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Needle-free jet injector intradermal delivery of fractional dose inactivated poliovirus vaccine: Association between injection quality and immunogenicity

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ABSTRACT

Introduction: The World Health Organization recommends that as part of the polio end-game strategy a dose of inactivated poliovirus vaccine (IPV) be introduced by the end of 2015 in all countries currently using only oral poliovirus vaccine (OPV). Administration of fractional dose (1/5 of full dose) IPV (fIPV) by intradermal (ID) injection may reduce costs, but its conventional administration is with Bacillus Calmette-Guerin (BCG) needle and syringe (NS), which is time consuming and technically challenging. We compared injection quality achieved with BCG NS and three needle-free jet injectors and assessed ergonomic features of the injectors.

Methods: Children between 12 and 20 months of age who had previously received OPV were enrolled in the Camaguey, Cuba study. Subjects received a single fIPV dose administered intradermally with BCG NS or one of three needle-free injector devices: Bioject Biojector 2000® (B2000), Bioject ID Pen® (ID Pen), or PharmaJet Tropis® (Tropis). We measured bleb diameter and vaccine loss as indicators of ID injection quality, with desirable injection quality defined as bleb diameter ≥5 mm and vaccine loss <10%. We surveyed vaccinators to evaluate ergonomic features of the injectors. We further assessed the injection quality indicators as predictors of immune response, measured by increase in poliovirus neutralizing antibodies in blood between day 0 (pre-IPV) and 21 (post-vaccination).

Results: Delivery by BCG NS and Tropis resulted in the highest proportion of subjects with desirable injection quality; health workers ranked Biojector2000 and Tropis highest for ergonomic features. We observed that vaccine loss and desirable injection quality were associated with an immune response for poliovirus type 2 ($P = 0.02$, $P = 0.01$, respectively).

Conclusions: Our study demonstrated the feasibility of fIPV delivery using needle-free injector devices with high acceptability among health workers. We did not observe the indicators of injection quality to be uniformly associated with immune response.

1. Introduction

The Global Polio Eradication Initiative (GPEI) was formed in 1988, and since its inception progress has been robust, with annually reported cases decreasing from 350,000 in 1998 to 342 in 2014 [1]. The GPEI's polio eradication and end-game strategy 2013–2018 outlines the path to achieving eradication and transitioning into a post-eradication era [2,3]. This strategy calls for the global introduction of at least one dose of inactivated poliovirus vaccine (IPV) into the routine immunization schedules of all countries currently using only oral poliovirus vaccine (OPV) by the end of 2015.

Currently, 122 OPV-only countries plan to introduce IPV into their routine immunization schedules between mid-2014 and

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late 2015 [4]. Rapid IPV introduction on a global scale presents many challenges including cost, supply, injection safety and health worker capacity. Assessment of innovative, affordable, safe and effective IPV strategies is therefore paramount. Dose-sparing strategies including intradermal (ID) administration of fractional dose of IPV (1/5th of full dose or 0.1 ml dose, referred to as fIPV) have been previously assessed with good immunogenicity and safety outcomes [5–11]. However, ID injection is conventionally administered using the Mantoux technique with BCG NS and requires health workers who are specially trained.

Using needle-free ID jet injectors to deliver fIPV could extend IPV supply, reduce cost, minimize injection safety risks, optimize the ease and reliability of ID fIPV delivery, and facilitate IPV introduction, particularly in resource-limited settings [12,13]. A variety of ID delivery devices have been developed, however to date, comparisons of novel ID devices to conventional ID BCG NS for fIPV delivery have not been available. Evaluation of ID device performance by measuring indicators of injection quality (bleb diameter and vaccine loss indicated by injection site wetness) has been used to inform device development, however the clinical relevance of these indicators for IPV immunogenicity was previously unknown.

A randomized control trial conducted in January 2013 in Camaguey, Cuba, compared immune responses between an IPV full dose administered intramuscularly and fIPV administered intradermally by BCG NS or one of three different needle-free jet injectors; it was demonstrated that ID fIPV delivery resulted in inferior immune response compared to full-dose intramuscular (IM) delivery and that two of the three needle-free injectors achieved similar immune response as with the use of the BCG NS [7].

Data obtained during the study were used to evaluate the different fIPV methods of delivery. In our study, we assessed the relationship between each fIPV method of delivery and indicators of desirable injection quality; we analyzed health worker ergonomic preferences for the different fIPV methods of delivery to assess their suitability for programmatic use. Further, we evaluated the association between currently used indicators of desirable injection quality to predict immune response.

2. Methods

2.1. Study population and design

As part of the serological randomized-control study, children 12–20 months of age who had previously received OPV were selected through health center registers [7].

After obtaining informed consent from parents or guardians, children were randomized to receive IPV through one of five study arms: full IPV dose intramuscularly or fIPV dose via one of four ID delivery methods, conventional BCG NS, B2000, ID Pen, or Tropis. All IPV doses were administered in the upper right arm [7].

2.2. Vaccine and injection devices

Sanofi Pasteur supplied IPV; each 0.5 ml dose contained 40, 8, and 32 D antigen units of poliovirus types 1, 2, and 3, respectively, with the presumption that 0.1 ml contained 8, 1.6, and 6.4 antigen units of poliovirus types 1, 2, and 3, respectively.

The needle-free jet injector devices included the Bioject Biojector 2000 (B2000), Bioject ID Pen (ID Pen), and PharmaJet Tropis (Tropis). B2000 is a CO_2 cartridge powered device, produced by Bioject Medical Technologies Inc., ID Pen and Tropis are spring powered prototypes produced by Bioject Medical Technologies Inc. and PharmaJet, respectively; B2000 was designed for IM, subcutaneous and ID injection delivery (when used with an ID spacer), ID Pen and Tropis were designed exclusively for intradermal vaccine administration.

2.3. Device performance and injection quality

Injector device performance was evaluated by measuring bleb diameter and vaccine loss as indicators of ID injection quality. Desirable injection quality was defined as bleb diameter ≥5 mm and <10% vaccine loss. These specifications are based on Mantoux technique data for tuberculin ID delivery and the needle-free jet injector ISO standard and have been used to inform ID device development [14–19].

The bleb diameter was measured by marking the outer rims of the bleb with a pen and recording the distance between the marks in millimetres with a ruler. Bleb diameter is often interpreted as the extent of intradermal localization of the injection. Vaccine loss as indicated by the liquid on the surface of the skin was measured by applying filter paper to collect liquid on the skin surface immediately after fIPV injection. The wet spot on the filter paper was then circled and the circle diameter compared to a reference template graded 0–5. Vaccine loss was graded using the following: grades 0, 1, and 2 indicated a dry injection site, <5% and 5–10% of vaccine loss, respectively, or <10 μl of a 0.1 ml dose volume. Wetness grades 3, 4, and 5 indicated 10–20%, 20–40%, and >40% vaccine loss, respectively.

Health workers completed an anonymous questionnaire evaluating the four different fIPV delivery methods and nominated their preferred method. Seven key ergonomic features were scored for each injector, including appropriate size, whether the device was intuitive to use, if repetitive use of the device resulted in hand pain, ease of filling the needle-free syringe, ease of visualising and removing air bubbles, ease of resetting, and whether the device was quiet during operation. The scores were given on a scale from 1 to 5 where 1 indicated a negative response and 5 indicated a positive response.

2.4. Laboratory analysis

Blood samples were collected from subjects using a heel-stick device on days 0, 3, 7, and day 21 after vaccination then centrifuged. Sera were then transported to Camaguey central laboratory for storage at −20 °C until shipment to Pedro Kouri Institute, Havana. Sera were tested for neutralizing antibodies to all three poliovirus types using standard neutralization assays [20] with one exception, the highest dilution of sera tested was 1:16,384, which was above the commonly used highest dilution of 1:2048. Laboratory personnel were blinded to the study arms linked to the serum samples.

Seroconversion was defined as change from seronegative to seropositive where reciprocal titers of poliovirus neutralizing antibodies increased from <8 to ≥8; in children with baseline titer ≤362, boosting of immunity was defined as ≥4-fold increase in antibody titers 21 days after fIPV administration. We defined immune response as either seroconversion or boosting between days 0 and 21.

2.5. Statistical analysis

We calculated the proportion of children that met the individual indicators of injection quality (>5 mm bleb diameter and <10% vaccine loss) as well as the proportion of children that met both indicators, which we defined as desirable injection quality (≥5 mm bleb and <10% vaccine loss) by injector device. We assessed health worker ergonomic preference by calculating the ergonomic score nominated by the health worker as a proportion of the maximal potential score per device.

To determine the relationship between indicators of injection quality and immune response, we compared bleb size, vaccine loss,

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