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A randomized trial of rotavirus vaccine versus sucrose solution for vaccine injection pain

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ABSTRACT

Objective: Sucrose solutions are analgesic in infants. Oral rotavirus vaccine contains sucrose, however, it is not known if it possesses analgesic properties. The objective was to compare the analgesic effectiveness of rotavirus vaccine to sucrose solution when administered prior to injectable vaccines.
Methods: Infants 2–4 months of age receiving oral rotavirus vaccine and two separate injectable vaccines on the same day were randomized to rotavirus vaccine (Rotarix™) first followed by the injectable vaccines and sucrose (Tootsweet™) afterwards, or vice versa. Pain was assessed by blinded raters using the Numerical Rating Scale (NRS, range 0–10) (parents, clinicians), or Modified Behavioural Pain Scale (MBPS, range 0–10) and cry duration (observers). Data were analyzed using *t*-tests or χ^2-tests; Bonferroni correction was applied to correct for multiple comparisons, as appropriate.
Results: Altogether, 120 infants participated: 60 were randomized to rotavirus vaccine first. Groups did not differ in demographics, including; age ($p = 0.448$) and sex ($p = 0.464$). The mean pain score (standard deviation) for both vaccine injections did not differ between infants given rotavirus vaccine first versus sucrose solution first: observer MBPS, parent NRS and clinician NRS scores were 7.4 (1.6) vs. 7.7 (1.6), 4.9 (2.1) vs. 5.8 (2.1), and 4.2 (2.1) vs. 4.6 (2.2), respectively. Similarly, there was no difference between groups in cry duration.
Conclusion: Rotavirus vaccine did not differ from sucrose solution in reducing injection-induced pain. Based on the findings, it is recommended that rotavirus vaccine be administered prior to injectable vaccines in infants aged 2 and 4 months.

1. Introduction

Over 90% of young children demonstrate severe distress during vaccine injections [1]. Pain treatments such as sucrose solution are uncommonly used [2–4], despite a plethora of evidence demonstrating effectiveness [5]. Inadequate pain management can lead to negative experiences with vaccination and parental non-compliance with vaccination schedules [6]. Parents are dissatisfied with current analgesic practices [2,7] and when pain-relief is provided to their children, both parents and health care providers report better satisfaction with medical care [8]. Under-utilization of analgesics during vaccination is largely attributed to the additional time and resources needed to implement them [2]. Finding feasible and cost-neutral pain-reducing methods would therefore be of interest to both clinicians and parents.

Oral rotavirus vaccine was added to the immunization schedule in Canada in 2010 and is usually given in conjunction with injectable vaccines at 2 and 4 months of age. There has been no guidance provided to clinicians about the order of administration of the oral rotavirus vaccine relative to injectable vaccines given at the same time, resulting in variability in clinical practice. Some clinicians administer the vaccine after injectable vaccines once the infant is calm, asserting that injection-induced infant crying increases the risk of spitting up the vaccine. Others administer the vaccine prior to injectable vaccines, asserting that because

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the rotavirus vaccine contains sweet-tasting substances (1073 mg sucrose/1.5 mL (71.5%), Rotarix™ product monograph, GlaxoSmithKline) and sucrose is known to be analgesic in infants, it can provide analgesia during the injections.

Of available pain interventions, sucrose solution has been widely recommended for use in infants due to a robust evidence base supporting its effectiveness and widespread experience with its use in the hospital setting [9,10]. At present, there are no studies that have evaluated the analgesic properties of rotavirus vaccine. If rotavirus vaccine is demonstrated to reduce vaccine injection-induced pain, the sequence of vaccine administration could be standardized to begin with rotavirus vaccine such that exogenous sweet-tasting solutions might not need to be given. The objective of this study was to compare the analgesic effectiveness of rotavirus vaccine to sucrose solution for reducing pain from vaccine injections in infants.

2. Materials and methods

2.1. Study design, participants and setting

We conducted a randomized controlled trial including healthy infants attending an outpatient paediatric clinic (KinderCare) in Toronto, Canada. Infants between 2 and 4 months of age receiving oral rotavirus vaccine in conjunction with primary immunizations [i.e., Diphtheria, Tetanus and acellular Pertussis/Inactivated Polio/*Haemophilus influenza* type b (DTaP-IPV-Hib, Pediacel™) and Pneumococcal conjugate vaccine (PCV, Prevnar™)] were included. We excluded infants with impaired neurological development; history of seizures; receiving sedatives or narcotics in preceding 24 h; or infants whose parents were unable to use study tools. Infants were allowed to participate in the trial only once. The study received approval by the University of Toronto Research Ethics Board and informed consent was obtained from parents.

2.2. Study procedures

The randomization sequence was generated off-site by an individual not involved in the study using a computer random number generator. Infants were randomly allocated in a 1:1 ratio to 1 of 2 groups: (1) rotavirus vaccine (containing 71.5% sucrose) 1.5 mL (Rotarix™) orally using a syringe 2 min prior to vaccine injections, then sucrose 24% solution 2 mL (Tootsweet™, Equinox Specialty Products Inc.) orally 1 min following vaccine injections (group 1); or (2) sucrose orally using a syringe 2 min prior to vaccine injections, then rotavirus vaccine 1 min following vaccine injections (group 2).

Treatment allocation was concealed using sequentially numbered opaque sealed envelopes (SNOSE). A research assistant prepared the study solutions for each consecutive infant in a separate room, away from clinic staff and parents. Hence parents, clinicians injecting vaccines, and other clinic staff were blinded to treatment allocation. Both sucrose and rotavirus vaccine were transferred from their original packaging to identical 3 mL oral syringes. A white sticker label was affixed to the barrel of each syringe indicating the order of administration (1 or 2). Both solutions were indistinguishable by colour and the volume was obscured by the label. The research assistant inserted the study solutions into a plastic baggy and placed them in the examination room of the infant with the injectable vaccines, as per usual practice at the clinic.

Infants were videotaped using a handheld videocamera beginning from just prior to administration of the first solution, and continuing throughout both injections and for up to 2 min following administration of the second solution. Allvaccines were administered using a 25 gauge 22 mm needle. The first vaccine was injected in the left anterolateral aspect of the thigh and the second in the right. All infants benefited from pain-reducing measures, including: intramuscular injection without prior aspiration; and DTaP–IPV–Hib administration prior to PCV [11]. Altogether, 4 clinicians were involved in administering vaccinations. Mothers did not breastfeed nor use swaddling.

2.3. Study outcomes

Right before and after both injections, parents and clinicians independently rated infant pain using an 11-point Numerical Rating Scale (NRS), where 0 = no pain, and 10 = worst possible pain. Pain was assessed later from videotapes by research assistants blinded to treatment allocation using validated tools, including: the Modified Behavioural Pain Scale (MBPS) [12] and crying time. The MBPS assesses infant behaviour in 3 domains: facial expression, vocalizations and body movements. A total score is generated by summing domain scores and varies from 0 to 10. The MBPS was scored during the 15 s preceding and following each injection. Reliability was assured by re-coding 20% of infants and demonstrating an intraclass correlation coefficient of >0.8. Separately, cry duration was assessed immediately after vaccinations in 1 min intervals for 2 min following the first injection. Crying was defined as audible vocalization in the presence of facial grimacing.

Infant tolerance following administration of the study solutions and during vaccine injections (i.e., spitting up, gagging) and parent satisfaction with pain control (assessed using a 0–4 point Likert scale, where 0 = very dissatisfied, 1 = somewhat dissatisfied, 2 = no opinion/don't know, 3 = somewhat satisfied, and 4 = very satisfied) were also recorded.

2.4. Sample size calculation and statistical analysis

Using data from a previous study [13], a sample size of 56 per group permitted a 15% difference [14] in MBPS pain score to be detected with 80% power and a two-sided alpha level of 0.05. We included 60/group (120 altogether) to account for drop-outs and missing data.

The primary outcome analysis compared post-injection MBPS scores for each vaccine injection and overall mean of both injections between groups using a *t*-test. Secondary outcomes (NRS scores, cry duration, tolerance, parent satisfaction) and demographics were compared using *t*-tests or χ^2-tests, as appropriate. A significance level of 0.05 was considered significant for the primary outcomes. Bonferroni adjustment was applied to secondary outcomes to correct for multiple hypothesis testing; the resulting significance level was 0.005. We used an intent-to-treat analysis approach. All analyses were conducted using the Statistical Package for the Social Sciences™ v. 22 (IBM).

3. Results

3.1. Participant flow

The study was conducted between July 30, 2014 and November 18, 2014. Of the 175 parents approached for participation, 120 (69%) agreed to participate. Non-participants did not differ from participants with respect to sex distribution and mean weight: 48% male vs. 53% male; $p = 0.627$, and 5.9 kg (standard deviation = 1.0) vs. 5.8 kg (1.0); $p = 0.709$, respectively. Altogether, 60 infants were randomized to rotavirus vaccine first and 60 to sucrose solution first. Outcome data were available in all 120 infants (Fig. 1).