Vaccine xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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

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ARTICLE INFO

Article history:
Received 7 February 2015
Received in revised form 18 March 2015
Accepted 13 April 2015
Available online xxx

NCT02174705
Keywords:
Rotavirus vaccine
Sucrose
Pain management
Vaccination
Infant

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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http://dx.doi.org/10.1016/j.vaccine.2015.04.057
0264-410X/

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).

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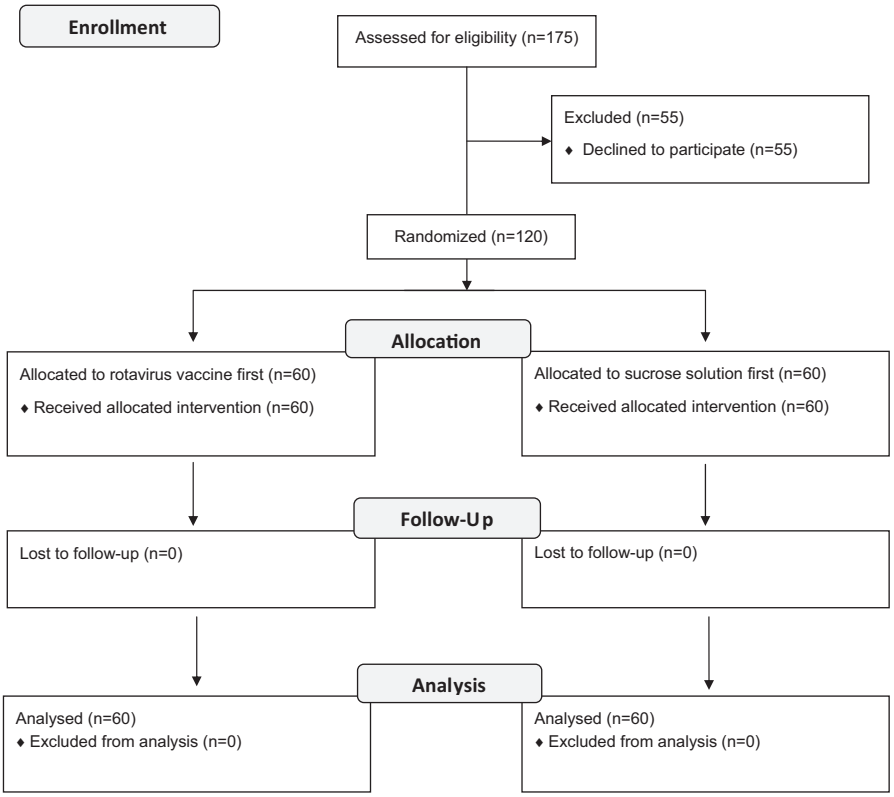

Fig. 1. Flow of participants in the study.

3.2. Participant characteristics

There were no statistically significant differences ($p > 0.05$) in demographic characteristics between groups (Table 1). Seven infants in each group were born pre-term (<37 weeks gestation); all of them, however, were born at ≥32 weeks gestation. The time between the first and second vaccine injection was 58 s (16) for infants in the rotavirus group vs. 57 s (13) for infants in the sucrose group; $p = 0.660$.

3.3. Pain outcomes

Infant pain scores are displayed in Table 2. Observer MBPS scores following the first and second injections and the overall mean MBPS score for both injections did not differ between infants in the rotavirus vaccine first group and the sucrose solution first group. Similarly, there were no differences in parent and clinician NRS scores (Table 2). Cry duration in the first and second min was 13 s (16) vs. 16 s (15), $p = 0.391$; and 27 s (18) vs. 31 s (17), $p = 0.353$, respectively. There was no difference between groups in parent satisfaction with respect to pain control: 3.3 (1.0) vs. 3.4 (0.9); $p = 0.636$.

3.4. Safety outcomes

Two infants in the rotavirus vaccine group spit up during its administration compared to 1 in the sucrose group ($p = 1.0$). In all cases, solutions were re-administered without incident. There were no other instances of spitting up or gagging during the injections or during administration of the second solution.

4. Discussion

Reducing vaccination pain has important implications for health outcomes in infants as untreated pain can lead to negative

Table 1
Characteristics of participating infants.

	Rotavirus vaccine ($n = 60$)	Sucrose solution ($n = 60$)	p-Value
Gestational age at birth (wks)	38.8 (2.0)*	39.2 (2.0)*	0.272
Sex (male)	34 (57)	30 (50)	0.464
Ethnicity (caucasian)	37 (62)	36 (60)	0.852
Mode of nutrition (breastfed)	47 (78)	47 (78)	1.0
Siblings (none)	35 (58)	41 (68)	0.687
Age at vaccination (days)	93 (32)	89 (33)	0.448
Weight at vaccination (kg)	5.9 (1.1)*	5.8 (0.9)	0.651
Receiving 2-month routine vaccinations	33 (55)	38 (63)	0.353
Elapsed time from clinic arrival to first solution (min)	45 (15)*	42 (16)	0.267
Infant held by parent during vaccinations	44 (73)	46 (77)	0.673
Infant using non-nutritive sucking during vaccinations	7 (12)	7 (12)	1.0
Parent using toy during vaccinations	2 (3)	0 (0)	0.154

Values are mean (standard deviation, SD) or frequency (%); data analyzed using t-test or chi squared test, as appropriate.
* $n = 59$.

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Table 2
Infant pain scores during vaccination.

Phases of the procedure	Rotavirus vaccine ($n = 60$)	Sucrose solution ($n = 60$)	p-Value*
Pre-injection (baseline)			
Observer MBPS	3.0 (2.1)	2.7 (1.7)	0.477
Parent NRS	0.2 (1.0)	0.1 (0.4)	0.272
Clinician NRS	0.3 (0.8)	0.1 (0.5)	0.285
First injection			
Observer MBPS	5.8 (2.9)	6.5 (2.7)	0.171
Parent NRS	3.0 (2.3)	3.9 (2.6)	0.066
Clinician NRS	2.3 (2.2)	3.0 (2.4)	0.110
Second injection			
Observer MBPS	9.0 (0.6)	9.0 (0.9)	0.810
Parent NRS	6.8 (2.4)	7.7 (2.0)	0.046
Clinician NRS	6.1 (2.4)	6.3 (2.3)	0.643
Mean of both injections			
Observer MBPS	7.4 (1.6)	7.7 (1.6)	0.261
Parent NRS	4.9 (2.1)	5.8 (2.1)	0.032
Clinician NRS	4.2 (2.1)	4.6 (2.2)	0.269

Values are mean (standard deviation, SD); data analyzed using t-test.
MBPS = Modified Behavioural PainScale, NRS = Numerical Rating Scale.
* p-Value adjusted using Bonferroni correction to 0.005 for secondary outcomes, including parent and clinician NRS scores. Using this cut-off, there were no statistically significant differences between groups.

experiences with vaccination and parental non-compliance with future vaccinations [6]. This study compared the effectiveness of rotavirus vaccine, an oral vaccine currently co-administered with injectable vaccines, to oral sucrose solution, an established pain-reducing treatment for infant vaccinations [5]. The results demonstrated insufficient evidence of a difference between rotavirus vaccine and sucrose solution using validated behavioural measures of infant pain including; observer MBPS, parent NRS, clinician NRS and cry duration. Moreover, parent overall satisfaction with pain management did not differ between groups. Both solutions were well tolerated by infants; a small percentage (<3%) of them spit up during administration, with no difference between groups. Taken together, these results provide evidence for the effectiveness of rotavirus vaccine in reducing injection-induced pain.

These results have important implications for clinical practice. At present, sucrose is not routinely administered in infants undergoing vaccine injections [2–4] despite its well established effectiveness for reducing pain [5]. Underutilization of sucrose may be due, at least in part, to the lack of a marketed product for outpatient use. Given that oral rotavirus vaccine is routinely co-administered with injectable vaccines, there is the opportunity to exploit its analgesic effects by standardizing the order of its administration to precede vaccine injections. This can be easily accommodated in any clinical setting.

We postulate that the analgesic effect of rotavirus vaccine is due at least in part to the high concentration of sucrose (715 mg/mL, or 71.5%) that is present in the formulation, which is within the range that has been used to manage vaccination pain, and above the concentration of the sucrose solution (240 mg/mL, or 24%) used in the present study. A recent meta-analysis suggested that a concentration threshold of >20% is analgesic [15]. It is unclear however, if a dose-response relationship exists at concentrations that are >20% [15]. While we did not demonstrate superiority of the more concentrated rotavirus vaccine, it is interesting to note that pain scores were consistently lower in the rotavirus vaccine group compared to the sucrose group, regardless of the pain scale used. A power calculation using the observed mean scores for the MBPS, clinician and parent NRS for both injections suggests that between 170 and 900 infants would be needed to detect a difference between groups with 80% power and alpha = 0.05.

Strengths of the present study include the study design features utilized which improve internal validity, including; randomization which reduced selection bias, blinding of important personnel (clinicians, parents) which reduced performance and detection bias, and complete outcome data which reduced attrition bias. There are also design features that improve external validity, including; investigation of a clinically relevant question to stakeholders, inclusion of infants across ages that are eligible for rotavirus vaccination, inclusion of multiple individuals to deliver vaccine injections, pragmatic delivery of study interventions, use of clinically relevant pain assessment methods, and concomitant use of other feasible pain interventions (i.e., administration of the most painful vaccine last and intramuscular injections without aspiration) [11]. Moreover, 75% of parents held their infants during vaccination and holding is also an effective pain-relieving intervention [11]. That these interventions are cost-neutral and feasible for implementation enhances the applicability of the results across vaccination settings.

It is important to note, however, that despite the use of multiple pain management interventions in both groups, the mean infant pain score for both injections was typically in the moderate (4–6) to high (7–10) range. The goal of pain management during infant vaccinations should be to prevent pain rather than to reduce it due to its iatrogenic nature. Clearly, the analgesic regimen used in the present study, while feasible, does not achieve this level of analgesia and additional interventions are needed. These interventions must be sufficiently effective to provide additive benefit beyond the level of analgesia achieved by the regimen used. At present, an analgesic regimen that achieves 'no pain' has not yet been determined; however, there are some additional interventions that may be used to enhance results, including; breastfeeding and topical anaesthetics [5].

It is also possible that administering sucrose solution and rotavirus vaccine together prior to injectable vaccines is superior to either sucrose or rotavirus vaccine alone. The present study was not designed to answer this question. There is a study however, that evaluated the effectiveness of sucrose (vs. water) followed by rotavirus vaccine, injectable vaccines and then a post-injection physical intervention (vs. control) in 2 and 4 month old infants [16] that provides some information about this question. The results demonstrated that infants in the sucrose group had significantly

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less pain than those in the water group, but only in the absence of the post-injection physical intervention. There was no benefit of sucrose in the presence of the post-injection physical intervention. Taken together, the results suggest that the effects of sucrose solution when added to rotavirus vaccine may depend on other pain interventions concurrently being used (i.e., different effects are possible under different experimental conditions). As such, sucrose solution should not be assumed to contribute analgesia if co-administered with rotavirus vaccine. Under these circumstances, one may wish to consider the use of alternative pain interventions with a different mechanism of action.

Limitations of the study include the small sample size which limits confidence in the results. In addition the same research assistants that prepared the study solutions videotaped infants during vaccinations and therefore may have introduced bias during data collection. The research assistants, however, did not participate in the procedure nor disclose the identity of the solutions. In addition, all study procedures were standardized. That baseline pain scores and procedure characteristics did not differ between groups provides evidence of a lack of systematic error during data collection.

In conclusion, there was no evidence of a difference in analgesic effectiveness between rotavirus vaccine and sucrose solution when administered prior to routine vaccine injections in infants 2 and 4 months of age. On the basis of these results, it is recommended that rotavirus vaccine be given prior to injectable vaccines for the added benefit of pain relief. Addressing pain may in turn, lead to improved satisfaction with the vaccination experience for families and improved compliance with future vaccinations.

Funding source

No external funding was secured for this study. Sucrose 24% solution supplies for the trial were provided by Equinox at no charge to investigators. Equinox was not involved in any aspect of the study.

Contributions of authors

Anna Taddio conceptualized and designed the study, provided administrative and supervision for the study, carried out the analysis, drafted the initial manuscript, and approved the final manuscript as submitted.

Daniel Flanders, Eitan Weinberg, Carol McNair, and Moshe Ipp conceptualized and designed the study, assisted in the interpretation of data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Supriya Lamba, Charmy Vyas, and Andrew F Ilersich assisted in the design of the study, acquisition and analysis of data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

All authors approved the final manuscript as submitted.

Acknowledgements

We wish to thank all the parents who participated with their infants and the staff at KinderCare for assistance with aspects of data collection and analysis.

Conflict of interest statement

A Taddio received research funding from Pfizer and study supplies from Ferndale and Natus for a separate clinical trial related to vaccination pain. The other authors have no conflicts of interest relevant to this article to disclose.

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