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Review Article

Microneedle: Effective Means for Vaccination

Kazuyoshi Kaminaka[1], Chikateru Nozaki[2, *]

[1]Development Department, KM Biologics Co., Ltd., Kumamoto, Japan

[2]Department of Medical Technology, Kumamoto Health Science University, Kumamoto, Japan

Email address:

nozaki@kumamoto-hsu.ac.jp (C. Nozaki)

[*]Corresponding author

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Abstract: Vaccines have greatly contributed to the prevention of infectious diseases. Most current vaccines are inoculated by intramuscular or subcutaneous injection using syringes. These inoculation methods involve pain, bleeding, fear, needlestick accidents. One promising method that can overcome these disadvantages is vaccination using microneedles. MN materials are already FDA-approved for implantation or parenteral delivery for other applications. MNs can increase the transdermal permeability and deliver vaccine compounds including proteins, genetic materials and so on. There are several types of microneedles. Among them, a number of research and development has been carried out on coated MN and dissolving MN. The surface of coated MN is coated with the vaccine. On inserting into the skin, the vaccine is directly deposited into the epidermis or the upper dermis layer. Dissolving MNs are fabricated with biodegradable polymers by encapsulating the vaccine into the polymer. After inserting dissolving MN into the skin, dissolution takes place which releases the vaccine. Conventional influenza vaccines and universal vaccine candidates have been shown to be delivered to the body using MN and to have effective immunogenicity. DNA vaccines are simple to induce both of cellular and humoral immune response that make them attractive vaccine candidates. A disadvantage of DNA vaccines is their poor immunogenicity in intramuscular administration. Hepatitis B virus DNA has been shown to induce effective immunity by administration using MN with an adjuvant. This review introduces concrete works for microneedle vaccines against influenza and hepatitis B.

Keywords: Microneedle, Vaccine, Influenza, Hepatitis B

1. Introduction

Administration without pain, bleeding and needle-stick injury is the ideal way of vaccination. Since antigens in general vaccines are proteins, simply sticking the antigen to the skin does not penetrate from the skin. The skin is the largest organ in the human body and is designed to carry out a wide range of functions [1-3]. It has barrier properties to ensure that the underlying organs are protected from physical, chemical or microbial insults. The thickness of the epidermis varies depending on location, ranging from 60 μm on the eyelids to 800 μm on the palms. The subcutaneous fat layer, sub-cutis, subdermis or hypodermis, lies between the overlying dermis, and the underlying body constituents [4]. Its main functions are to impart physical support to the dermis and epidermis, act as a heat insulator [due to the high content of adipose tissue], and to provide nutritional support.

Most vaccines are administered via subcutaneous (SC) or intramuscular (IM) routes. Hypodermic injections are associated with pain and distress that might lead to poor patient compliance and require highly trained personnel for administration. They are associated with a risk of disease transmission due to the possibility of needle-stick injuries or reuse of contaminated needles.

SC or IM routes of application relies on the presence of dendritic cells (DCs) in the tissues that take up the antigen, process it and present it to T lymphocytes in the draining lymphoid organs. Whereas subcutaneous fat and muscle tissue contain relatively few DCs, the dermis and the epidermis are densely populated by different subsets of DCs. Consequently, antigen delivery by hypodermic injection will bypass the

skin's immune cells leading to less efficient vaccination. For this reason, the skin represents an ideal site for vaccine delivery, as vaccination at this site will evoke strong immune responses at much lower doses of antigen than intramuscular vaccines [5]. One of the most promising delivery systems is a microneedle (MN), which are needle-like structures with a length of less than 1 mm that are used to deliver drugs into the skin in a minimally invasive and potentially pain free manner [6-11]. Research and development on MNs have been conducted so far. Such works are introduced in this article.

2. Microneedle (MN)

There are mainly three types of MNs as shown in Figure 1. Hollow MNs have an empty space inside which is filled with the vaccine dispersion or solution. The surface of coated MN is coated with the vaccine. On inserting into the skin, the vaccine is directly deposited into the epidermis or the upper dermis layer. In cases of Hollow MN or coated MN, each material is divided into metal one or plastic one. Dissolving MNs are fabricated with biodegradable polymers by encapsulating the vaccine into the polymer. After inserting MN in the skin, dissolution takes place which releases the vaccine.

MN materials are already FDA-approved for implantation or parenteral delivery for other applications. By piercing the skin, transdermal permeability has been increased by as much as four orders of magnitude and shown to deliver compounds including proteins, genetic materials (e.g., oligonucleotides and plasmid DNA) and latex particles of viral dimensions *in vitro* and *in vivo* [12].

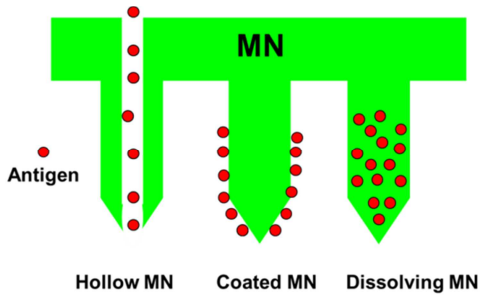

Figure 1. *Different types of Microneedles.*

3. Influenza Vaccine Delivered to Human Skin Using a Coated MN Patch

Germain J. P. et al reported a randomised, partly-blinded, placebo-controlled trial that represents the first use in humans of the MN to deliver a vaccine [13]. The material of MN used in their study is silicon of non-biodegradable polymer. Figure 2 shows the schematic of their MN vaccine. In their study, healthy volunteers received a single vaccination at day 0 by the MN coated with split inactivated influenza virus or by IM administration with split inactivated influenza virus. Their results showed that MN vaccination was safe and acceptable. All adverse events were mild or moderate. Most subjects receiving MN patch vaccinations preferred the MN vaccine compared with their past experience of IM administration. There was an increase in the geometric mean haemagglutination inhibition (HAI) titers compared to baseline for the MN patch and IM groups at day 7 and day 21, while there was no increase in HAI titer in any of placebo group. A similar pattern of responses was seen with the microneutralization assays.

They concluded that Influenza vaccination using the MN patch appeared to be safe, and acceptable in this first time in human study, and induced similar immune responses to vaccination by IM administration. They suggest that MN patch has the potential to be an effective approach for vaccination with influenza and other vaccines.

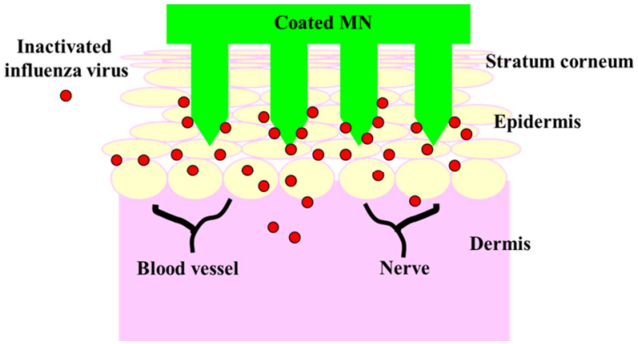

Figure 2. *Coated MN in the skin.*

4. Universal Influenza Vaccine Using a Dissolving MN Patch

Zhu et al reported the skin vaccination using biodegradable MN patch against influenza [14]. They used a dissolving MN patch fabricated from biodegradable high molecular weight materials. They designed fusion proteins by replacing the hyperimmunogenic region of Flagellin (FliC) with four tandem copies of the ectodomain of matrix protein 2 (M2e) and two subtypes of whole inactivated influenza virus vaccines (H1N1 and H3N2). M2e is a conserved surface antigen and a promising target for the development of universal influenza vaccines [15, 16]. Their MN patch encapsulated a M2e-FliC fusion protein and two types of whole inactivated influenza virus vaccines. The schematic of their MN vaccine was shown in Figure 3.

Their data showed that mice receiving this tri-component influenza vaccine via MN patch acquired improved IgG1 antibody responses with more balanced IgG1/IgG2a antibody responses and enhanced cellular immune responses, including increased populations of IL-4 and IFN-γ producing cells and higher frequencies of antigen-specific plasma cells compared with intramuscular injection. In addition, stronger germinal center reactions, increased numbers of Langerin-positive migratory dendritic cells, and increased cytokine secretion were observed in the skin-draining lymph nodes after immunization with the tri-component influenza MNP vaccine. The MN patch -immunized group also possessed enhanced protection against a heterologous reassortant

A/Shanghai/2013 H7N9 influenza virus infection. Furthermore, the sera collected from M2e-FliC MN patch -immunized mice were demonstrated to have antiviral efficacy against reassortant A/Vietnam/1203/2004 H5N1 and A/Shanghai/2013 H7N9 virus challenges. They concluded that the immunological advantages of skin vaccination with their MN patch vaccine could offer a promising approach to develop an easily applicable and broadly protective universal influenza vaccine.

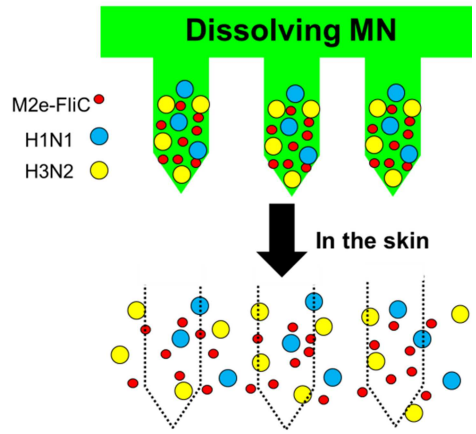

Figure 3. *Influenza Vaccine Using a Dissolving MN.*

5. DNA Vaccine for Hepatitis B Virus Using Dissolving MN Patch

DNA vaccines are simple to induce both of cellular and humoral immune response that make them attractive vaccine candidates [17-19]. DNA vaccines are based on bacterial plasmids that encode vaccine antigens driven by efficient eukaryotic promoters. DNA vaccines have many advantages over traditional vaccines with vaccine design being straightforward, generally only requiring one-step cloning into plasmid vector thereby reducing cost and production time. Plasmid DNA is stable at room temperature, avoiding the need for a cold chain during transportation. However, a disadvantage of DNA vaccines is their poor immunogenicity in intramuscular administration. Transcutaneous immunization (TCI) via MN is a promising alternative delivery route to enhance the vaccination efficacy.

Qiu Y et al [20] reported the novel dissolving MN -based TCI system loaded with cationic liposomes encapsulated with hepatitis B virus (HBV) DNA vaccine and CpG oligodeoxynucleotides (ODN) as adjuvant. CpG ODNs are short synthetic single-stranded DNA molecules containing unmethylated CpG dinucleotides in particular sequence contexts (CpG motifs). CpG ODNs coadministered with vaccines improve the function of professional antigen-presenting cells and boost the generation of humoral and cellular vaccine-specific immune responses [21].

Their dissolving MN consists of dissolving polyvinylpyrrolidone MNs array, where in the tips are loaded with antigen and adjuvant encapsulated in liposomes. Their previous data showed that the MNs could effectively be inserted into the skin and completely dissolve within 3 min [22]. The DNA for their HBV vaccine is a plasmid vector encoding the middle (pre-S2 plus S) envelope proteins of HBV. In their study, immune groups were divided into (i) dissolving MN containing only DNA;(ii) dissolving MN containing DNA and CpG ODN; (iii) dissolving MN containing cationic liposome [Lip]+DNA; (iv) dissolving MN containing Lip+DNA+CpG ODN; (v) IM immunization with Lip+DNA; (vi) IM with Lip+DNA+CpG ODN and (vii) DMA containing Lip+CpG ODN. Their results showed that dissolving MN vaccination with Lip+DNA or Lip+DNA+CpG ODN induced similar anti-HBsAg IgG titers with IM immunization. And also, their antibody subtype tests showed CpG ODN could significantly improve the IgG2a/IgG1 ratios and get a more balanced Th1/Th2 immune response. They concluded that the novel dissolving MN -based TCI system can effectively deliver HBV DNA vaccine into skin, inducing effective immune response and change the immune type by adjuvant CpG ODN.

6. Conclusion

Most current vaccines are intramuscular or subcutaneous injections with syringes. These vaccination using syringes includes the pain, bleeding and fear, needlestick accidents. Inoculation methods using MNs have been developing in order to reduce disadvantages caused by syringe injections. There are mainly three types of MNs (Hollow MN, Coated MN, Dissolving MN). Hollow MNs have an empty space inside which is filled with the vaccine dispersion or solution. The surface of coated MN is coated with the vaccine. On inserting into the skin, the vaccine is directly deposited into the epidermis or the upper dermis layer. In cases of Hollow MN or coated MN, each material is divided into metal one or plastic one. Dissolving MNs are fabricated with biodegradable polymers by encapsulating the vaccine into the polymer. After inserting MN in the skin, dissolution takes place which releases the vaccine. Conventional influenza vaccines and universal vaccine candidates have been shown to be delivered to the body using MN and to have effective immunogenicity. DNA vaccines are simple to induce both of cellular and humoral immune response. A disadvantage of DNA vaccines is their poor immunogenicity in intramuscular administration. Hepatitis B virus DNA has been shown to induce effective immunity by administration using MN with an adjuvant. Since some of MN vaccines are in clinical trials, MN vaccines are expected to be on the market in the near future.

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