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Randomized controlled study of fractional doses of inactivated poliovirus vaccine administered intradermally with a needle in the Philippines☆

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SUMMARY

Objective: Comparison of a fractional inactivated poliovirus vaccine (IPV) dose administered intradermally (ID) to a full dose administered intramuscularly (IM).
Methods: Healthy Filipino infants were randomized to receive IPV as either a fractional ($1/5^{th}$) dose ID by needle injection or a full dose IM at 6, 10, and 14 weeks and a booster at 15–18 months of age. Pre- and post-vaccination anti-polio 1, 2, and 3 titers were estimated. Adverse events were monitored throughout the study.
Results: Following primary series vaccination, anti-polio 1, 2, and 3 titers were ≥8 (1/dil) in 99–100% of participants, and the ID route was non-inferior to the IM route. Depending on the study group, antibody persistence was detected in 83–100% of participants, and the booster dose resulted in a strong anamnestic response in all groups. The incidence of adverse events in each group was similar, except for injection-site erythema (higher in the ID group).
Conclusions: Primary series and booster vaccination of a fractional IPV dose administered by the ID route was highly immunogenic and well tolerated. These data confirm the medical validity of using fractional ID doses of IPV. The programmatic feasibility of implementing affordable mass vaccination programs based on this delivery mode has yet to be established.

1. Introduction

The oral poliovirus vaccine (OPV) has been an important tool in moving towards the World Health Organization (WHO) goal of global eradication of poliomyelitis.[1] However, its use is linked to the occurrence of vaccine-associated paralytic poliomyelitis (VAPP), with several recent outbreaks due to circulating virus-derived polioviruses (cVDPV) having been identified in countries using OPV.[2,3] In 2007, the Advisory Committee on Polio Eradication recommended that efforts should be made to develop affordable inactivated poliovirus vaccine (IPV) as one of the alternatives towards discontinuation of OPV that would be practical for use in low-income settings.[4] Currently, numerous cost-reduction approaches are being promoted by the WHO and are being evaluated, including reduction in the number of administrations (reduced schedule), reduction in the antigen content by use of adjuvants, and optimization of vaccine production processes or use of poliovirus seed strains that are less infectious or not infectious at all.[5] In addition, intradermal delivery of a reduced dose of IPV is envisaged as a way to reduce the cost of the polio vaccine. While such a dose-reduction approach has previously been validated in terms of immunogenicity for numerous vaccines,[6–8] its proof-of-concept and programmatic feasibility in polio vaccination with modern IPVs has not been fully established.

The first reports of the immunogenicity of IPV administered intradermally (ID) in adults and children were by Salk in 1953.[9,10] Soon after the availability of the first commercial IPVs in 1955, several European and American vaccination programs relied for a while on vaccinations with IPV administered ID by the Mantoux technique (using a needle).[11–17] Later, with the availability of the modern IPV (the so-called enhanced-potency IPV), three separate proof-of-concept studies were carried out in India in the 1990s, in which a fractional dose of IPV administered by the ID route demonstrated that one-fifth of the intramuscular (IM) volume is immunogenic when delivered ID with needles. None of these studies, however, was randomized versus IM.[18–20] ID administration by the Mantoux technique has several disadvantages, including the inability to precisely determine the volume of the administered vaccine due to leakage at the site of injection, the necessity for training and skill, and the time needed to perform the injection. The development and use of multi-use nozzle jet injectors (MUNJIs) has been tainted by subject-to-subject blood-borne contamination. Now the envisaged approach is to use

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disposable syringe jet injectors (DSJIs), with either disposable, pre-filled syringes to be inserted in the injectors, or disposable syringes that are inserted into the injector device for administration after filling at the time of use from a vaccine vial presentation.[21] Various manufacturers are currently developing affordable DSJIs.

Recently, the WHO sponsored two studies in Cuba and in Oman with two different IPV vaccines used with two different schedules (6–10–14 weeks in Cuba and 2–4–6 months in Oman).[22,23] The vaccines were administered either ID using a DSJI filled at the time of use (Biojector® 2000 (Bioject), customized for an ID administration) or by IM route using a regular syringe and needle. The primary objective of these WHO-sponsored studies was to demonstrate non-inferiority in terms of seroconversion for the ID route compared to the IM route. Although both studies demonstrated clinically relevant immunogenicity of the vaccines following ID administration, non-inferiority was not demonstrated in the Cuban study. The overall response (seroconversion and median titers) was lower for the 6–10–14 week schedule compared to the 2–4–6 month schedule, and lower in the ID groups compared to the IM groups.

To complete these recent investigations, we conducted a randomized controlled trial in the Philippines to compare the primary series and booster immunogenicity of IPV by ID administration using the Mantoux technique to the IM route when used with the most challenging (least immunogenic) schedule (i.e. at 6–10–14 weeks of age – the Expanded Programme on Immunization (EPI) schedule). The ID route remains unlicensed as a route of administration for polio vaccine, and the primary objective of the primary series part of our study was to assess the non-inferiority of the fractional dose of IPV administered ID in comparison to the full dose administered IM, in terms of seroprotection (percentage of subjects with antibody titers $\geq$8 (1/dil)), using the non-inferiority definition used by most National Regulatory Agencies (NRAs) for licensure purposes, defined as the lower limit of the two-tailed 95% confidence interval (CI) of the observed difference between the fractional ID group versus the full dose IM group being $<$5 percentage points. The immunogenicity endpoints for the booster part of the study were to check for antibody persistence a year after the primary vaccination and to describe the immunogenicity and safety of the booster dose administered ID or IM. We also assessed the safety and reactogenicity of IPV administration by both routes.

2. Materials and methods

2.1. Study design and participants

The primary series vaccination study was a randomized, controlled, open-label, phase II study conducted at the University of the East Ramon Magsaysay Memorial Medical Center, Manila, Philippines. Healthy infants were randomized to receive either a fractional (1/5th of the IM volume) dose of IPV by the ID route or a full dose via the IM route, as per the EPI schedule at 6, 10, and 14 weeks of age. Participants were excluded either at the time of screening (0 to 7 days after birth, at which time the study was explained) or at the first vaccination (6 weeks of age) if they had illnesses or health issues (established by clinical examination and/or medical history), which could have interfered with the study, or a congenital or acquired immunodeficiency, or human immunodeficiency virus, hepatitis B antigen, or hepatitis C seropositivity.

Study participants who completed the primary vaccination series and returned for the booster study then received the same fractional ID or full IM dose of IPV as was received in the primary series.

Study protocols for the primary series study and the booster vaccination study were approved by the ethics committee at the study center and the studies were conducted in accordance with the Edinburgh revision of the Declaration of Helsinki, Good Clinical Practice (GCP), International Conference on Harmonisation (ICH) guidelines and the European Directive 2001/20/EC for clinical studies conducted outside the European Union. A signed informed consent form was obtained from the parent or other legally acceptable representative of each participant before any study procedure was performed.

2.2. Study vaccines and administration

The IPV vaccine, IMOVAX® Polio, batch numbers A0190-1 and A0427-2 for the primary vaccination and batch numbers D0051-1 and B0281-5 for the booster vaccination, was manufactured and supplied by Sanofi Pasteur, Lyon, France. The vaccine for ID administration was supplied as 5-ml vials, with each 0.1-ml dose containing 8, 1.6, and 6.4 D antigen units of types 1, 2, and 3 poliovirus, respectively. The vaccine for IM administration was supplied as 0.5-ml pre-filled syringes, with each dose containing 40, 8, and 32 D antigen units of types 1, 2, and 3 poliovirus, respectively. The fractional dose was administered ID in the right upper arm with a syringe mounted with a 13-mm 30-gauge needle, and the full dose was administered IM in the anterolateral area of the right thigh with a syringe equipped with a 16-mm 25-gauge needle.

Concomitantly in the study, participants received, free of charge, commercially available diphtheria–tetanus–whole-cell pertussis–*Haemophilus influenzae* type b (DTwP–Hib; 2, 4, 6 months of age) and hepatitis B (0, 1, 6 months of age) vaccines $\geq$10 days before or after the IPV vaccination (not assessed as part of our study).

2.3. Immunogenicity assessment

During the primary series vaccination, blood samples for the immunogenicity assessments were collected just before the first dose and 1 month after the third dose. For the booster study, blood samples were collected just before the booster dose and 1 month later.

The seroneutralization assay to determine the anti-polio 1, 2, and 3 antibody titers was conducted by Focus Diagnostics, Inc.[24] This assay measures the viability of poliovirus-sensitive Vero cells that are exposed to neutralizing antibodies in the serum sample mixed with poliovirus strains 1, 2, and 3, which act as a challenge virus. For this trial, wild-type poliovirus strains 1, 2, and 3 (Mahoney, MEF-1, and Saukett, respectively) were used instead of the Sabin strains used by most laboratories because of containment concerns. The Karber method was used to determine the serial dilution that neutralized 50% of the challenge virus. Results were expressed as titers (1/dil). The lower limit of quantification for the assay was 4 (1/dil).

The primary endpoint for the primary series study was the seroprotection rate (% of subjects with anti-polio antibody titer $\geq$8 (1/dil)) 1 month after primary series, with secondary endpoints being the geometric mean titer (GMT) for anti-polio 1, 2, and 3 in each group. In addition, as a post-hoc analysis to make the results of this study comparable with the two WHO-sponsored studies, the seroconversion rates were estimated descriptively for both the primary series and booster vaccinations. Seroconversion was defined as a $\geq$4-fold increase in post-primary series antibody titers over the expected titer at that time, calculated taking into account the decline of maternally derived antibodies measured in the pre-primary series sample. An anti-polio antibody half-life of 28 days was assumed.[25] The endpoints for the booster phase were similar to those used in the primary series study.