Vaccine 33 (2015) 3384–3391

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Skin thickness in young infants and adolescents: Applications for intradermal vaccination

Akihiko Saitoh[a,*], Yuta Aizawa[a], Isamu Sato[b], Harunobu Hirano[c], Takatsugu Sakai[d], Masaaki Mori[e]

[a] Department of Pediatrics, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan
[b] Yoiko-no-Syounika Sato Clinic, Niigata, Japan
[c] Department of Pediatrics, Saiseikai Niigata Daini Hospital, Niigata, Japan
[d] Department of Pediatrics, Niigata Medical Center, Niigata, Japan
[e] Department of Pediatrics, Yokohama City University, Yokohama, Japan

ARTICLE INFO

Article history:
Received 6 December 2014
Received in revised form 31 March 2015
Accepted 22 April 2015
Available online 2 May 2015

Keywords:
Skin thickness
Intradermal injection
Infant
Adolescent
Deltoid
Suprascapular

ABSTRACT

As compared with standard intramuscular and subcutaneous vaccines, intradermal (ID) vaccines elicit a more potent immune response in both adults and children, with equivalent dosage or antigen dose sparing.

Recently, various devices for ID injection have been developed; the length of needles ranges in 0.6–1.5 mm. However, skin thickness must be measured to determine optimal needle length for ID vaccines. Use of ID vaccines in infants and children is appealing because children require more vaccines than do adults; however, information on skin thickness in infants and children is limited. We used ultrasound echography to measure skin thickness in Japanese infants aged 2 months ($n = 78$) and adolescents aged 13–15 years ($n = 82$). Mean (range) deltoid and suprascapular skin thickness was 1.67 mm (1.16–2.39 mm) and 1.83 mm (1.24–2.60 mm), respectively, in infants and 1.81 mm (1.25–3.00 mm) and 2.43 mm (1.51–3.95 mm), respectively, in adolescents. Among infants who underwent re-measurement of skin thickness at age 6 months ($n = 11$), mean deltoid skin thickness (1.84 mm) was significantly greater than at age 2 months (1.60 mm) ($P < 0.001$). In contrast, no significant difference was observed in suprascapular skin thickness (1.79 mm vs. 1.67 mm, respectively; $P = 0.17$). Gender was not associated with skin thickness in either age group. Skin thickness was positively correlated with body weight in adolescents ($r = 0.43$, $P < 0.001$ in deltoid region; $r = 0.30$, $P = 0.01$ in suprascapular region). In conclusion, this is the first study to evaluate skin thickness in different age groups of children, including at age 2 months. Skin thickness gradually increased from age 2 months to age 13–15 years, but no consistent trend was noted in analysis stratified by measurement site, gender, or age. These findings suggest that an appropriate length of ID device needle for infants and children is likely to be less than 1.2 mm and a special device with shorter length of needle is warranted for infants and children.

1. Introduction

Intradermal (ID) vaccine administration is an efficient means of eliciting immune response. Skin is rich in antigen-presenting cells such as Langerhans cells and dermal dendritic cells [1]. A number of studies have reported that enhanced immune response led to higher antibody titers or antigen dose sparing as compared with standard intramuscular (IM) and subcutaneous (SC) injection [2–5].

The Mantoux technique is a standard ID injection technique commonly used for tuberculosis testing. The procedure requires a needle to be inserted into the skin at an angle of 10–15 degrees and a length of 2–5 mm. Because the needle tip must be manually guided into the thin layer of the skin, the technique requires specific training and does not ensure consistency of administration volume and accuracy of appropriate depth for ID injection [6,7].

Several types of ID delivery devices have been developed to make the technique simpler and more consistent, including jet

Abbreviations: ID, intradermal; IM, intramuscular; SC, subcutaneous; WHO, World Health Organization; HBV, hepatitis B virus.

* Corresponding author at: Department of Pediatrics, Niigata Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-dori, Chuo-ku, Niigata 951-8510, Japan. Tel.: +81 25 227 2222; fax: +81 25 227 0778.
E-mail address: asaitoh@med.niigata-u.ac.jp (A. Saitoh).

http://dx.doi.org/10.1016/j.vaccine.2015.04.081
0264-410X/

Table 1
Clinical characteristics of participants.

(A) Infants (age 2 months)

		Male (n = 38)	Female (n = 40)	Total (n = 78)
Age (days)	Mean	69	69	69
	SD	8	6	7
	Range	61–89	61–87	61–89
Birth weight (g)	Mean	3123	3133	3128
	SD	435.3	319.6	377.9
	Range	2528–4200	2620–3900	2528–4200
Height (cm)	Mean	58.5	57.3	57.9
	SD	2.7	2.0	2.4
	Range	54.2–65.7	53.5–61.9	53.5–65.7
Weight (kg)	Mean	5.68	5.34	5.51
	SD	0.73	0.56	0.66
	Range	4.39–7.84	4.33–7.07	4.33–7.84

(B) Adolescents (age 13–15 years)

Age (years)	13			14			15		
Gender (n)	Male (10)	Female (21)	Total (31)	Male (20)	Female (13)	Total (33)	Male (9)	Female (9)	Total (18)
Height (cm)									
Mean	156.1	157.4	157.0	163.8	158.4	161.7	166.1	159.2	162.7
SD	8.2	5.3	6.3	5.6	6.7	6.5	6.1	3.8	6.1
Range	143.0–166.5	145.0–169.0	143.0–169.0	153.2–173.0	149.0–168.1	149.0–173.0	160.0–179.0	154.6–167.0	154.6–179.0
Weight (kg)									
Mean	46.1	45.0	45.4	51.7	49.7	50.9	54.1	51.2	52.7
SD	7.4	5.7	6.2	15.0	4.7	11.9	9.2	7.4	8.2
Range	34.0–60.0	33.0–58.0	33.0–60.0	33.3–110.0	42.0–54.6	33.3–110.0	40.0–72.0	44.0–68.6	40.0–72.0

SD, standard deviation.

injection and single- and multi-microneedles. In 2009, the ID influenza vaccine Intanza® (Sanofi Pasteur, Lyon, France) was licensed in Europe [8], to be administered in combination with the Soluvia® ID injection device (Becton, Dickinson and Company, Le Pont de Claix, France). Intanza®/Fluzone intradermal have marketed in more than 40 countries to date, including the US, Australia, Canada, Korea and countries in Europe, but not in Japan. This injection system has a single 30-gauge, 1.5-mm-long needle, the proximal end of which is fixed to a glass pre-filled syringe. An attachment guides the needle perpendicularly during skin insertion and controls insertion depth [9]. The needle length was determined on the basis of adult skin thickness, i.e., approximately 2 mm [10], and the device is thus licensed for use in adults older than 18 years.

New ID delivery devices should make standard ID delivery simpler and more consistent, both for influenza vaccines and other vaccines. Children receive multiple vaccines during early infancy and childhood; 12 injections before 1 year old and 8 injections before 2 years of age on schedule recommended by the Japan Pediatric Society. Therefore, use of the new ID device might allow for development of new vaccination strategies in infants and children. However, before ID injection can be applied to infants and children, appropriate needle lengths must be determined for these groups. Unfortunately, information on skin thickness in infants and children is limited.

Using ultrasound echography, we investigated skin thickness in infants (age 2 months) and adolescents (age 13–15 years), to assist in future development of ID vaccines and devices for children. The infant age group was selected because multiple infant vaccines—including the *Haemophilus influenza*e type b, pneumococcal conjugate, and diphtheria, pertussis, tetanus, and inactivated polio vaccines—are started after age 2 months. To the best of our knowledge, no studies evaluated skin thickness at this young age group. The 13–15 years age group was selected because adolescents receive the same dosage of influenza vaccine (0.5 mL) as adults in Japan.

2. Methods

2.1. Study population and data collection

2.1.1. Infants (age 2 months)

The subjects were recruited between September 2013 and February 2014 at the pediatric clinics of Yoiko-no-Syounika Sato clinic, Saiseikai Niigata Daini Hospital, and Niigata Medical Center, Niigata, Japan. Two-month-old infants were enrolled and informed consent was obtained from their parents before participation. All participants were healthy Japanese boys and girls aged 60–89 days. Children were excluded if they (1) were born before 36 weeks' or after 42 weeks' gestation, (2) weighed 2500 g or less at birth (low birth weight), (3) had visible skin issues at the study target skin sites, (4) had a serious illness or chronic condition, or (5) had any condition that the physicians responsible judged to be inappropriate for study inclusion. Skin thickness was evaluated at the deltoid and suprascapular regions, and body weight and height were measured to assess the association between these anthropometric variables and skin thickness. The reasons why the skin regions were selected were previous literatures evaluated the two sites [10,11], and the regions were recommended as ID vaccination site by World Health Organization (WHO) [12]. In addition, it is valuable to compare our results with the previous results from other countries. The clinical characteristics of the 78 infants are summarized in Table 1A.

2.1.2. Follow-up measurement of infants (age 6 months)

To investigate the impact of growth during infancy, 11 of the 78 infants (14%) underwent follow-up measurement of skin thickness at the same body sites at 6 age months. The eligible subjects in 2 months old study were asked to join again the follow-up measurement at the time when post hoc protocol has been approved. The subjects whose parents wrote informed consent were post hoc recruited at the Yoiko-No-Syounika Sato clinic in June 2014.