Microneedle patch vaccine

A potential approach for overcoming the barriers to widespread vaccination

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ABSTRACT

Vaccinations are an important means of controlling communicable diseases, especially in developing countries where patients do not have regular access to adequate healthcare. However, barriers such as cost and lack of resources are particularly problematic in the developing world and limit the adoption of vaccines. Meanwhile, in developed nations, the fear of injections contributes to the growing problem of vaccine avoidance and hesitancy. To address these barriers, a microneedle patch vaccine was recently created by Dr Prausnitz and his research team at the Georgia Institute of Technology in Atlanta, in which application of the patch to the skin allows polymer microneedles containing the vaccine to puncture the epidermis, dissolve, and elicit an immunogenic response. Research using rodent and primate models have demonstrated this technology's effectiveness, and a human clinical trial using an influenza microneedle patch vaccine is currently being conducted. Future trials are being planned for microneedle patch vaccines against measles and polio as well. This technology's nearly pain-free administration, portability, and relative ease of delivery can help address patients' apprehensions to hypodermic needles and lessen administration costs and efforts. While the microneedle patch vaccine is a promising vaccination modality that can potentially be used to overcome the barriers to vaccination, further studies will need to be conducted to determine adverse events. Also, strategies for patient education and potential legal issues will need to be addressed before widespread use of this novel vaccination modality.

INTRODUCTION

Vaccinations are an essential means of primary disease prevention on both an individual and population level, with the WHO estimating that vaccines prevent 2.5 million deaths per year.¹ However, many barriers still exist for the widespread administration of vaccinations, such as healthcare costs, resource constraints, poor accessibility, fear of needles, and concerns about adverse events. An often cited concern amongst patients of all age groups is pain with vaccine delivery.² Underutilization of vaccines poses a public health problem when herd immunity cannot be maintained. This is particularly a concern in developing countries, where the barriers to vaccination are magnified due to poor healthcare infrastructure or lack of education.¹ In order to improve the usage and acceptance of vaccines, endeavours should be made to identify ways to minimize costs and resources associated with vaccine use, and to address any fears that the public may have regarding vaccines.

Current vaccine delivery modalities include intramuscular, intradermal, and subcutaneous injections using a hypodermic needle, oral administration, and intranasal spray.^{3,4} Additionally, recent developments have been made in delivering vaccines through a transdermal route, for which techniques range from adhesive patches containing a liquid drug reservoir to chemical agents that disrupt the skin to increase drug permeation.⁵ However, these transdermal methods have not been optimized for vaccine delivery as they have been shown to cause skin irritation and prohibitively restrict the size of vaccine particles.⁵

MICRONEEDLE PATCH VACCINE

A new method of transdermal vaccine administration, called the "microneedle patch vaccine", was recently developed by Dr Mark Prausnitz and his research group to address some of the issues limiting widespread vaccine adoption. The microneedle patch vaccine is comprised of an adhesive patch the size of a postage stamp on which 50 to 100 solid "microneedles" are distributed (Fig. 1).⁶ In initial studies, the microneedles were made of stainless steel,⁶ but dissolvable polymer microneedles have since been used as they have been shown to deliver vaccine more effectively.⁷ Additionally, the dissolvable microneedles were shown to be more immunogenic than the stainless steel microneedles in mice.⁷

Figure 1. Microneedle patch containing 100 dissolvable microneedles. A 25-gauge hypodermic needle is shown on the left for size comparison. The microneedles have been magnified in the inset photo.^{8,9}

The Prausnitz research group has optimized the production of dissolving microneedles by testing microneedle strength, vaccine stability, adequate vaccine delivery, and immune response.⁷ To manufacture the microneedles, a liquid mixture containing monomeric vinyl pyrrolidone, the free radical initiator azobisisobutyronitrile, and the vaccine solution is poured into a previously-made

mold, which is then subjected to UV light for polymerization of the vinyl pyrrolidone. Afterwards, the dried array is peeled out of the mold using an adhesive patch.^{7,8,10} While this vaccine solution requires a higher concentration of antigen than standard hypodermic needle solutions, the studies have employed novel methods to produce higher titers. For example, a continuous cell lineage, Vero cells, is able to produce solutions with higher concentrations of the measles antigen for incorporation into microneedles and has been used instead of the standard chicken embryo fibroblasts.⁸

To administer the vaccine, the patch is pressed firmly onto the skin and left on for at least 10 minutes to allow the water-soluble microneedles to dissolve.⁸ The microneedles measure approximately 750 µm long, 250 µm wide at the base, and 5 µm in radius at the tip; the deep nerve endings are not reached during skin puncture to ensure nearly painless delivery.¹⁰ Following skin puncture, rapid epidermal resealing has been observed with stainless steel needles that have similar dimensions, with recovery of normal skin barrier function within 2 hours.¹¹ While epidermal healing time has not been reported in humans for the dissolvable microneedles, it has been shown that the microneedles dissolve within 10 minutes in rhesus macaques with no apparent bleeding nor swelling,⁸ and the epidermis presumably reseals shortly afterwards. After administration, the patch can simply be thrown away in regular waste as the microneedles are no longer present on the patch.⁶ Testing of the influenza vaccine in mice and the measles vaccine in rats and rhesus macaques has shown that this manner of vaccination is as immunogenic as hypodermic administration due to the proximity of immune cells to the skin.^{8,12,13} Specifically, the blood antibody titers measured daily after patch vaccine administration were comparable to those elicited by subcutaneous injection, and these titers were correlated with immunoprotective levels. While human immunoprotectivity has not yet been reported, current and future clinical trials will assess the degree of immune response elicited through the patch vaccine method.¹⁴⁻¹⁶

ADVANTAGES THAT ADDRESS THE BARRIERS TO VACCINATION

The microneedle patch vaccine offers many benefits that promise its wide implementation in the future. Firstly, the administration is quick, easy to carry out, and nearly painless. Therefore, this vaccine method can be an alternative for patients who are afraid of large needles and pain upon delivery. This generally results in a more efficient vaccination procedure. Because the microneedles dissolve into the skin to exert the vaccine's effects, leaving only the patch to be discarded, no special disposal is needed, no needle-stick injuries would occur, and there would be no risk of parenteral disease transmission. Hence, the potential for self-administration of vaccines exists, but still under the supervision of a health care provider to monitor for anaphylaxis or adverse events. A feasibility study examining patients' opinions of the microneedle patch vaccine upon self-administration showed that patients were more willing to accept vaccines using the new vaccination method versus conventional hypodermic needles.⁶ The microneedle patch vaccine could therefore address the psychological impediments of vaccine

administration.

From a financial standpoint, the mass-manufacturing process of the microneedle patch vaccine has been predicted to be of similar cost to hypodermic needles, with the exception of the initial start-up.¹² Also, compared to conventional liquid vaccines, stringent storage requirements such as refrigeration are not required, as the Prausnitz group demonstrated that the live attenuated measles microneedle vaccine patch with added preservatives (including trehalose, carboxymethylcellulose, and surfactant) met WHO standards of vaccine stability when left at room temperature for 30 days.¹² Therefore, vaccination costs may be reduced since the benefits of the microneedle patch vaccine, such as storage, maintenance of the cold chain, and disposal would reduce administration costs.¹² Furthermore, the patches are small and portable, which would facilitate transport particularly to developing countries and thus allow greater opportunity for patient access to immunization.

FUTURE DIRECTIONS

Given that the microneedle patch vaccine is a relatively new advancement, there are still concerns that will need to be addressed before this method can be used commercially. Firstly, criticism may come from anti-vaccination communities, as the dissolved microneedle chemicals, especially polymerized vinyl pyrrolidone, may be viewed as potentially dangerous foreign substances. However, polymerized vinyl pyrrolidone, which has been used as a plasma expander and an additive in pharmaceuticals, food, and cosmetics, has been shown to be non-toxic and excreted from the body.¹⁷ Nevertheless, since there have only been a limited number of studies conducted regarding the safety of the microneedle patch vaccine delivery system in humans, more research will be needed using larger sample sizes to determine the frequency of allergic or other adverse events. A phase one clinical trial for microneedle patch delivery of the flu vaccine is currently underway, using the 2014 to 2015 season trivalent inactivated influenza vaccine solution, to investigate safety and feasibility.¹⁴ Additionally, clinical trials for measles antigen are expected to start in 2017 and in the near future for polio antigen, which received a \$2.5 million grant from the Bill & Melinda Gates Foundation.^{15,16} Dr Prausnitz also founded Micron Biomedical, Inc. in 2014 to commercialize the technology.¹⁶

Additionally, administration techniques will need to be perfected. For instance, a study examining administration of the microneedle patch itself found that many subjects were not applying enough force to cause the microneedles to puncture the skin when pressing the patch onto the skin.⁶ As a solution, the same study recommended thorough education on administration techniques, as well as the use of a snap device that gives auditory feedback when adequate pressure is applied.⁶ Also, legal concerns may arise, especially for unsupervised self-administration, which would include potential injury, anaphylaxis, adverse events, and lack of documentation. Therefore, healthcare providers will need to ensure that immunization procedures are still followed when providing patients with the patch vaccine, such as communicating comprehensive information about the product, assessing for contraindications, and

judging competence.

SUMMARY

Microneedle patch vaccines promise many benefits that would make this vaccine administration technology preferable over the existing methods. Because of its ease of administration and portable nature, this modality can be used for more widespread vaccine campaigns, particularly in developing countries where patients may have difficulty accessing healthcare centres. If the upcoming trials prove successful, the microneedle patch can potentially be generalized to other vaccines or even other classes of medication. However, concerns such as safety assurance, proper education, and possible legal issues regarding self-administration need to be addressed before adopting this administration route for widespread use. Ultimately, the microneedle patch vaccine is a novel technology that presents as a potentially important tool for public health, as it may overcome some of the barriers to immunization and promote both individual and societal primary disease prevention.

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