in Iran may be because of this reason.

Increasing the Antigen (Ag) dosage is one of the factors of adverse effect risk in Iran; it needs to be studied before every decision whether decreasing the Ag will lead to same protection or less protection.[7]

BCG vaccine is a live attenuated vaccine that needs to be cultured for each batch of vaccine. Characteristics of each batch may differ from another. So it should be announced by the manufacturerthe batch has been delivered to each health center to follow to find the agents influencing side effects increasing.

Finally, it seems it should have considered all mentioned considerations above and some more which is not listed in this review. Then we can evaluate the side effect risks and have a standardized general study of at least for 5 years and 20000 newborns for adverse effects rate.

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