Vaccine 26 (2008) 3197–3208

Contents lists available at ScienceDirect

Vaccine

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

Review

Intradermal vaccine delivery: Will new delivery systems transform vaccine administration?

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ARTICLE INFO

Article history:
Received 5 February 2008
Received in revised form 17 March 2008
Accepted 24 March 2008
Available online 22 April 2008

Keywords:
Intradermal injection
ID injection
Vaccine delivery

ABSTRACT

There has been a recent resurgence of interest in intradermal vaccine delivery. The physiological advantages of intradermal vaccine delivery have been known for some time, but the difficulties associated with performing an intradermal injection have historically limited its use. New delivery systems currently in development facilitate convenient intradermal vaccination, unlocking the potential advantages of this delivery route, and potentially transforming vaccine delivery.

Contents

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1. History of intradermal vaccination

The discovery of the principles of vaccination is often described as one of the most important developments in public health. The practice of inoculating small amounts of material from sick patients, such as powdered smallpox scabs or pus, into the nose or skin of healthy individuals to prevent disease was widespread across parts of Africa, Asia and the Ottoman empire, before inoculation into the skin – variolation – was introduced to Europe in 1721. Inoculated patients would generally develop a milder form of the disease than that occurring naturally. However, the risk of death from smallpox remained. It was not until 1796 that the first vaccination was carried out as practiced today by Edward Jenner in the United Kingdom based on his observation that milkmaids who had contracted cowpox through contact with cowpox pustules were not getting smallpox. Initially Jenner's findings were not well received and it took 44 years for variolation to be forbidden by an Act of Parliament and a further 13 years for vaccination against smallpox to be made compulsory in Britain in 1853 [1].

The next important development was made by the French physician Charles Mantoux in 1910 when he published his clinical research on the intradermal injection of tuberculin as a diagnostic skin test for tuberculosis disease [2]. Not only was this technique used for tuberculosis diagnosis, but it formed the basis for intradermal (ID) injection of vaccines, a technique still used today for vaccines such as rabies and BCG [3,4].

In 1967 the WHO launched a global programme to eradicate smallpox which, 150 years after Jenner's discovery, was still affecting 10–15 million people each year. Eradication of the disease was finally confirmed by the World Health Assembly in 1980 [5] A major contribution to this achievement was the development of the bifurcated needle by Benjamin A. Rubin. This needle was specifically designed to ensure the delivery of about 2 μl, but sufficient, quantity of this very potent vaccine into the dermis. It helped healthcare workers to correctly deliver vaccine to the most efficient site for immunization against smallpox. Vaccination was done by dipping the bifurcated needle into the vial of vaccine to pick up a minute drop of vaccine solution between the needle's two prongs, then by jabbing the skin – typically in the deltoid region – several times with a brisk movement perpendicularly to the skin surface [6].

The first renewed interest in intradermal immunization using a needle and syringe injection system in controlled clinical trials was reported by Tuft in 1930 [7]. This study reported an equivalent immune response and an improved adverse event profile with a smaller dose of typhoid vaccine when injected intradermally relative to subcutaneous injection [8]. Subsequently to these reports several studies aiming to evaluate the efficiency and utility of intradermal delivery route such as vaccine dose reduction were conducted using different commercially available vaccines including influenza [9–11], measles [12,13], cholera [14], rabies [15,16], hepatitis B [17–20], polio virus [21–24] aiming to evaluate the optimal route of immunization for preventive vaccination. In spite of the large number of published clinical trials comparing post-immunization humoral immune responses, the evaluation of the benefit and utility of intradermal delivery suffers from the absence of a consistent clinical design and standardized investigational method permitting an efficient side-by-side comparison and meta-analysis. The vaccine antigen concentration/immune response curve has rarely been thoroughly evaluated to detect and characterize the minimal, maximal and optimal antigen concentrations in various population segments which correspond to the clinical indication of investigated vaccine. Nevertheless, vaccines can be generally categorized into three groups: (i) those for which intradermal delivery induces better responses than by intramuscular results has been observed in separate clinical trials; and (iii) vaccine remaining to be investigated such as combo vaccines, meningococcal. Potential benefits of the intradermal delivery route as measured by post-immunization immune response depend upon the type of vaccine. For example, it is well documented that the immune response after intradermal administration of one-tenth of an intramuscular dose is equivalent to the full dose given intramuscularly for rabies and hepatitis B vaccines, but not for trivalent influenza vaccine [25–29]. One confounding factors leading to mixed clinical study results with trivalent influenza vaccine is the priming by previous natural infection; primed adult subjects produce equivalent immune response with reduced dose of antigen delivered by intramuscular as well as intradermal delivery routes [29,30]. In contrast, intradermal influenza vaccination in elderly subjects (15 and 21 μg of haemagluttinin/strain/0.1 ml dose) induced a humoral immune response superior to the IM control against all three strains [31]. Clinical studies in subjects with chronic medical conditions such as kidney failure, with or without haemodialysis, suggest that intradermal delivery of hepatitis B vaccine induces a better immune response than intramuscular injection [27,28,32]. Meta-analysis of clinical trials evaluating rabies vaccine prepared on diploid cells indicated that the persistence of specific humoral antibodies is at least equivalent to that observed with intramuscular delivery; the same results are observed with hepatitis B vaccine [25,33]. The local skin reactivity usually observed at the injection site after intradermal vaccine inoculation reflects the physiological local inflammatory response due to immune response induction and is characterized by spontaneously reversible redness at the injection site for a maximum period of 2 days without local sequelae. Systemic adverse event profiles are equivalent whatever the delivery route.

2. Current situation and future needs of innovative vaccine delivery systems

An ideal vaccine is safe, cost-effective, and efficient after a single dose [34]. The way in which a vaccine is delivered can have considerable bearing on these factors through its influence on the efficiency of the procedure, the dose required, compliance, and safety. For vaccination to succeed holistically in contributing to public health, vaccine delivery systems must allow efficient delivery without compromising product stability during storage and transport and without negatively influencing patient perception. To be considered safe, new delivery systems should reduce the risk of injury and infection of healthcare workers, and prevent illicit reuse. A delivery system combining all these qualities would facilitate the vaccination of greater portion of the population.

Currently licensed vaccines are delivered via one of five main administration routes: intramuscular for the majority of vaccines including hepatitis A and B, rabies, influenza and diphtheria–tetanus–pertussis-based combination vaccines; subcutaneous for vaccines such as measles, mumps and rubella, and yellow fever; intradermal for BCG and rabies; intranasal for live attenuated influenza vaccine, and oral for poliomyelitis, cholera, rotavirus and typhoid fever. With the rare exception of jet injectors, intramuscular, subcutaneous, and intradermal routes are accessed using needles. These techniques, whilst having proven efficacy in terms of achieving the required immune response, have some drawbacks relating to safety and patient compliance [35,36]. The invasive nature of the parenteral injection procedure and the potential for inappropriate reuse of equipment exposes patients to the risk of transmission of blood borne pathogens. Additionally, the use and disposal of equipment is associated with the risk of needle-stick injury. The introduction of safer devices engineered to prevent nee-

to lessen these concerns. However, the perceived or real pain and trauma sometimes associated with needle-based vaccination can be barriers to vaccination uptake, particularly by needle-phobic individuals [37,38]. These drawbacks, and the development of new types of vaccines, are some of the reasons driving the pharmaceutical industry and public health organizations to search for new delivery methods that are safe, cost-effective and efficient.

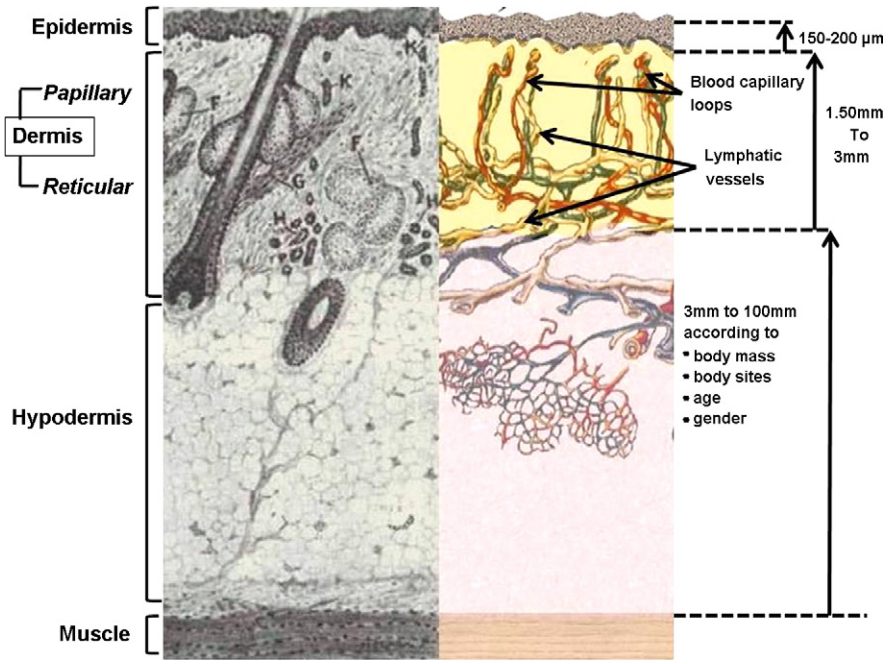
While the majority of vaccines in clinical development are envisioned as needle and syringe products, a number of research groups and vaccine manufacturers are exploring the advantages of new parenteral delivery systems as well as of mucosal and transcutaneous delivery [39]. Mucosal delivery is currently only used for live attenuated vaccines against poliomyelitis, typhoid fever (oral), rotavirus and influenza (nasal) [40,41]. Mucosally administered vaccines have a number of benefits. They eliminate the risk of transmission of blood borne diseases and needle stick injury. They can potentially be given by personnel with little medical training, which provides significant practical and cost benefits, particularly in the context of large-scale immunisation programmes in the developing world [42]. This route can also, in theory, elicit both mucosal and humoral immunity, offering advantages against diseases contracted via mucosal surfaces [43]. However, there are also a number of drawbacks. The live attenuated viruses in oral poliomyelitis vaccine (OPV) can revert to virulence, causing vaccine-associated paralytic poliomyelitis (VAPP) in the vaccinated child or their close contacts, particularly in the immuno-depressed subjects [44]. This has resulted in a shift from the use of OPV to the use of injectable poliomyelitis vaccine containing inactivated virus, especially in countries that have eliminated naturally occurring polio [45]. Oral vaccines have to overcome problems associated with poor absorption or degradation within the digestive system that may require the concomitant administration of antacids [46]. Finally, to date no mucosal vaccine adjuvant is available with the required safety and efficacy [44]. Such safety issues were encountered with an intranasal adjuvant-containing influenza vaccine that was associated with the occurrence of facial palsy [47].

3. Skin physiology and immunology

3.1. Skin anatomy

An increasing understanding of skin physiology means that this organ is now recognized as a potentially excellent site for vaccination. It is easily accessible and has both cellular and humoral immune system components. The skin is comprised of three primary layers from outside to inside: epidermis, dermis and hypodermis (Fig. 1). Vaccine delivery into these layers is known, respectively as transdermal, intradermal and subcutaneous vaccination.

The epidermis is the outermost layer of the skin and acts as a physical barrier, preventing chemicals and micro-organisms from entering the body and stopping excess body water loss. This layer is generally 50–200 μm thick, depending on the body region and has four sublayers: the outermost stratum corneum, below which is the stratum granulosum, the stratum of Malpighii or spinosum, and finally the stratum basale (or germinativium). Keratinocytes constitute approximately 90% of the epidermis; the remaining cells are melanocytes and Langerhans dendritic cells. While Langerhans cells account for only about 1% of cells, they cover nearly 20% of the surface area due to their horizontal orientation and long protrusions [48]. The epidermis does not have its own blood supply; cells in lower levels receive nutrients via diffusion from blood capillaries in the dermis. Cells form within the stratum basale and migrate through to the stratum corneum where they are sloughed off. During this process, which lasts approximately 30 days, cells become keratinised. It is the stratum corneum with its layer of keratinised cells that is so important in the skin's role as a physical barrier. The stratum corneum is also the greatest barrier to effective transdermal vaccine delivery. To be effective, it is critical that the vaccine be delivered to the Langerhans cells. This implies that a transdermal delivery method must include a system to disrupt, either physically or chemically, the stratum corneum, allowing antigens to pass through this layer and onto the Langerhans cells for antigen presentation.



The dermis lies beneath the epidermis and is comprised of collagen, elastin and reticular fibres. It is a tough, flexible and very elastic layer between 1.5 and 3 mm thick, arranged into two sublayers: the papillary dermis and the reticular dermis. The papillary dermis is the upper and the thinner of the two and consists of loosely arranged connective tissue. The reticular dermis consists of a network of horizontally running collagen fibres, connective tissue, and a very dense network of capillary blood and lymphatic vessels in which dermal dendritic cells, monocytes, polymorphonuclear lymphocytes and mast cells circulate. Lymphatic vessels drain the dermis to satellite lymph nodes. Fibroblasts are the most abundant type of cells in the dermis. Endothelial cells forming the wall of blood and lymphatic channels play a key role in the inflammatory and immune cells as well as fluid movements in dermis. Endothelial cell contribute to various physiological effects in the skin including vasodilation increased permeability, increased vasomotion, production of cytokines converting adherent leukocytes into mobile cells, angiogenesis and trafficking of antigen presenting cells, T and B effector cells [49].

The hypodermis, or subcutaneous tissue, is a layer of loose connective tissue and elastin located immediately beneath the dermis. The arteries and veins that drain the skin dermis issue from the vascular plexus located in subcutaneous tissue. When entering the skin dermal arteries form a dense network of capillary loops in the papillary dermis layer. Numerous lymphatic vessels draining the skin dermis pass through the hypodermis before reaching draining lymph nodes. The hypodermis is the main tissue for fat storage.

Anatomical variations of skin according to body site, gender, age and ethnic origin are important parameters to consider for dermal vaccination. For example, skin thickness – an essential parameter for intradermal vaccination – is known to vary significantly between different parts of the body [50–54]. In a recent study designed specifically to investigate skin thickness at the usual areas for intradermal vaccination (deltoid, suprascapular, upper abdomen and thigh) in groups of people of different age, sex and ethnic origin, skin was found to be on average 1.5 mm thick at the thigh and between 1.8 mm and 2.7 mm at the other body sites, with no major differences between the different population subgroups considered [55]. Indeed skin thickness was found to vary less between people of different body mass index, age, gender and ethnic origin than it did between different body sites on people with the same demographic characteristics [55]. The average thickness of the skin appears to remain relatively unchanged in the age range of 18–70 years [56]. Skin is thinner in women than in men by 0.06–0.2 mm, but minimal skin thickness in women is greater than 1.5 mm in all cases [55–58]. The absence of a significant effect of the ethnic origin on the skin thickness at deltoid, and suprascapular body sites has also been reported in studies in US [54] and Japan [59]. This consistency in skin thickness across people with different demographic profiles represents a major advantage over classic intramuscular vaccination as, to correctly perform an intramuscular vaccination, it is important to select the appropriate needle length based on considerations of the muscle mass of the injection site, the amount of subcutaneous fat, and the weight of the patient [52,60].

3.2. Skin and immune response

The skin generates both innate (antigen non-specific response without immunological memory) and adaptive immune responses (antigen specific response with immunological memory), Table 1. While the adaptive response is primordial in generating a response to vaccination and generally becomes more effective with each successive encounter with an antigen [63], innate immune mechanisms also play a key role as they are activated first in response to pathogen invasion or contact with foreign antigens. The key group of immune cells involved in the skin's innate immune response is dendritic leukocytes: Langerhans cells in the epidermis and dermal dendritic cells in the dermis [63–68].

In 1868 Paul Langerhans, driven by the interest in the anatomy of skin nerves, identified a population of dendritically shaped cells in the suprabasal region of the epidermis after impregnating human skin with gold salt [65]. These cells are known as antigen-presenting cells, called Langerhans cells after their discoverer. Although substantial numbers of dendritic leukocytes reside and circulate in the skin, only some of them are Langerhans cells, the majority being phenotypically different from Langerhans cells and generically called dermal dendritic cells [64]. Both Langerhans cells and dermal dendritic cells are bone marrow-derived leukocytes highly specialized in antigen-presenting properties. These cells, in association with macrophages recruited from circulating blood and infiltrating dermis tissue, are the gatekeepers of the immune systems. Compelling evidence exists that Langerhans cells and dermal dendritic cells, as members of the family of antigen-presenting cells play a pivotal role in the induction of adaptive immune response against pathogens and any other antigens and haptens which compromise the host homeostasis. The immunogenic potential of antigen-presenting cells from both epidermis and

Table 1
Innate and adaptive skin immune system

Functional components of skin immune system	Cells of the skin immune system		
	Resident	Recruited	Recirculating
Innate			
Reactive oxygens	Keratinocytes	Monocytes	Natural killer cells
Ligands Toll receptors	Endothelial cells	Granulocytes	Dendritic cells
Heat shock proteins	Langerhans cells		
Cytokines: IL-1, IL-6, TNFα			
Chimiokines: CC, CXC			
Adhesion molecules			
Neuropeptides			
Eicosanoids			
Immune tolerance: T regulator, IL-10, TGFβ			
Adaptive			
Antigen recognition and presentation	Mast cells	Mast cells	Pro-monocytes
Cytokines: IL-1, IL-6, TNFα	Macrophages	Epitheloid cells	
IL-2, IL-12, IL-18, INFα	T lymphocytes	T lymphocytes	T lymphocytes
Chimiokines: CC, CXC	Dendritic cells	B lymphocytes	
Adhesion molecules			

dermis tissues is regulated by cell surface receptors triggered by ligands secreted or presented by other somatic cells, or alternatively, by microbial products (danger or competence signals) [66]. Danger signals are represented for example by DNA rich in CpG repeats in bacteria, or other Toll-like receptor ligands [66,67]. Many of the receptor structures that sense such signals are essential components of the innate immune system. They are used to recognize molecular patterns demarking infectious nonself, as well as normal and abnormal self. The response to danger signals leads to tissue perturbation as evidenced by increased secretion of GM-CSF, TNF-α, IL-1 by keratinocytes and other skin cells. The antigen-presenting cells that pick up the antigen, process it, and re-express part of it as peptide/MHC complex on the surface are also profoundly affected by danger signals or danger signal-induced cytokine. The alterations of Langerhans cells and dermal dendritic cells include the increased expression of MHC antigens, co-stimulatory molecules, and cytokines such as IL-1β, IL-6, IL-12, as well as the enhanced emigration of these cells from the skin to the paracortical area of draining lymph nodes. At this site, the skin-derived dendritic cells provide the activation stimuli to naïve resting T cells surrounding them. This occurs in an antigen-specific fashion and thus results in the expansion of the respective clone(s) to mature into extremely potent immuno-stimulatory cells that controls the development of adaptive immunity [68]. Some evidence also exists that dermal dendritic cells that have not received such competence signals are not stimulatory, but actively down regulate or prevent potentially harmful immune responses by tolerizing T cells or by inducing T cells with suppressive properties (regulatory T cells) [69,70]. Several studies have indicated that protein or peptide delivery through the epidermis can lead to production of specific IgE due to a Th2-regulated response as well as immune tolerance status by regulatory T-cells [71–75]. As a consequence, in addition to the immuno-surveillance activity, the skin immune system secures the homeostasis of the skin integument by preventing the development of exaggerated, tissue destructive immune responses against per se innocuous moieties such as auto-antigens, allergens and haptens. Interestingly, a clinical study in healthy adults evaluating epidermal delivery of live-attenuated measles vaccine through disrupted stratum corneum relative to intramuscular route strongly suggests that resident antigen-presenting cells in epidermis were unable to boost the antibody response [76].

3.3. Skin immune response and sun exposure

It has been suggested that sun exposure may affect local or systemic immune responses through release of inflammatory mediators [80]. The question may be raised whether such effects may particularly influence responses to intradermal immunization. UV radiation below 290 nm is absorbed by the ozone layer in the stratosphere and does not reach the Earth's surface. The UVB wavelengths range from 280 to 315 nm and from 315 to 400 nm for UVA. Solar UV radiation is 95–98% UVA and 25% UVB. The most obvious clinical effects of the sun exposure are sunburn and tanning, but include more complex biological effects such as DNA photo damage, immunosuppression and vitamin D synthesis. These biological effects are radiation dose-dependent and the amount of UV radiation penetrating the epidermis and dermis is the critical factor. For instance, the stratum corneum of the epidermis is able to dissipate 90% of UVB radiation, and no more than 10% of UVB reaches the dermal-epidermal junction area. In addition, melanin present in high concentration in the epidermis acts as UV radiation filter. The biological effects of UVB on the skin immune response was actively investigated, the main changes being the depletion of Langerhans the release of pro-inflammatory cytokines such as TNF-α, IL-10, TGF-β, α-MSH and CGRP [77–80].

4. Clinical experience, techniques and devices for intradermal vaccination

Considerable clinical research has been conducted to compare the intradermal route with other routes of vaccine delivery (Table 2) and into new techniques for intradermal delivery to eliminate some of the problems associated with the methods currently available. This section will describe the available techniques, as well as those in clinical research or earlier development.

4.1. Current methods

4.1.1. Mantoux injection technique

The standard intradermal injection technique consists of stretching the surface of the skin and inserting the tip of a 27G, 3/8 in. short bevel needle attached to a plastic 1 ml disposable syringe. The needle is inserted bevel upwards, almost parallel to the skin surface and vaccine is injected slowly into the uppermost layer of the skin [81]. If placed properly, there is considerable resistance to injection and a raised papule immediately appears which can cause pain during injection. The correct placing of the needle-tip in the dermis is critical to avoid fluid injection difficulties due to inelastic skin or age-related anatomic changes [53,58,61,62,81]. This technique, introduced by Charles Mantoux over 95 years ago as a diagnostic skin test for tuberculosis disease [2] has not been pursued for the vast majority of vaccines due to its inherent difficulties. This technique is associated with a poor consistency of the injected volume, due in part to the difficulty of performing it correctly, but also to the unavoidable leakage of vaccine from the injection site, fluid wastage when filling disposable syringes and when purging the needle of air, and the large dead volume of the assembled disposable needle and syringe [82–84]. In many cases, intradermal vaccination according to Mantoux has proved to be comparably immunogenic to the comparator even at a reduced dose, due to the skin's ability to generate a strong immune response [3,27,85–91]. This comparable efficacy at lower doses suggests that intradermal injection can have considerable benefits over other injection techniques when mass vaccination is necessary, as the reduced dose means improvement of vaccine availability and of health economic ratios if an injection system that is easier to practice becomes available.

4.1.2. Bifurcated needle

While working for Wyeth Laboratories in 1965, Benjamin Rubin developed his two-pronged needle for smallpox vaccination by skin scarification by grinding the eyelet of a sewing machine needle into a fork shape. This was the first example in modern medical history of a device specifically designed to deliver vaccine intradermally. The small space between the two tines was able to hold about 2 μl of vaccine solution but only part of this volume that was actually introduced into the skin and precise control of dose delivery accuracy was not possible. The needle was jabbed into the papillary dermis skin layer, yielding a spot of blood. Bifurcated needles with features for protecting health-care workers against needle-stick injuries are commercially available.

4.1.3. Multipuncture

The percutaneous BCG delivery using single or multipuncture devices was introduced by Sol Roy Rosenthal in 1939, and developed worldwide by the Merieux Institute [92–94]. The multipuncture unit is a cylinder-like device with small needles, 1 mm

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