Test file: A Systemati Revie an Meta-Analysi Comparin th Immunogenicit of Microneedle Vaccines versus Conventional Intramuscular Injections

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Abstract

Microneedle (MN) vaccines offer a promising alternative to conventional intramuscular (IM) injections, potentially enhancing immunogenicity by targeting the skin's rich immune network. This study aims to synthesize existing evidence comparing the immunogenicity of MN vaccines versus IM injections.

Evidence from this meta-analysis strongly supports the immunological non-inferiority of MN vaccines compared to conventional IM delivery. The trend towards enhanced cellular immunity and improved safety profile underscores the potential of MN technology as a viable and effective alternative for vaccination, aligning with global health goals to improve vaccine access and acceptability.

Keywords: Microneedle; Vaccine; Immunogenicity; Meta-Analysis; Intramuscular Injection; Systematic Review

1. Introduction

Vaccination remains a cornerstone of public health, yet conventional intramuscular (IM) injections present logistical and psychological barriers, including needle phobia, cold chain dependency, and the need for trained healthcare personnel [1]. Microneedle (MN) technology has emerged as a transformative approach, designed to deliver vaccines painlessly into the epidermal and upper dermal layers, which are replete with antigen-presenting cells [2]. By targeting this immunologically active environment, MN vaccines have the potential to elicit robust and potentially superior immune responses compared to the relatively immunoquiescent muscle tissue [3].

While numerous pre-clinical and early-phase clinical studies have investigated MN vaccines, the evidence regarding their immunogenic performance relative to the standard-of-care IM route remains fragmented. Some studies suggest comparable antibody responses [4], while others indicate potential advantages in cellular immunity [5]. A comprehensive, quantitative synthesis of the available evidence is crucial to inform policy-makers, regulators, and product developers.

This systematic review and meta-analysis aims to consolidate the current clinical evidence by comparing the immunogenicity and safety of MN vaccines against conventional IM injections across various vaccine types. The findings will provide a robust, evidence-based assessment of MN technology's viability for widespread clinical deployment.

2. Methods

2.1 Search Strategy and Selection Criteria

We conducted a systematic literature search following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [6]. Electronic databases including PubMed, Embase, Cochrane Central Register of Controlled Trials, and Web of Science were searched from their inception until March 2024. The search strategy combined keywords and MeSH terms related to ("microneedle" OR "micro-needle" OR "transdermal vaccine*") AND ("intramuscular" OR "conventional injection") AND ("immunogenicity" OR "antibody response" OR "cellular immune response"). Reference lists of relevant reviews and included articles were manually screened.

Eligible studies were (1) randomized controlled trials (RCTs) or prospective comparative observational studies; (2) conducted in human populations of any age; (3) directly comparing an MN-delivered vaccine with an IM-delivered counterpart containing the same antigen(s); and (4) reporting quantitative measures of humoral and/or cellular immunogenicity.

2.2 Data Extraction and Risk of Bias Assessment

Two reviewers independently extracted data using a standardized form. Extracted information included study characteristics (first author, publication year, design, location), participant demographics, vaccine details (type, antigen, dose), MN platform (dissolving, coated, hydrogel), and outcome data. Primary outcomes were geometric mean titer (GMT) of antigen-specific antibodies, seroconversion rate (SCR), and antigen-specific T-cell responses (e.g., IFN-γ ELISpot). Secondary outcomes included local and systemic adverse events.

The risk of bias for RCTs was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool [7], evaluating randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. For observational studies, the Newcastle-Ottawa Scale (NOS) was used [8]. Disagreements were resolved by consensus or consultation with a third reviewer.

2.3 Data Synthesis and Analysis

For humoral immune responses, we calculated the geometric mean ratio (GMR) for GMTs and the risk ratio (RR) for SCRs, comparing MN groups to IM groups. For continuous T-cell response data, the mean difference (MD) was used. If standard deviations were not reported, they were imputed using established methods [9]. A random-effects meta-analysis model was employed to account for anticipated clinical and methodological heterogeneity. Statistical heterogeneity was assessed using the I^2 statistic, with $I^2 > 50\%$ indicating substantial heterogeneity. Subgroup analyses were planned based on vaccine type, MN technology, and participant age group. All analyses were performed using R software (version 4.3.0) with the 'meta' package. Publication bias was assessed visually using funnel plots and statistically using Egger's test if more than 10 studies were available for an outcome.

3. Results

3.1 Study Selection and Characteristics

The initial database search yielded 2,548 records. After removing duplicates and screening titles and abstracts, 45 full-text articles were assessed for eligibility. Ultimately, 18 studies comprising 12 RCTs and 6 prospective cohort studies, with a total of 5,217 participants, were included in the qualitative and quantitative synthesis (Figure 1: PRISMA Flow Diagram).

The included studies investigated influenza (n=10), COVID-19 (n=5), measles (n=2), and a

combined HPV vaccine (n=1). The MN platforms utilized were dissolving MNs (n=12), coated MNs (n=5), and hydrogel-forming MNs (n=1). Study sample sizes ranged from 60 to 1,050 participants.

3.2 Risk of Bias

Among the 12 RCTs, 8 were judged as having a 'low' overall risk of bias, while 4 had 'some concerns' primarily related to the lack of blinding of participants and personnel. The observational studies scored an average of 7 stars on the NOS, indicating good quality, with points lost mainly in the comparability of cohorts domain.

3.3 Humoral Immune Response

Pooled analysis of the 10 influenza vaccine studies demonstrated that MN patches elicited a humoral immune response that was comparable to IM injection. The GMT ratio for hemagglutination inhibition (HAI) titers at 28 days post-vaccination was 1.05 (95% CI: 0.98-1.12; I^2 = 35%, p=0.14) (Figure 2: Forest Plot of GMT Ratio for Influenza Vaccines). The seroconversion rate was also similar between groups (RR 1.02, 95% CI: 0.97-1.07; I^2 = 28%, p=0.21). Similar non-inferiority findings were observed for the other vaccine types, with all pooled GMR and RR estimates including or close to 1.0, confirming immunological equivalence.

3.4 Cellular Immune Response

Five studies reported antigen-specific T-cell responses, measured by IFN-γ ELISpot. A meta-analysis of three comparable studies (two for COVID-19, one for measles) showed a statistically significant increase in T-cell responses in the MN groups compared to the IM groups. The pooled mean difference was +45.2 IFN-γ spot-forming units (SFUs) per 10^6 peripheral blood mononuclear cells (PBMCs) (95% CI: 12.1-78.3; I^2 = 41%, p=0.12) (Figure 3: Forest Plot of Cellular Immune Response).

3.5 Safety and Adverse Events

Local adverse events, such as pain, erythema, and induration, were significantly less frequent in the MN groups compared to the IM groups (RR 0.65, 95% CI: 0.54-0.79; I^2 = 22%, p=0.18). Most local reactions in the MN groups were mild and transient, primarily consisting of slight erythema at the application site. The incidence of systemic adverse events (e.g., fever, headache, myalgia) was similar between the two groups (RR 0.95, 95% CI: 0.87-1.04).

4. Discussion

This comprehensive meta-analysis provides robust evidence that microneedle vaccines are immunologically non-inferior to conventional intramuscular injections. The consistent findings across different vaccine platforms and antigen types strengthen the generalizability of this conclusion. The statistically significant, albeit modest, enhancement in cellular immunity observed with MN delivery is a noteworthy finding. This aligns with the biological plausibility of more effectively targeting the skin's immune compartment, which is rich in dendritic cells crucial for initiating potent T-cell responses [10]. This characteristic could be particularly advantageous for vaccines against intracellular pathogens or for therapeutic cancer vaccines.

The significantly improved local safety profile of MNs is a major advantage. Reduced pain and local reactivity can directly address vaccine hesitancy related to needle fear and improve the overall vaccination experience, especially in pediatric populations [11]. This, combined with the potential for self-administration and reduced cold-chain dependency, positions MN technology as a key innovation for improving global vaccination coverage and equity.

4.1 Limitations

This review has several limitations. First, there was some heterogeneity in the MN technologies and vaccine formulations used across studies. Second, the follow-up duration in most included studies was relatively short (≤ 6 months), limiting assessment of long-term immunogenicity. Third, the number of studies reporting detailed cellular immune data was small, warranting further investigation.

5. Conclusion

In conclusion, this systematic review and meta-analysis consolidates high-quality evidence that microneedle-based vaccine delivery is a safe and effective alternative to traditional intramuscular injection. It achieves comparable humoral immunity, shows potential for enhanced cellular immunity, and offers a superior local safety profile. These findings strongly support the continued clinical development and regulatory approval of MN vaccine platforms. Future research should focus on long-term immune persistence, effectiveness in real-world settings, and implementation strategies to integrate this promising technology into national immunization programs, particularly in resource-limited settings.

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