

Live attenuated varicella vaccine may affect the sensitivity of tuberculin skin test

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Abstract

Background: Tuberculin skin test (TST) has been the most commonly used test for diagnosis of tuberculosis (TB) infection in China for many years, because of well-established algorithms for test interpretation and a good cost-effectiveness. To our knowledge, there is no report or guideline on the influence of varicella vaccine on the sensitivity of TST in China. This paper aims to explore the effect of live attenuated varicella vaccine on the sensitivity of TST.

Methods: A retrospective cohort study was carried out in a high school in Wuxi, Jiangsu province in 2020. TST and emergency varicella vaccine were administered to students in grade one of the high school which had both TB and varicella cases. The mean diameter of induration of TST were compared between 73d before varicella vaccine, 9d and 120d after varicella vaccine respectively. The retrospective cohort study was used to analyze the effect of live attenuated varicella vaccine on TST.

Results: There were 45 students in the class of the high school had three TST, and 22 of them were vaccinated varicella. After 9 days of varicella vaccination, the mean diameter of induration was significantly smaller than that before the vaccination of 73 days and after the vaccination of 120 days ($p < 0.05$), respectively. Moreover, there is no significant difference for mean diameter of induration between the TST before the vaccination of 73 days and after the vaccination of 120 days ($p = 0.551$). The retrospective cohort study analysis indicated that 9 days after varicella vaccination (RR, 6.071, 95%CI, 1.667–22.116, $P = 0.007$) was associated with the changed mean induration diameter of TST. After vaccination of 120 days (RR, 3.474, 95%CI, 0.333–36.240, $P = 0.346$) was not associated with the changed mean induration of TST.

Conclusions: Live attenuated varicella vaccine may temporarily affect the sensitivity of tuberculin skin test.

Background

Although tuberculin skin test (TST) is over a century old, it continues to be used in high endemic tuberculosis (TB) settings as a diagnostic tool for determining latent TB infection (LTBI)^[1]. People with LTBI do not show symptoms of TB and are not infectious, but they are at risk of developing active disease and becoming infectious. Preventing active TB by proper diagnosis and treatment of LTBI in high risk population is important for individuals and public health^[2]. Traditionally, TB infection screening is conducted by TST, the TST measures delayed type hypersensitivity (DTH) response to intradermal injection of purified protein derivative (PPD), a crude mixture of several mycobacterial antigens which are common to *M. tuberculosis*, *Mycobacterium bovis* BCG^[3]. TST is the major tool used worldwide for diagnosis of TB infection because of well-established algorithms for test interpretation. In addition, TST is easy to use and it has a good cost-effectiveness^[4]. Therefore, TST has been the most commonly used test in China for many years, especially in testing for LTBI of freshmen physical examination, and high-risk population after TB public health event. However, the sensitivity of TST may be reduced by

malnutrition, severe TB diseases and immunodeficiency. Some studies also have reported the depression of its sensitivity with active infections such as measles, influenza, rubella, poliomyelitis, typhus, and varicella^[5]. Live, attenuated vaccination such as measles, poliovirus type1, killed poliovirus, yellow fever virus and mumps also depresses its sensitivity^[6-9]. However, Nalbant has registered a dissenting opinion concerning the effect of infectious diseases on TST, and Berkovich's results with the same live attenuated mumps virus and similar test groups were quite different^[10, 11]. To our knowledge, there is no report or guideline on the influence of varicella vaccine on the sensitivity of TST in China. This paper describes a retrospective cohort study, which aims to explore the effect of live attenuated varicella vaccine on the sensitivity of TST.

This paper is a special case in a high school in Wuxi City, Jiangsu Province, China, which had an outbreak of varicella when dealing with a tuberculosis epidemic. On December 27, 2019, there happened a TB case in one of classes in grade 1 in the school. According to "Standard requirements for tuberculosis control in schools in Jiangsu Province"^[12], on January 6, 2020, the Wuxi Centers for Disease Control and Prevention (CDC) organized the TST for close contacts of the TB case in class 5, grade 1. In addition, all the students in the class did TST in their freshman physical examination on October 15, 2019.

It takes about more than a month from infection with M tuberculosis to producing an allergic response, and in the early stages of the response, the TST is unresponsive. The Wuxi CDC organized the second TST after three months of the first TST, try to make sure the false-negative TST doesn't happen. Due to the outbreak of covid-19, the high school resumed classes in early April 2020. The second TST for the teachers and students who had negative TST results in the first TST in the class on April 27, 2020.

Since October 31, 2019, there had been continuous cases of varicella in the school, which reported by the health care teacher in the school. The first case of varicella was reported in the TB case class on December 26, 2019. Experts from Wuxi CDC determined that there was an outbreak of varicella in this school. According to the requirements of "Implementation Plan of Incorporating varicella vaccine into the Immunization Program for school-age Children in Wuxi"^[13], emergency vaccinations should be carried out as early as possible in kindergartens and schools with varicella outbreaks according to risk assessment^[14]. Close contacts who do not have a history of varicella, have no history of varicella vaccine, or have less than two doses of varicella vaccine should receive 1-dose of varicella vaccine within one week after the outbreak of the epidemic. Vaccination as soon as possible, within 3-5 days post-exposure, can be effective in preventing disease and reducing the severe cases of varicella^[15, 16]. Moreover, vaccination should be sufficient to ensure reaching and sustaining vaccine coverage $\geq 90\%$ ^[13]. There are total 345 students of the school were given the emergency varicella vaccine from November 2, 2019 to December 28, 2019. Twenty-four students, who from the TB case class, got the emergency vaccination of varicella on December 28, 2019.

Methods

Administration of the TST by the Mantoux Method

Trained nurses performed the TST according to the Mantoux technique using five units of the PPD(Chengdu institute of biological products, China). The mean diameter of induration at 72 hours was measured by the same two examiners. The TST reaction was considered positive when the induration was $\geq 5\text{mm}$ ^[17]. The TST was divided into 4 groups according to the mean diameter of induration: (1) $< 5\text{ mm}$ or no reaction, negative, (2) $\geq 5\text{ mm}$, $< 10\text{ mm}$, mild positive, (3) $\geq 10\text{ mm}$, $< 15\text{ mm}$, moderately positive, (4) $\geq 15\text{ mm}$ or $< 15\text{ mm}$ with the local presence of double circles, blisters, necrosis and lymphangitis, strongly positive.

Emergency varicella vaccination

In December 2018, liangxi district began to implement emergency vaccination against varicella outbreaks in accordance with the "Implementation Plan of Incorporating varicella vaccine into the Immunization Program for school-age Children in Wuxi". Trained nurses performed the emergency vaccination using 3.3 lgPFU of the live varicella vaccine (Shanghai institute of biological products, China). 0.5 ml live varicella vaccine was injected subcutaneously at the attachment of the lower margin of the lateral deltoid muscle of the upper arm.

Statistical analysis

We conducted a retrospective cohort study in May 2020, students in the class who got the emergency varicella vaccine were allocated to the exposed group, and others was allocated the non-exposed group. We compared the mean diameter of induration among the freshman TST in October 2019 (73 days before varicella vaccination), TST in January 2020 (9 days after varicella vaccination), and TST in April 2020 (120 days after varicella vaccination), and change of mean diameter of induration between the three TSTs. Relative risk (RR) was obtained from the ratio of incidence among the vaccinated and the non-vaccinated groups. P-values < 0.05 were considered to be statistically significant. All statistical analyses were performed with R3.6.

Results

Basic characteristics of the students with TST and varicella vaccination

There were a total of 50 students in the class, including 28 boys and 22 girls. The mean age of the students was 15.38 years, aged from 15 to 17 years. All of the students in the class did TST in October 2019, which showed the positive rate was 48.00%, and no strong positive was found. In January 2020, a total of 46 students in the class did TST, and none of them showed positive results. A total of 48 students in the class did TST in April 2020, and 19 of students were showed positive results, the positive rate was 39.58%. The mean diameter of induration was compared among 45 students who got three TSTs (Fig. 1). In addition, close contacts of TB who were more than 15 years old had a chest X ray (CXR) that is not suggestive of TB disease on January 3, 2020. There are 22 students were vaccinated varicella of the 45 students who had three TSTs.

Three TST results before and after varicella vaccination

After 9 days of varicella vaccination, the mean diameter of induration was significantly smaller than that before the vaccination of 73 days and after the vaccination of 120 days ($p < 0.05$), respectively. Moreover, there is no significant difference for mean diameter of induration between the TST before the vaccination of 73 days and after the vaccination of 120 days ($p = 0.551$) (Table 1).

Table 1
Comparison of the induration of the TST at the class of high school students at different times (n = 45,mm)

time	before vaccination of 73 days	after vaccination of 9 days	after vaccination of 120 days
Mean diameter of induration(mm)	3.678 ± 4.283	0.056 ± 0.373*	3.433 ± 4.704
*p < 0.05 compared the TST before the vaccination of 73 days and after the vaccination of 120 days, respectively.			

The risk factor of the TST results

Compared between the vaccinated and non-vaccinated, 9 days after varicella vaccination (RR, 6.071, 95%CI, 1.667–22.116, P = 0.007) was associated with the changed mean induration of TST. After vaccination of 120 days (RR, 3.474, 95%CI, 0.333–36.240, P = 0.346) was not associated with the changed mean induration of TST (Table 2).

Table 2
Effect of live attenuated varicella vaccine on the TST in the students

	compared with the TST before the vaccination of 73 days, the number of persons with changed mean induration diameter			
	after vaccination of 9 days		after vaccination of 120 days	
	changed	no-changed	changed	no-changed
vaccinated	15	7	3	19
non-vaccinated	6	17	1	22
p-Value	0.007		0.346	
Relative risk(95%CI)	6.071(1.667–22.116)		3.474(0.333–36.240)	

Discussion

This is a special case of infectious disease in a high school, the observations are rare in China. In this paper, we found varicella vaccine may temporarily suppress the TST reaction with induration diameter; however, due to the lack of blood biochemical index detection, we were not able to analyze the related immune molecules. The mechanism of varicella vaccine induced depression of TST is unknown. Lymphocytes may play the major role in immunologic recognition and the expression of delayed hypersensitivity. Some observations have shown that the exposure of tuberculin-sensitive lymphocytes to measles virus in vitro inhibits their mitotic response to tuberculo-protein^[18]. However, these investigators have also demonstrated that ECHO virus type 9 infections do not suppress tuberculin hypersensitivity^[7].

In this paper, we considered several factors that may influence the results of TST. At the first is the PPD, We did not find the possible risks of PPD in storage and transportation. In addition, the batch number of PPD which was used in January and April 2020, was the same and also produced by the same manufacturer. Secondly, the nurses performed the TST were same and had been trained in "TST operation Practice". The mean diameter of induration at 72 hours was measured by the same two examiners, who are also professionally trained. Moreover, 9 days after varicella vaccination, nine teachers in the class also got TST as close contacts of TB, and two of them showed positive results while the students did not show any positive results. Although the teacher and the student's injection conditions are exactly the same. Studies^[19, 20] have shown that TB disease may temporarily suppress the DTH response to a TST. In this case, CXR were taken of all close contacts aged 15 years and over, and no abnormalities were found. Over time, after natural infection with tuberculosis or BCG vaccination, TST will be weakened or negative, and when repeated with the same dose after a period of time, TST will resume positive reaction. In this paper, 24 students in the class showed positive reaction in October 2019, but showed negative reaction in January 2020. In April 2020, the TST results of 24 students were showed positive reaction again, which indicated that the TST may be false-negative in January 2020.

The analysis results of this paper suggest that special attention should be paid to the factors that may affect the results of TST, thus to avoid false-negative or false-positive TSTs. Immunization schedules and TST must be established with attention to these observations. American Thoracic Society suggested that if the TST is indicated after a live, attenuated vaccine, it will likely be most accurate if 6 weeks have passed since vaccine administration^[5].

Conclusions

Live attenuated varicella vaccine may temporarily affect the sensitivity of tuberculin skin test.

Abbreviations

TST: Tuberculin skin test;

TB: Tuberculosis

LTBI: Latent TB infection

DTH: Delayed type hypersensitivity

PPD: Purified protein derivative

CDC: Centers for Disease Control and Prevention

CXR: Chest X ray

RR: Relative risk

Declarations

Ethics approval and consent to participate

The study was approved by Ethics Review Committee, Wuxi NO.8 People's Hospital. All methods were performed in accordance with the relevant guidelines and regulations. All of the students under 16 years old had written informed consent signed by their parents or guardians.

Consent for publication

Not applicable.

Availability of data and materials

All data used to support the findings of this study are available from the corresponding author upon request.

Competing interests

The authors declare that they have no relevant financial interests.

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Authors' contributions

All authors were involved in the public health event. TL wrote the first draft of the manuscript. QZ, ZX and XS revised it. CQ, HQ, ZD and YK collected and analyzed the data.

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Figures

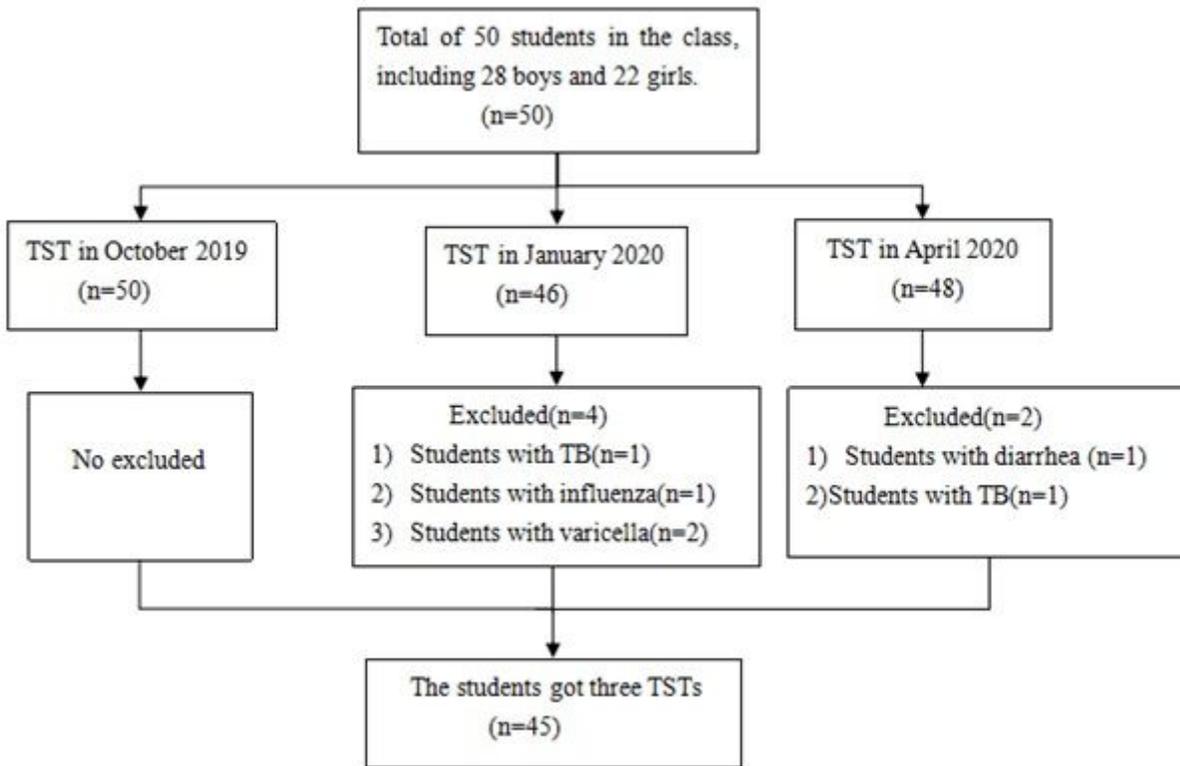


Figure 1

Flowchart of students with TST and varicella vaccination enrolled in this study.