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Intradermal fractional booster dose of inactivated poliomyelitis vaccine with a jet injector in healthy adults

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ABSTRACT

For global eradication of poliomyelitis, inactivated poliovirus vaccine (IPV) needs to become available in all countries. Using fractional-doses (reduced-doses) may impact affordability and optimize the utilization of the production capacity. Intradermal administration has the potential to lower the dose without reducing immunogenicity. A needle-free jet injector may be a reliable way to administer vaccines intradermally. The primary objective of this randomized controlled trial was to compare the immunogenicity and tolerability of fractional-dose intradermal IPV (Netherlands Vaccine Institute, NVI) booster vaccination administered with a jet injector (PharmaJet) to full-dose and fractional-dose intramuscular vaccination with a needle and syringe. Immunogenicity was assessed by comparing the differences in the post-vaccination $\log_2$ geometric mean concentrations of neutralizing antibodies (GMC) between the study groups. A total of 125 Dutch adult volunteers with a well-documented vaccination history were randomized to one of four groups: full-dose intramuscular needle (IM-NS-0.5), full-dose intramuscular jet injector (IM-JI-0.5), 1/5th dose intramuscular needle (IM-NS-0.1), 1/5th dose intradermal jet injector (ID-JI-0.1). Vaccination with the JI was less painful (87% no pain) than vaccination with a NS (60% no pain), but caused more transient erythema (JI 85%, NS 24%) and swelling (JI 50%, NS 5%). Intradermal vaccination caused less vaccination site soreness (ID 16%, IM 52%). At baseline all subjects had seroprotective antibody concentrations. After 28 days, GMC were slightly lower in the ID-JI-0.1 group than in the reference group (IM-NS-0.5). The differences were not statistically significant, but the stringent non-inferiority criterion (i.e. a difference of 1 serum dilution in the microneutralization assay) was not met. After one year, differences in GMC were no longer apparent. In contrast, intramuscular vaccination with a fractional dose administered with a needle (IM-NS-0.1) was statistically inferior to full-dose intramuscular vaccination. This shows that intradermal but not intramuscular delivery of fractional-dose IPV may be sufficient for routine polio vaccination.

1. Introduction

The new Global Polio Eradication Initiative has set a target for complete interruption of the transmission of poliovirus [1]. After eradication, cessation of oral poliovirus vaccine (OPV) is needed to prevent outbreaks due to circulating vaccine derived poliovirus [2,3]. Countries must then decide whether to stop all routine immunization against polio or to continue immunization with inactivated poliovirus vaccine (IPV). One of the prerequisites for cessation of the use of OPV is therefore to make IPV affordable and suitable for use in developing countries [4]. The worldwide production capacity for IPV is limited and the current weighted-average purchase price per dose of vaccine, when purchased by the United Nations Children's Fund, is $0.15 for trivalent OPV and approximately $3 for IPV [5]. Strategies to reduce this 20-fold cost increase include intradermal (ID) delivery of a fractional (reduced) antigen dose, intramuscular (IM) delivery of a fractional dose, or delivery of fewer doses. Administering vaccines intradermally is thought to enhance their immunogenicity because of the high density of antigen presenting cells in the dermis [6–9]. In a trial in the Philippines, a fractional dose of IPV administered intradermally with a needle at 6, 10 and 14 weeks and at 15–18 months, induced similar seroprotection rates but lower antibody titers than full-dose intramuscular IPV [10].

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Intradermal vaccination with a needle and syringe can be difficult, particularly in small children. A needle-free jet injector may be a reliable way to administer vaccines intradermally. It requires little training and reduces the risk of needle-stick injuries. In a trial in Oman, a fractional dose of IPV administered intradermally with a needle-free jet injector (Biojector® 2000) at 2, 4 and 6 months of age induced similar seroconversion rates but lower antibody titers than three full intramuscular doses [5]. In a similar trial in Cuba, in which infants were vaccinated at 6, 10 and 14 weeks after birth, which is a suboptimal immunization schedule for IPV [11,12], both the seroconversion rates and antibody titers were lower after fractional-dose intradermal vaccination than after full-dose intramuscular vaccination [13]. In both trials, parents preferred administration with a jet injector over injection with a needle [5,13]. No data are yet available on long-term protection and booster responses after vaccination with fractional-doses in infants.

These studies could not distinguish whether the intradermal site of administration or the lower antigen dosage were responsible for the lower immunogenicity of fractional-doses, because the study design did not include a third arm with fractional-dose IPV given intramuscularly. In anticipation of subsequent trials in infants as the primary target for polio eradication, this trial was designed to compare the immunogenicity and safety in adult volunteers with a well-documented vaccination history of a fractional booster dose of IPV administered intradermally with PharmaJet injection system, to both full- and fractional-dose IPV (Netherlands Vaccine Institute, NVI) injected intramuscularly with a needle and/or jet injector. The PharmaJet injection system is a handheld spring-powered injector and therefore suitable for use in developing countries.

2. Methods

2.1. Ethics statement

All participants provided informed consent. The study was approved by the Dutch ethics committee, the Central Committee on Research Involving Human Subjects (protocol number NL29671.000.09; EU Clinical Trials Register EUDRACT 2009-015175-27; Netherlands Trial Register 2196).

2.2. Study design

This was a single-center, randomized, controlled, non-inferiority trial conducted at Leiden University Medical Center in The Netherlands, between August 2010 and February 2012. Subjects were vaccinated between August 2010 and January 2011. The primary objective was to evaluate the tolerability (vaccination site and systemic reactions) and to compare the immunogenicity 28 days after vaccination of a fractional booster dose of IPV administered intradermally with a needle-free jet injector (ID-JI-0.1), with standard full-dose intramuscular vaccination administered with a needle and syringe (IM-NS-0.5). Secondary objectives were (i) to compare the safety and immunogenicity of full-dose intramuscular IPV booster vaccination administered with a jet injector (IM-JI-0.5), with IM-NS-0.5, and (ii) to compare the immunogenicity of ID-JI-0.1, with fractional-dose intramuscular IPV administered with a needle and syringe (IM-NS-0.1). Healthy Dutch adult volunteers who had received exactly 6 combined DTP-IPV vaccinations according to the National Immunization Program (i.e. at age 3 months, 4 months, 5 months, 11 months, 4 years and 9 years) were eligible. Exclusion criteria were: any IPV booster dose after 10 years of age, any OPV dose.

Photograph 1. PharmaJet Needle-free Jet Injection System for intradermal delivery. The ID injector used in this study was an investigational version of the FDA 510k-cleared v1.0 SC/IM device.

2.3. Vaccine and jet injector

Per participant we used one vial of IPV (NVI, lot 814AB, 0.5 mL per vial, expiration date: 05 Nov 2011) containing formaldehyde-inactivated poliovirus (strains Mahoney, MEF-1 and Saukett), type 1, 2 and 3: 40:8:32 D-antigen units respectively, and formaldehyde: 0.025 mg in phosphate buffer. The jet injector that was used was the PharmaJet Needle-free Jet Injection System. Separate jet injectors and single-use needle-free syringes were used for intramuscular and intradermal administration. The ID injector used in this study was an investigational version of the FDA 510k-cleared v1.0 SC/IM device. Modifications to permit ID delivery included a smaller main spring, a longer ejection pin to limit syringe fill volume to 100 μL, and the ability to continuously vary the main spring pressure through the use of spring preload system. With the exception of orifice diameter modifications, syringes were identical to SC/IM syringes (Photograph 1).

2.4. Randomization and procedures

The sponsor (NVI) prepared 125 sealed envelopes indicating allocation to one of the four treatment groups. The envelopes were numbered in random order using a random number generator (www.random.org). The study was not blinded. A single investigator included and vaccinated all participants (D.S.). The reference group, IM-NS-0.5, received one full-dose vaccination with IPV (40:8:32 DU in 0.5 mL) administered intramuscularly with a 25-gauge needle and 1.0 mL syringe. Study group IM-JI-0.5 received one full-dose (0.5 mL) vaccination administered intramuscularly with a jet injector. Study group IM-NS-0.1 received one fractional-dose vaccination with IPV (8:1.6:6.4 DU in 0.1 mL) administered intramuscularly with a 25-gauge needle and 1.0 mL syringe. Study group ID-JI-0.1 received one fractional-dose vaccination (0.1 mL) administered intradermally with a jet injector. Vaccinations were injected into the deltoid muscle of the right arm, except for intradermal vaccinations, which were injected in the skin overlying the posterior deltoid (Photograph 2). In all study-groups, we measured residual moisture, defined as vaccine remaining on, rather than in the skin, with a quantitative filter paper. Blood samples were taken at baseline (immediately before vaccination) and at day 7 (6–8), day 28 (25–31) and day 365 (330–400) after vaccination. For four days, participants filled out a diary on vaccination site and systemic reactions and recorded use of medication. Participants measured the size of vaccination site redness, swelling and induration using a caliper that was designed to measure the size of skin reactions. Adverse events occurring after four days were collected by