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THE ROLE OF VACCINE PATCHES IN PEDIATRICS: FUTURE OR FALSE HOPE?

Weissenstein A, Villalon G, Luchter E, Bittmann S*
Ped Mind Institute, Medical and Finance Center Epe, Germany

ABSTRACT

Background

Vaccinations play an important role in prevention of diseases in children. Children often dislike going to a pediatrician, as they associate their visit with pain. A new field of research is the vaccine patch, which promises an almost pain-free vaccine application as well as further positive aspects of improved storage, distribution and safety. This paper provides an review of the effective mechanism and the advantages in the use of vaccine patches as well as their current status in clinical studies.

Methods

The literature cited was found by searching the PubMed, BIOSIS, and ISI Web of Science databases for the term ‚vaccine patches". Excluded were papers where other devices than patches with microneedles have been used for vaccination.

Results

This paper reviews data on the effectiveness of vaccine patches and other aspects such as safety, distribution and storage are described.

Conclusion

Vaccine patches have many advantages such as a safe application, a fast distribution, cost-saving in production and storage, and promise an almost painless vaccination. The effectiveness has been proved in animal studies, however, in humans there are no successful clinical studies at the moment.

INTRODUCTION

Painful vaccinations with a syringe and a needle are one of the main causes why children are afraid of visiting the doctor. At present, healthy children are vaccinated approximately twenty times in Germany with different vaccines until they are 18 years old [1]. Of all medical treatments, needles are the most unpopular devices among children [2]. In addition to the pain that is associated with the puncture, needles are furthermore the cause of anxiety, fear and behavioral disturbance [3].

Not only children are affected by needle phobia, approximately 10% [4] of the population or even more [5] are affected by fear of needles. The conventional vaccination with syringe and needle, however, is only one vaccination method of many and has many serious flaws. These are potential transmissions of blood-borne infections [6] and the reuse of needles in developing countries where approximately 30% of the vaccinations are not safe [7]. Additionally, the muscle is not the ideal location for vaccinantions, as it does not have a high density of antigen-presenting cells. As a result, new vaccination methods are developed, but many are more expensive than the conventional needle and syringe, because of the vaccine applicants themselves, the complex distribution paths and the application of the vaccine.

A different possibility of vaccination without needles is a vaccination gun. The vaccine is applied with a high pressure (approximately 85kPa) through the skin in the subcutaneous tissue. The vaccine guns appear to be unsuitable for vaccination, especially for children, and the use of vaccine guns was prohibited in 1985 on recommendation of the federal health office because of sterility reasons [8]. Another option would be the oral vaccination, which has been successfully used against poliomyelitis, though the effectiveness has subsided in the case of simultaneous occurrence of gastrointestinal infections and the ingestion of antibiotics. The oral vaccination against poliomyelitis is also not suitable for immune-suppressed patients, as the vaccine is a live vaccine, and in random cases the disease can be triggered

Corresponding Author :
stefanbittmann@gmx.de

through the pathogen [9]. That is why the use of the vaccine has not been recommended since 1999 in Europe.

That is why pediatric doctors follow the development of alternative vaccination methods with great interest. Recently, a new vaccine application method has been developed: vaccine patches with microneedles. These are postulated to be economical and have many advantages in storage and application. Furthermore, they should spare children as well as adults, the conventional and painful vaccination with a needle. These vaccine patches raise many questions concerning the clinical efficacy and if they are really a new, safer and less painful vaccination method than the conventional needle and syringe.

METHODS

We report a review of the structure, the effective mechanisms, the possible application, advantages in storage, and clinical efficacy of vaccine patches with microneedles. The literature cited was found by searching the PubMed, BIOSIS, and ISI Web of Science databases for the term *,,vaccine patch".* Excluded were papers where other devices than patches with microneedles have been used for vaccination.

RESULTS

Description and immunological classification of vaccine patch

On each vaccine patch are about 100 microneedles, which consist of polymers. They are 650 micrometers long with pointed tips and arranged in many rows. After the patch has been applied to the skin, the microneedles are inserted into the skin and they dissolve after a few minutes together with the vaccine [10]. The needles reach the stratum corneum, where a high number of antigen-presenting cells, especially the epidermal Langerhans cells and dendritic cells are located [11-13]. Because of the high number of immunoreactive cells in the skin a stronger immune response can be generated from the intradermal injection than from the conventional intramuscular injection [14]. That is the reason why a lower antigen quantity can be used in the intradermal injection than in the intramuscular injection, in order to obtain a sufficient immune response [10]. This would even be more cost-saving in the production. On the other hand this effect is still questionable, as in other recent performed studies these quantity-saving advantages have not occurred [15, 16]. In transcutaneous immunization the presence of an adjuvant is required, in order to obtain a sufficient immune response. When an adjuvant is applied together with the antigen, it gives the Langerhans cells an activation signal for maturation, so that they transform in potent antigen-presenting cells [17]. In vaccine patches polyvinylpyrrolidone (PVP) has proved to be a safe adjuvant, as it is biocompatible, mechanically stable and highly water-soluble [18]. It dissolves after application together with the vaccine and is safely eliminated from the body [18]. The effective mechanism of vaccine patches have been tested in mice. In a study carried out by Sullivan et al. one group of mice has been vaccinated against influenza with a vaccine patch, and the other group has been vaccinated with a needle and syringe. Thirty days later the mice were infected with the influenza virus. Both groups showed resistance against the virus. After three months the immunized mice were exposed again to the influenza virus. It was found that the immune system of the animals vaccinated with microneedles fought the virus better, than the animal that have been vaccinated with a needle [17]. The authors of this study concluded that the vaccination with a vaccine patch is equal to the vaccination with needle and syringe, and might even be better.

Safety, Infection, Pain and Bleeding

Microneedles are minimal-invasive application systems, which have been developed for safety reasons, as the main risks are blood-borne infections. Any lesion of the skin can be an entrance for the various microorganisms that colonize the human skin [19], and can induce local as well as systemic infections. Microneedles which are arranged in hundreds, maybe even thousands, may pose a safety risk. On the other hand the risk of an infection is determinded by many different factors: the size and number of needles, the penetration depth into the skin, the number of microorganisms that penetrate the skin, and the individual disposition of the patient. Experiences with hollow needles show that the greatest risk of infection during vaccination occurs with contaminated needles [20], but as the microneedles are sterile and only used once, there is no great risk of infection. Clinical studies show that it is extremely unlikely that through vaccine patches induced lesions, infections may occur in everyday clinical [21, 22]. However, these studies have been performed on healthy humans, and the potential risk of infection cannot be evaluated for immunosuppressed patients. Studies on humans

have shown that the vaccination with microneedles is associated with only very little or even no pain at all [23]. Detailed studies have shown, that the length of the microneedles correlates with the degree of pain.

An extension of the microneedles from 500 µm to 1,500 µm (i.e. a tripling of the length) results in a seven times greater pain in humans [24]. When instead of 5, fifty microneedles where used (i.e. a ten-fold multiplication) than the pain level only increased by 2,5-fold. In all cases the pain during the application of microneedles was many times less than during the application of a 26 Ga injection needle [10]. The epidermis does not contain blood vessels, and the superficial capillary bed is located in the upper dermis, near the dermal-epidermal connection [25]. Microneedles, which penetrate deeper than 100 µm into the skin could reach the capillaries, but even with microneedles with a length from 500-1000µm no bleeding occurred. From a length of 1,5mm, sometimes a drop of blood appears [24]. Studies that have used microneedles for penetration into the skin have shown, that no significant skin irritation, such as erythema or edema have occurred [26, 27].

Application, Logistics, Storage, Disposal, Production and Distribution

Vaccine patches look and work like a nicotine patch or sticking plaster, and they should be applied the same way. After withdrawing a protection and thus exposing the microneedles, the patch is pressed into the skin. After several minutes, the patch can be removed and disposed of. A major advantage of the vaccine patch is in particular the simplified logistics, especially in the distribution of vaccine doses during pandemic diseases [10]. In this case, specifically the speed of distribution is of utmost importance. The use of microneedles would be able to meet the demands for vaccines faster than conventional needles, as a lower dose of the vaccine can be used for the intradermal injection. Given the fact that the production of vaccines is the limiting factor for the rapid distribution during impending pandemics, the production of fewer doses of vaccine would accelerate the distribution considerably [28, 29]. The vaccine patch would further occupy less space than the conventional vaccination application system with a needle, a syringe, a vial of lipophilized vaccine and diluent vials, which can easily occupy a space more than one cubic decimeter together with their packaging. In contrast, vaccine patches need much less space. The thinnest plaster-based vaccination systems are significantly less than one cubic centimeter in size and further have a flat profile, which is well suited for storage. There is no reconstitution, no sharp, blood-contaminated waste and lower production costs. The vaccine patch is much cheaper and can be stored simultaneously in several locations [10].

DISCUSSION

Vaccine patches with microneedles have many advantages, but also disadvantages. The vaccinations are associated with less pain and may therefore improve the compliance in children and help to take away their fear from vaccinations. This would decrease the degree of psychological and physical stress, which would facilitate the visit to the pediatrician considerably. In the future the manufactures of the vaccine patch want to make it possible that the patients themselves can apply the vaccine patch [10], and in our case, the parents on their children. However, many errors can occur during the procedure. The skin must be disinfected properly in order to reduce the number of bacteria [30]. Even before the application, the patch cannot be scratched diagonally above the skin, or otherwise a big part of the vaccine dose is lost [10]. Furthermore, it must be ensured that the vaccine patch is not contaminated in any case before it has contact with the skin, or the risk of infection increases considerably. With all these possible application errors, the question remains whether or not untrained parents are able to correctly apply the vaccine patch on their children. It is more likely that they still have to visit the pediatrician, even for the reason that the vaccination must be documented correctly. However, the procedure of the vaccination with vaccine patches would shorten the time spent at the doctors, as the vaccine patch doesn't need to be filled like a syringe. The skin must only be disinfected and the vaccine patch can be applied. Parents then could later remove the patch themselves and discard it. This could lead to time savings, which would have a positive effect on the daily schedule of the pediatric practice.

What does rather not speak for the vaccine patch as a new improved application method are studies carried out by the company Intercell AG. In a randomized, placebo controlled phase III trial, carried out in 2010, 2036 European travellers to Mexico and Guatemala were vaccinated with a vaccine patch in order to reduce the incidence of diarrhea caused by E. coli. In this study no statistically significant effects were observed [31]. In

another trial carried out by Intercell the vaccine patch has failed a phase II study for avian H5N1 influenza [32]. Unfortunately these reports are only press releases and cannot be accessed in a journal.

CONCLUSION

The basic idea of the vaccine patch is the rapid distribution in the event of an influenza pandemic, as well as an almost pain-free vaccination. The vaccine patches are less expensive than a syringe and needle both in production and storage, and easier to handle. The patches show a high potential for the future, but need to be improved in the areas of security, application and, most important of all, effectiveness. The perspectives in pediatrics are very good: the vaccine patch is almost painless and therefore is tolerated much better by the children, as the vaccination with the needle. In conclusion it can be stated that the vaccine patches are indeed a good idea, but currently there are no convincing clinical studies on humans.

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