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Clinical performance and safety of adapters for intradermal delivery with conventional and autodisable syringes

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ABSTRACT

Although the number of vaccines and diagnostic tests currently delivered intradermally is limited, this route of administration offers potential advantages due to the high concentration of antigen-presenting cells in the skin. One factor which may in part be limiting development and use of intradermal (ID) administration is concern about the ease and reliability of the needle and syringe-based Mantoux technique. A phase I clinical study was conducted to evaluate two ID adapters that have been developed as injection-delivery aids to increase the safety, simplicity, and reliability of ID injection: a prototype autodisable, intradermal (ADID) adapter for autodisable (AD) syringes, and a marketed side-merge adapter (SMA). Thirty healthy adult volunteers each received six injections of 0.1 mL of sterile saline solution. Each adapter was used to give injections into the upper deltoid, forearm, and suprascapular regions of each volunteer. The needle-bevel orientation during injection was random. Injection performance was determined by measuring wheal size and fluid leakage. Wheals were similar in size for the ADID adapter (mean 9.9 ± 0.17 mm) and SMA (mean 9.8 ± 0.15 mm). In all of the injections completed with the SMA, and 98% of those completed with the ADID, fluid leakage was less than 10% of the intended injection volume. Minor skin abrasions were the only adverse events. Based on self-reporting of pain, injections were well tolerated (mean pain score of 2 on a 0–10 scale). ID delivery using the SMA and ADID adapters appears safe and effective.

1. Introduction

Vaccines have led to dramatic decreases in global infectious disease morbidity and mortality [1], including the eradication of smallpox [2]. A variety of options for vaccine delivery exists, including intramuscular (IM), subcutaneous (SC), and intradermal (ID) injections and nasal, oral, and transcutaneous methods. Currently, IM and SC are the most common routes of injection for the majority of vaccines. However, the ID route offers several potential advantages. First, the skin contains a higher concentration of antigen-presenting cells than the SC tissue or muscle. These cells perform an essential role in processing and presenting antigens, and are critical components of the adaptive immune system response. Therefore, delivery of vaccines to the epidermis or dermis may result in superior immune responses when compared to IM or SC [3]. The increased concentration of antigen-presenting cells available with ID delivery may allow a reduced amount of antigen required for effective immune response with some vaccines. This dose-sparing effect could reduce the cost per dose of vaccines and increase availability of vaccines with limited or expensive antigens. Also, the potential superior immune response may reduce the need for adjuvants for some vaccines.

Unfortunately, the most common method of ID delivery can be difficult to perform, particularly if the user's experience is limited. ID injection is typically administered using the Mantoux technique

Abbreviations: AD, autodisable; ADID, autodisable, intradermal; AE, adverse event; ID, intradermal; IM, intramuscular; SC, subcutaneous; SMA, side-merge adapter; UNICEF, United Nations Children's Fund.

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[4], which requires special training. Even with experienced vaccinators, there is the risk of improper depth of delivery, which reduces the availability of the antigen to the antigen-presenting cells in the skin. The risk of improper delivery is accentuated if the patient moves. Concerns have been reported in the difficulty of correct implementation of the technique, the time needed, the required training, and the potential resulting variability of injection performance, though opinions vary and little objective data is available on the subject [5–8]. These factors present a challenge to vaccine manufacturers that are considering the use of ID injection as a delivery method for current or new vaccines.

Despite its limitations, however, the Mantoux technique has been the conventional method of ID injection for more than 100 years [4]. In particular, the Bacille Calmette-Guérin (BCG) vaccine for tuberculosis is given to approximately 100 million infants each year using this method [9]. Other existing vaccines delivered intradermally include rabies vaccine and a recently introduced inactivated influenza vaccine in a prefilled-ID delivery device. Many vaccines may have the potential to be delivered intradermally in the future, including new-generation tuberculosis, inactivated poliovirus, hepatitis A, and human papillomavirus vaccines [10,11]. Additionally, ID injection is used for tuberculosis diagnosis by skin tests using purified protein derivative (PPD), as well as for allergy tests and to deliver local anesthetics.

The side-merge adapter (SMA) is currently marketed by West Pharmaceutical Services, Inc. (West) in the USA and Europe and is promoted as an easy-to-use, low-cost aid for ID injections using the Mantoux technique with currently available needles and syringes [12]. The SMA holds the needle parallel to the skin's surface at a consistent depth as the needle penetrates the skin, ensuring the needle tip is placed into the skin to the correct depth. This delivery device aids the vaccinator and may minimize training needs and increase reliability and repeatability of correct needle placement. Preclinical studies showed a 60% increase in the success of bleb formation using an adapter compared to the traditional Mantoux technique (I.T., unpublished data). The SMA is a single molded component which is designed to be inexpensive to manufacture and is intended for one-time use only, as it could be contaminated by bodily fluids during use. However, the SMA could potentially be removed from the syringe and reused.

The United Nations Children's Fund (UNICEF) and the health care authorities of many developing countries require the use of immunization syringes equipped with an autodisable (AD) feature to prevent reuse and cross-contamination [13]. The autodisable, intradermal (ADID) adapter integrates the development experience of the SMA and is intended for one-time use with an AD syringe. The AD feature, a pivoting section of the ADID adapter, is enabled during activation of the device, after merging the ADID adapter with the syringe and prior to injection. Hooks on both sides of the pivoting section (illustrated in Fig. 1C and D) permanently engage the adapter body when the adapter is activated. The ADID adapter design prevents the reuse of the adapter with any syringe.

We conducted an unblinded, phase I clinical trial to evaluate the safety, reliability, and precision of injections of two ID adapter designs by delivering saline in healthy adult volunteers.

2. Methods

Injections were administered in the upper deltoid, forearm, and suprascapular regions, which is consistent with the sites used for tuberculin testing and in one ID rabies vaccination regimen. The clinical study received institutional review board approval from PATH's Research Ethics Committee, and was registered on www.ClinicalTrials.gov (registration number NCT01943110).

2.1. Devices

Both the SMA and ADID adapter have a similar skin-contacting interface and represent variations on a core design approach. The SMA is a United States Food and Drug Administration-cleared device which was evaluated in a 2011 clinical study and found to successfully deliver injections intradermally (Fig. 1A) [14,15]. The ADID adapter (Fig. 1B) has operating characteristics similar to the SMA and is intended for use with AD syringes. The design prevents reuse of the adapter. Both adapters are disposable, single-use components, injection-molded in medical-grade polycarbonate. The adapters fit on syringes with a fixed needle (Fig. 1A and B). The adapters are placed on the syringe by the user after the syringe is filled from a conventional vial. For both adapters, refilling the syringe through the needle, which is not recommended, would require removal of the adapter.

The ADID adapter functions similarly to the SMA. The AD syringe is filled with vaccine and then merged with the ADID adapter. The adapter is activated by a non-reversible engagement of the hooks on its pivoted section with the main adapter body. The activation aligns the protruding needle parallel to the skin. The ADID adapter prevents subsequent attachment of the adapter to a new AD or conventional syringe, thereby preventing cross-contamination. The AD feature of the syringe itself prevents reuse of the combined ADID adapter/AD syringe assembly.

2.2. Clinical evaluation

Each study participant received six injections of 0.1 mL of sterile saline solution containing 0.9% sodium chloride (Hospira, USA) in the upper deltoid, forearm, and suprascapular regions, on each side of the body in a predetermined, randomized order. Three injections into the identified sites were delivered using the SMA with a commercially available insulin syringe (1-mL Ultra-Fine Needle insulin syringe with fixed 27-gauge, ½-inch needle; BD, USA). The other three injections were delivered using the investigational ADID adapter with an AD syringe (0.1-mL syringe with fixed 27-gauge, ½-inch needle; Helm Medical AG, Germany). The bevel orientation of the needle was not controlled for either adapter. A single research health care worker received training by the investigators on use of both ID adapter designs prior to the study, and performed all of the injections.

2.3. Injection quality and safety assessment

We assessed injections by (1) recording whether ID wheals were formed and measuring their diameters; (2) measuring liquid on the surface of the skin after injection; (3) evaluating the safety of injections; and (4) assessing tolerability (pain). Photographs were taken of each injection site to document wheal formation and size.

Wheals were measured using a clear template with circles with diameters in 1-mm increments. Averages for each group are reported as means ± standard error of the mean. A threshold of ≥5 mm was defined as a successful injection, based on literature reports of wheal sizes obtained from a 0.1-mL injection [16–18]. The amount of liquid that failed to penetrate the skin, or that leaked out of the injection site, was measured using absorbent paper (Whatman Qualitative Filter Paper, Grade 3; Sigma Aldrich, USA). Immediately after the injection, moisture on the surface of the skin was absorbed with the paper. A pen was used to mark the perimeter of the blot formed by the absorbed fluid. The blot outline was later compared to a reference template and categorized by liquid volume. This method has been validated by PATH through bench testing and determined to be accurate at quantifying small volumes of liquid. An arbitrary cutoff of ≤10 μl of liquid was used as a performance standard, representing injections in which ≥90%