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Immune responses after fractional doses of inactivated poliovirus vaccine using newly developed intradermal jet injectors: A randomized controlled trial in Cuba

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ABSTRACT

Introduction: The World Health Organization recommends that, as part of the new polio endgame, a dose of inactivated poliovirus vaccine (IPV) be introduced by the end of 2015 in all countries using only oral poliovirus vaccine (OPV). Administration of fractional dose (1/5th of full dose) IPV (fIPV) intradermally may reduce costs, but its administration is cumbersome with BCG needle and syringe. We evaluated performance of two newly developed intradermal-only jet injectors and compared the immune response induced by fIPV with that induced by full-dose IPV.

Methods: Children between 12 and 20 months of age, who had previously received two doses of OPV, were enrolled in Camaguey, Cuba. Subjects received a single dose of IPV (either full-dose IPV intramuscularly with needle and syringe or fIPV intradermally administered with one of two new injectors or with BCG needle or a conventional needle-free injector). Serum was tested for presence of poliovirus neutralizing antibodies on day 0 (pre-IPV) and on days 3, 7 and 21 (post-vaccination).

Results: Complete data were available from 74.2% (728/981) subjects. Baseline median antibody titers were 713, 284, and 113 for poliovirus types 1, 2, and 3, respectively. Seroprevalence at study end were similar across the intervention groups (≥94.8%). The immune response induced with one new injector was similar to BCG needle and to the conventional injector; and superior to the other new injector. fIPV induced significantly lower boosting response compared to full-dose IPV. No safety concerns were identified.

Interpretation: One of the two new injectors demonstrated its ability to streamline intradermal fIPV administration, however, further investigations are needed to assess the potential contribution of fIPV in the polio endgame plan.

1. Introduction

The global effort to eradicate poliomyelitis was launched in 1988. Since then the number of paralytic cases caused by polioviruses dropped from hundreds of thousands reported every year to less than 400 reported in 2013 and it is expected that eradication of wild polioviruses will be achieved in the next few years [1,2].

Sabin strains of polioviruses contained in oral poliovirus vaccine (OPV) can replicate for prolonged periods in individuals with immunodeficiency disorders or in communities with low population immunity, and potentially re-establish epidemic transmission [3,4]. Therefore, to complete poliovirus eradication, a strategy for the elimination of all polioviruses, including the attenuated Sabin strains, was needed. This strategy, referred to as the Polio Eradication and Endgame Strategic Plan 2013–2018 [5], calls for sequential withdrawal of OPV, starting with removal of the type 2 Sabin virus by replacing trivalent OPV with bivalent OPV (which does not contain type 2 virus), and universal introduction of at least one dose of inactivated poliovirus vaccine (IPV) to routine immunization schedules in OPV-only using countries. Unlike orally administered OPV, IPV needs to be injected. Data suggests that one dose of IPV

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will provide serological protection through priming or seroconversion to approximately 90% of naïve infants [6], and establish an immunity base for poliovirus type 2, that can be rapidly boosted in a threatening outbreak scenario. In addition to mitigating the risk of paralysis caused by vaccine-derived poliovirus type 2 (VDPV2), IPV also boosts mucosal immunity in previously OPV-vaccinated recipients [7].

Introduction of one dose of IPV into routine immunization schedules in OPV-only using countries is starting in 2014 and is planned to be completed in the second half of 2015 [5]. This introduction requires adequate funding, especially in low-resource countries. One solution to reduce additional costs in connection with IPV introduction is the development of affordable IPV, usually considered as an immunizing dose of IPV costing $0.50 or less. Dose sparing is among the strategies considered for achieving the target price of IPV. In previous trials intradermal administration of fractional IPV (1/5th of a normal IPV dose) demonstrated good safety and immunogenicity [8–12]. Fractional IPV (fIPV) may, therefore, be considered as a substitute to full-dose, intramuscular IPV in the polio endgame scenario by some countries. The intradermal administration is, however, technically difficult (i.e. BCG needles and syringes) or not suitable for wide-spread use in resource poor settings (i.e. jet injectors powered by CO2 cartridges).

In this trial, we compared the immune response induced by one fIPV dose administered by two newly developed spring-powered intradermal-only jet injectors with fIPV administrated by BCG needle and syringe or by a previously used jet injector requiring CO2 cartridges; in addition, we compared immune response induced by one full-dose IPV administered intramuscularly with that after intradermal fIPV.

The study was implemented in Cuba, the only country where polio vaccines are administered exclusively in campaigns (usually carried out in February and April of each year) targeting children below 3 years of age. It has been demonstrated that the OPV polioviruses disappear from the environment by June of each year, effectively providing an environment free of any poliovirus contamination between July and January of each year [3].

2. Methods

A randomized controlled clinical trial was carried out in the Cuban province of Camaguey in the central-eastern part of the island. Children who were born between May 2011 and January 2012 were selected through health center registers. Only children who received two doses of OPV in February and April 2012, as per Cuban immunization policy, were eligible to participate in the study. The study was conducted in January and February of 2013 and was finished before the start of the first OPV campaign of 2013.

After obtaining of informed consent, children were randomized into one of five study arms. One dose of IPV was administered; subjects in arm A received one full intramuscular dose with needle and syringe, in arm B one fIPV dose via BCG needle and syringe, in arm C one fIPV dose via injector X (the conventional jet injector requiring CO2 cartridges), in arm D they received one fIPV dose via newly developed jet injector Y and in arm E one fIPV dose via newly developed jet injector Z.

Injector X was the Biojector 2000® Needle Free Injection System produced by Bioject Medical Technologies Inc., injector Y was the prototype Intradermal (ID) Pen Injector also produced by Bioject Medical Technologies Inc. and injector Z was the prototype Tropis Needle-Free Injector produced by PharmaJet®. The Intradermal (ID) Pen Injector and Tropis are spring-powered devices that are under development exclusively for intradermal vaccine administration while Biojector 2000® is a CO2 powered device requiring CO2 cartridges. Biojector 2000® was designed to be used for intramuscular, subcutaneous as well as intradermal injections.

Subjects were bled by heel stick devices on the day of enrolment (prior to IPV administration), and on days 3, 7 and 21. The blood specimens collected at the health centers were allowed to clot and centrifuged. Sera were separated and transported to the Camaguey central laboratory, where they were stored at −20° C until the shipment to the Pedro Kouri Institute in Havana. Here the sera were tested for the presence of poliovirus neutralizing antibodies using standard neutralization assays [13,14], with the following modification: the highest dilution of sera was 1:11,300, which is above the commonly used highest dilution of 1:1024 [15].

The health center staff followed-up the children for 1 h after vaccination, and then 1 day, 2 days, 3 days and 7 days after the IPV (or fIPV) administration, and recorded all adverse reactions.

IPV used in this trial was produced by Sanofi Pasteur as IMOVAX®, where each full IPV dose (0.5 mL) is formulated to contain 40 D antigen units of type 1, 8 D antigen units of type 2, and 32 D antigen units of type 3 poliovirus.

Seropositivity was defined as reciprocal titers of poliovirus neutralizing antibodies ≥8; seroconversion was defined as the change from seronegative to seropositive (from <8 to ≥8); and boosting was defined as ≥4-fold increase in titers. In this study, "immune response" combines both boosting and seroconversion. Inferiority was defined as a difference in immune response of ≥15%. An anamnestic response was defined as an immune response between day 0 and day 7; and a rapid anamnestic response was defined as an immune response between day 0 and day 3.

Chronic malnutrition was defined as a height-for-age *Z* score of less or equal to −2. Acute malnutrition was defined as a weight-for-height *Z* score of less or equal to −2.

After the end of the study a short questionnaire was administered to health care workers to assess ergonomic properties of the three devices.

3. Results

We enrolled a total of 981 children and randomized 729. There were 252 subjects who withdrew before randomization. The main reason for withdrawal was respiratory infection affecting children in the period between enrolment and randomization. There were 728/981 (74.2%) who completed at least the first and the last study visit as per schedule and were considered per protocol (Fig. 1).

Baseline seroprevalence did not differ between arms and was above 90% for poliovirus serotypes 1 and 2; and above 80% for type 3 (Table 1). Baseline antibody titers were surprisingly high in all study arms, but especially for poliovirus serotype 1; baseline titer ≥ 1024 was observed in 32.8% (239/729), 7.5% (55/729) and 2.9% (21/729) children for serotypes 1, 2 and 3, respectively.

Analysis of the immune response was restricted to subjects with baseline seroprevalence titer ≤ 362. The immune response achieved with the BCG syringe and with devices X and Z was no different; however, the immune response achieved with device Y was significantly lower ($p < 0.05$) for all three serotypes (Table 2). The immune response after fIPV was inferior to full-dose IPV for all three serotypes (Table 2).

Seroconversion between day 0 and 21 was analyzed among children who were seronegative for type 3 at baseline. This analysis was not possible for serotypes 1 and 2 because only very few children were seronegative at baseline for these serotypes. The seroconversion rate induced by fIPV was inferior when compared with full-dose IPV (Fig. 2). This was true for administration with BCG syringe as well as with the three needle-free injectors (Fig. 2).