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Microneedle technology for immunisation: perception, acceptability and suitability for paediatric use.

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Abstract

Introduction

Paediatric populations have been identified as desirable end-users of microneedle technology.

Aim

The aim of this literature review was to examine published research which explores the perceptions and acceptability of microneedle technology in both patients and HCPs.

Methods

A series of keywords and their synonyms were combined in various combinations and permutations using Boolean operators to sequentially search four databases (PubMed, Web of Science, EMBASE and CINAHL). Following removal of duplications and irrelevant results, 12 research articles were included in the final literature review.

Results

The opinions of patients, parents, children and HCPs were collated. A positive perception and a high level of acceptability predominated.

Conclusion

Microneedle technology research has been focussed on demonstrating efficacy with minimal focus on determining HCP/public perception and acceptability for paediatric use, exemplified by the paucity of studies presented in this review. Commercial viability will depend on HCP/public acceptability of microneedle technology. An effort must be made to identify the barriers to acceptance and to overcome them by increasing awareness and education in stakeholder groups pertaining to the paediatric population.

Introduction

Since its invention in 1853 (1, 2), the hypodermic needle has become the most widely used medical device (3), with an estimated 16 billion injections administered worldwide (4). This form of administration permits rapid delivery of plasma levels, careful titration of narrow therapeutic index drugs and administration of those exhibiting poor oral bioavailability by avoiding first pass metabolism and the degradative environment of the enteral system. Despite efficacy and widespread use, conventional hypo-dermic needles are associated with hazardous waste, accidental needle-stick, nosocomial infection as well as phobias, pain and significant anxiety in both adult and paediatric populations alike (3, 5-7). Guided by these concerns, research has been focused on the development of alternate drug delivery methods. One such method that has emerged is delivery via microneedle technology. Microneedles are designed specifically to target the outermost, rate-limiting, skin barrier layer, the *stratum corneum*, creating transient pathways for transcutaneous delivery (8). It is reported that microneedles can facilitate drug delivery through *stratum corneum* interruption without stimulating the pain receptors or blood vessels that lie beneath (9) thus being perceived as completely painless and devoid of bleeding. This technology has been used in a wide variety of pharmaceutical applications including the delivery of drugs (10-13) and macromolecules, namely vaccines, proteins and peptides (14-25). The major microneedle approaches employed in order to achieve facilitated delivery are solid, coated, hollow, dissolvable and swellable devices (26). Solid microneedles are primarily used for skin pre-treatment (22), whereby the needles puncture the skin, temporarily increasing permeability. This facilitates the passive diffusion of drug from a reservoir, typically in the form of a patch (26). Coated microneedles pierce the *stratum corneum*, the drug layer dissolves and the active is deposited in the skin (22, 26). Dissolvable microneedles are polymer based; the drug is incorporated into the formulation and is released as the system dissolves (22, 26). Hollow microneedles facilitate drug diffusion (22), via a method of intradermal injection that is similar to that of conventional parenteral delivery. Finally swellable micro-needles rapidly take up interstitial fluid upon skin insertion to form continuous, unblockable, hydrogel conduits from attached patch-like drug reservoirs to the dermal microcirculation (27). In spite of promising results, the commercial success of microneedle technology will depend on end-user acceptability. Acceptability refers to determining how well an intervention will be received by the target population and the extent to which a new intervention or its components may meet the needs of the target population and organisational setting (28). Interventions can often be developed without sufficient understanding of how the target population will embrace its activities (28). A formulation with poor patient acceptability will affect compliance, prescribing practices and ultimately commercial viability (29) thus the European

Medicines Agency (EMA) has recommended that acceptability studies form an integral component of pharmaceutical development.

Aim

The aim of this literature review was to examine published research which explores the perceptions and acceptability of microneedle technology in both patients and HCPs. A particular focus was placed on the amenability of this technology for use in the paediatric population, as children have been identified as desirable end-users (9).

Methods

Search strategy

Keywords and their synonyms or related terms were chosen which define the important concepts of the search. These included ‘acceptability’; ‘acceptance’; ‘perception’; ‘microneedle’; ‘paediatric’; ‘child’; ‘children’; ‘vaccination’; ‘immunisation’; ‘healthcare’; ‘public’; ‘parent’ and ‘guardian’. These keywords were combined in a variety of different permutations and combinations using the Boolean operators AND and OR. The same search was applied to four databases (PubMed; Web of Science; EMBASE and CINAHL), using Google as a search engine. No restrictions or advanced search filters were applied to the database searches. The search was repeatedly conducted from 6th October 2014 to 16th January 2015.

Results

The initial search across the chosen databases yielded 61 results. Following removal of duplications; 34 results remained. Table 1 summarises the inclusion and exclusion criteria applied by the author.

Table 1 Literature search inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Related to the perception and acceptability of microneedle technology Published in English language Human subjects	Not related to the perception and acceptability of microneedle technology Related only to microneedle technology No abstract available Only abstract available Literature reviews Conference proceedings

Eleven of these results were excluded based on the irrelevance of their title and/or abstract. The remaining 23 results were assessed in full and their relevance to the query was determined. This process returned nine relevant results and revealed a further three results that had not been included in the initial search. Therefore the final literature review included 12 results (Figure 1).

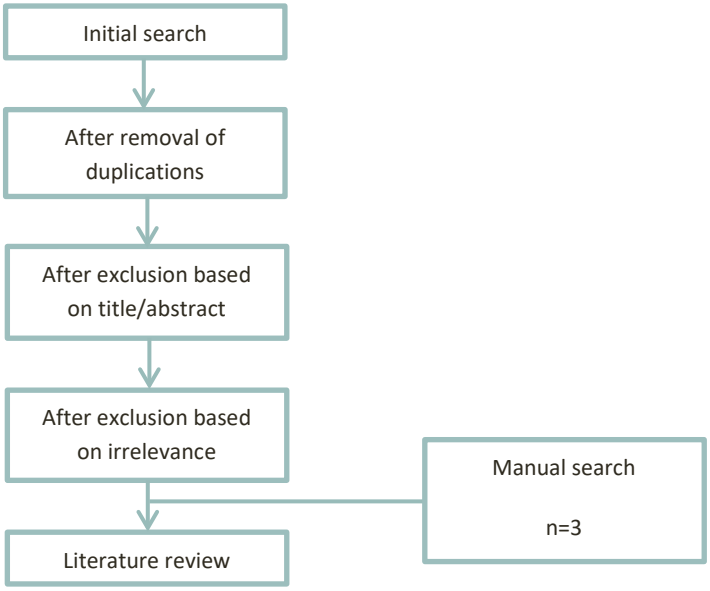


Figure 1 Literature search results

Discussion

The purpose of this review was to collate the literature which examined the perception and acceptability of microneedle technology for use in paediatrics. The literature search yielded 12 results directly related to the research query. Eight of the search results involved the actual administration of microneedle technology while the remaining four involved the hypothetical discussion of the technology. There are several methods to assess acceptability, both qualitative and quantitative. Popular and effective qualitative research methods include interviews and focus groups. These provide considerable opportunity for discussion between the researcher(s) and the target population. They also permit the researcher to probe topics as they emerge naturally in conversation, resulting in an in-depth understanding of forces that may impede or facilitate the intervention. During an interview, the interviewer engages an individual in a discussion about the proposed intervention. The individual may represent a member of the target population or an organisational representative with the experience to knowingly assess the acceptability of the intervention. Focus groups have been described as one of the most widely used qualitative research tools in the applied social sciences (28, 30), useful for designing healthcare interventions, pre-testing intervention materials, and establishing acceptable intervention implementation procedures. Interview techniques were used in three of the research papers presented here (31-33) and focus group methods were used in a further three (9, 31, 34). Focus groups are advantageous as they permit and facilitate a collective brainstorming, resulting in a "synergistic group effect" (28). In addition, focus groups are more cost effective in both time and resources. Quantitative research methods, to determine acceptability, were also used in several of the research papers presented here. The primary method of quantitative research was the use of questionnaires (8, 9, 32, 33, 35-40). Several of the papers employed previously validated questionnaires, for example Modified Theory of Reasoned Action (35), Vaccinees' Perception of Injection (40) and McGill Pain Questionnaire-Short Form (8), while the remainder developed questionnaires for the purpose of their research.

Perception and acceptability of microneedle technology

Eleven of the studies reported a positive response to microneedles with only one study reporting the contrary (36). Several recurring themes emerged which appeared to positively guide acceptability. These included; a perceived or actual reduction in pain associated with microneedle technology (8, 9, 31-35, 37-40); ease and convenience of administration (9, 32-35, 37-39); potential for self-administration (9, 34, 35) and attractive visual appearance (9, 31, 34, 37, 39). Conversely, several barriers to acceptability were identified; unfamiliarity with the technology (9, 31, 34); allergic potential (31, 34) and the inclusion of the term 'needle' in the name of the product (34). Research and development, particularly for paediatric markets, should focus on these barriers and strive to remove

them through patient education, the development of a hypoallergenic delivery system and the adoption of novel nomenclature e.g. ImmunPatch®, to eliminate the negative connotations associated with the term 'needle'.

It is also important to consider HCP acceptability of microneedles. It has been demonstrated that the majority of patients will reserve the ultimate healthcare decision for their HCP (31). Five of the papers presented in this literature review included the opinions of 711 HCPs (9, 32, 33, 38, 39). 90.65% (n=644) of those HCPs included declared a positive response to microneedle technology, with 76.37% (n=543) expressing preference for microneedle technology over conventional administration. Perceived benefits were similar to those mentioned by the general public, such as increased patient acceptability, especially in the needle-phobic (9, 38, 39) but HCPs acknowledged additional benefits such as improved immunogenicity and seroprotection (38, 39) and a reduced risk of needle-stick injury (9). However, several barriers to acceptability were acknowledged by HCP: risk of cross-contamination and an inability to ensure accurate delivery on microneedle application (9). Significant efforts have been made to address these concerns with devices based on biodegradable dissolving formulations receiving increased attention. Once inserted into the skin, these polymeric systems will either rapidly dissolve or undergo such morphological changes that disable effective skin penetration if applied to another individual (41, 42), thus preventing intentional or accidental cross contamination. An effort must be made to formulate the inclusion of a delivery indicator without significantly increasing the cost of production.

Perception and acceptability for use in immunisation

Vaccines are a key contributor to public health (43). Despite repeatedly demonstrating cost-effectiveness, the WHO has estimated that vaccine spending accounts for only 2–3% of the total pharmaceutical market. Total costs of providing immunisation services are divided into capital and recurrent costs (44, 45). Capital costs are identified as items that last longer than one year and are therefore incurred every few years rather than annually. Important capital costs for immunisation services are associated with cold chain equipment vehicles. Recurrent costs are those items consumed during the year, warranting regular purchase. Recurrent costs include the vaccines themselves and training activities (44). In recent years, the global vaccine market has undergone rapid growth. The impetus for this changing status is a combination of improved profitability with the development of 'blockbuster vaccines', defined as those with US sales of at least one billion dollars (46), such as Pfizer's Prevnar7® and Prevnar 13®, GSK's Rotarix® and MSD's Rotateq®, new funding opportunities with government grants and public–private partner-ships (43), and new manufacturing techniques, namely microneedle technology.

Vaccine delivery to the skin is a logical approach (26). The skin is an immunogenic organ, housing a high concentration of professional antigen presenting cells (47). This permits the induction of a strong immune response upon antigenic challenge (47). For this reason, microneedles are especially attractive for immunisation. They have demonstrated a compatibility with live, inactivated and subunit vaccines (12, 13), the ability to induce comparable and, in some cases, improved immunogenicity when compared to conventional vaccination (23-25, 48), coupled with significant dose sparing characteristics (25, 47). Microneedle-mediated vaccination could potentially reduce both the capital and recurrent costs associated with conventional immunisation programmes: their thermostability eliminates cold-chain transportation requirements (17, 20, 21) and their potential for self-administration could reduce the requirement for trained personnel to administer the vaccine. There are currently 12 clinical trials at various stages involving the delivery of vaccines using microneedle technology. Ten of these have been completed; one is actively recruiting, while the other has completed recruitment. Eleven of the 12 clinical trials involve vaccine delivery using hollow microneedles (Soluvia®, MicronJet®), while the remaining trial involves delivery using a dissolvable microneedle patch. Vaccine targets under trial include varicella zoster, polio and influenza (49). It is not possible to discuss vaccination without mentioning influenza. It is estimated that 5–10% of adults and 20–30% of children are infected with influenza globally per annum. Influenza vaccination is one of the most effective methods to prevent infection or complications from illness, providing approximately 70–90% protection against clinical disease in healthy adults aged 18–59, provided there is good correlation between the vaccine antigens and circulating viral strains (27). The requirement for re-vaccination on an annual basis as a result of viral antigenic shift and drift explains the popularity and commercial advantage of influenza vaccine development. This review presents the results of a first-in-humans study of microneedle patch acceptability for self-vaccination against influenza (35). In this study, etched, stain-less steel microneedles were mounted on adhesive foam backing. When this self-administered microneedle patch was offered to participants as an alternative to conventional vaccination, intent to vaccinate increased from 44% at baseline to 65%. This review also highlights the success of Intanza®, a trivalent, inactivated influenza vaccine that is delivered intradermally with the world's first proprietary microinjection system, Soluvia®. This system features a 30 gauge hollow microneedle designed for perpendicular administration into the intradermal space. The microneedle is pre-attached to a delivery system that limits the depth of insertion to 1.5 mm from the skin's surface. The needle is attached to a glass syringe prefilled with the vaccine dose and a needle shielding system that covers the needle post injection (50). The hollow microneedle within this system is 10–16 times shorter and 40% thinner than the conventional needles used for IM vaccinations (50). In addition, the microinjection system allows the precise administration of 0.1ml (50). The integrated needle-shielding

system is manually activated immediately after vaccination, minimising the risk of needle-stick injury, contamination and illicit re-use (50). Comparable acceptability studies of Intanza® have been undertaken in European countries such as the United Kingdom, France, Germany, Belgium, Spain, Czech Republic and Turkey as well as Australia and Argentina, compiling the opinions of 13,518 participants and 680 general physicians. Of the 10,740 adults that were vaccinated by Intanza®, 96.6% (95–98%) declared they were "satisfied" or "very satisfied" and 93.7% (85–99%) indicated that they would prefer to be vaccinated by this method, if given a future choice. The latter statistic is particularly significant as it provides an indication of potential uptake associated with microneedle-mediated influenza vaccination. Vaccination rates remain below the targeted coverage rate of 75% as recommended by the European Centre for Disease Prevention and Control. Many reasons have been hypothesised to explain this low vaccination uptake, including a low perception of risk, a general lack of accurate information about influenza and vaccination, a fear of possible side and perceived side effects and issues of cost, availability and convenience. This literature review has highlighted how microneedle technology using either a patch system (35) or the microinjection system Soluvia®, has the ability to ameliorate several of these concerns, exemplified by the fact that 30% of previously unvaccinated participants were willing to be vaccinated when offered this technology (35).

Perception and acceptability for use in paediatrics

In their exploratory study, Birchall *et al*. captured the views of the eventual end-users of microneedle technology (9). Focus groups comprising members of the public and HCPs were convened. In all seven focus groups, microneedle technology was identified as being "good for children". Questionnaires were further used to substantiate the outputs from the qualitative focus groups. This questionnaire revealed that 92% of public respondents agreed that microneedles would be ideal for the administration of medicines to children. Three of the papers presented in this review explored the use of microneedles in the paediatric population (31, 34, 36). One study explored children's views on microneedle use as an alternative to blood sampling and reported a positive response (34). Similarly, a second study assessed the views parents of premature babies on microneedle-mediated monitoring as an alternative to blood sampling and once again reported a positive response (31). A third study explored parent's attitudes toward multiple vaccinations at a single visit, with several alternate methods, including a microneedle device. This study reported that the microneedle device, MicronJet®, was not perceived as better than the conventional syringe (36). While this system is composed of four 0.6 mm hollow silicon microneedles, it is attached to a standard syringe barrel thus resembling a conventional vaccine system. This arrangement may explain the reduced acceptability reported in this study. Vaccination is one of the most common causes of iatrogenic pain in the paediatric population (51). This pain is a source of distress for children and their guardians and can

lead to pre-procedural anxiety, needle phobia in later life, mistrust in HCPs and healthcare avoidance, including non-adherence with vaccination schedules (52). While several techniques have been employed with varying success to manage pain during paediatric injections (topical anaesthetic, music distraction, oral distraction in infants, positioning techniques and pH alteration), the ability of microneedles to eliminate pain on injection is a significantly desirable attribute (31). In Ireland, the Health Service Executive (HSE) recommends 15 vaccinations (16 for females), to be administered from birth to approximately 14 years of age. Current vaccination practices typically involve administration of two or three vaccines concomitantly at a single visit. Research has demonstrated that the most notable reason influencing a guardian's comfort level with the maximum number of injections per visit for their child was avoiding too much pain and discomfort (53, 54). Therefore, there is a considerable commercial market for microneedle-mediated childhood immunisation. However, similar to other areas of medical research, the industry remains hesitant to invest in paediatric vaccines given the significant ethical implications associated with this special population. While the development of microneedle-mediated childhood vaccination programmes is a logical goal, microneedle technology could also be used in specific subgroups of the paediatric population to reduce treatment burden. For example, Gupta *et al*. concluded that insulin delivery using hollow micro-needles in children with Type 1 diabetes was less painful and had a more rapid onset of action compared to conventional administration (14, 55). Similarly Norman *et al.* demonstrated that intradermal insulin delivery using a hollow microneedle device resulted in less insertion pain and faster onset and offset of action in children and adolescents, suggesting that this reduction in pain may improve compliance with insulin delivery (56). Therefore, while the benefits of microneedle technology are multi-fold, their dose sparing characteristics, thermostability and reduced potential for needle-stick, pale in comparison to their ability to reduce pain when considering the paediatric population.

Conclusion

The purpose of this review was to determine the perception and acceptability of microneedle technology. Research in recent years has focussed on successfully demonstrating the efficacy of the technology with minimal focus on determining acceptability, as demonstrated by this review. The benefits of microneedle technology in vaccination, especially in the paediatric population are glaringly apparent. However, commercial viability will depend on acceptability of this technology by the primary stakeholders: parents who will decide the vaccination method and HCPs who will decide the vaccination mode. Therefore, research ought to focus on increasing awareness of the technology and promoting education in these stakeholder groups.

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