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Comparison of iatrogenic pain between rotavirus vaccination before and after vaccine injection in 2-month-old infants

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ABSTRACT

Oral rotavirus vaccine (RV) administration in conjunction with other injectable vaccines has been used worldwide. However, whether the sequence of RV administration is associated with the reduction of injection-induced pain remains unclear.

In this randomized controlled trial, we enrolled 6–12-wk-old healthy infants. The pain response of the infants was scored on the basis of their crying, irritability, facial expression, gagging and distress. A multivariate logistic regression model was used to compare the pain response after adjustment for possible confounders.

We enrolled 352 infants, of whom 176 infants received RV before injection (experimental group) and 176 infants received an RV after injection (comparison group). Sex, number of injections, main caregiver, feeding type, and RV type did not differ significantly between the 2 groups. Multivariate regression analyses showed that, at 30 s after the intervention, the episode of gagging was more frequent in the comparison group than in the experimental group ($p = 0.004$). At 180 s after the intervention, the infants cried more often in the comparison group ($p < 0.001$). Furthermore, the infants in the experimental group more often relaxed ($p < 0.001$), rested quietly ($p = 0.001$), and were smiling ($p = 0.001$) than did those in the comparison group.

Our results indicate that compared with oral RV administration after injection, oral RV administration before injection is more effective in reducing injection-induced pain in 2-mo-old infants. The findings can provide a clinical strategy for relieving pain from vaccination in young infants.

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Introduction

Rotavirus infection is one of the most common causes of severe acute gastroenteritis in children. Rotavirus immunization programs have been implemented for more than 10 y to reduce the burden of rotavirus-related gastroenteritis.[1] Two live oral vaccines against rotavirus gastroenteritis are available worldwide, RotaTeq™ (Merck & Co. Inc., Pennsylvania, USA) and Rotarix™ (GlaxoSmithKline Biologicals, Rixensart, Belgium).[2] RotaTeq is a pentavalent (G1, G2, G3, G4, and P) human-bovine reassortant vaccine that is administered thrice, and Rotarix is a human-attenuated monovalent vaccine administered twice. Both preparations contain sucrose. Injectable vaccines have been used in conjunction with an oral rotavirus vaccine (RV) for disease prevention.[3,4]

Injection for vaccination is one of the most common painful procedures. Pain during infancy can have long-term effects on physiologic and behavioral responses to vaccination.[5] Moreover, parents may be reluctant to vaccination because of its adverse effects.[6,7] When parents perceive an unfavorable experience during vaccination, they may hesitate to return for follow-up vaccinations and boosters in a timely manner.

Although RVs have been administered in conjunction with injectable vaccines, guidelines regarding the sequence of RV administration in relation to injection are lacking. In clinical practice, some clinicians administer RVs after injection; this method is more convenient because infants always open their mouths after injection. However, other clinicians administer RVs before injection to reduce pain from injection.[8] Nevertheless, studies comparing benefits of RV administration before injection with those of RV administration after injection are lacking. Therefore, the current study investigated whether RV administration before injection is superior to RV administration after injection with respect to pain reduction. The results of this study provide valuable information that can guide evidence-based interventions for reducing iatrogenic pain caused by vaccination.

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Table 1. Infant pain scale.

grade*	0	1	2
Crying Irritability	No crying Resting quietly	Whimper Irritation with flexed/ extended limbs	Vigorous crying Agitation with rigid limbs
Facial expression	No expression or smile	Grimace	Frown with trismus and chin shiver
Gagging	None	1 to 2 times	More than 2 times
Distress	Relaxed	Easy to comfort	Difficult to comfort

*Each category was scored separately.

Results

Demographics

We enrolled 352 infants, of whom 176 infants received an RV shortly before injection and 176 received an RV immediately after injection (Table 2). Sex, number of injections, main caregiver, feeding type, and RV type did not differ significantly between the experimental and comparison groups.

Positive versus negative pain response

Pain grades of 1 and 2 were categorized as positive pain response; by contrast, a pain grade of 0 was classified as a negative pain response. The comparison of pain responses between both groups is presented in Table 3. At 30 s after vaccination, pain responses of irritability, facial expression, and gagging were significantly lower in the experimental group than in the comparison group. Furthermore, at 180 s after vaccination, pain responses of crying, irritability, facial expression, and distress were significantly lower in the experimental group than in the comparison group. At 30 min after vaccination, both groups scored zero in all components of the pain scale.

The infant in both groups did not spit up during the administration of rotavirus and injectable vaccines. In all the infants, the RV was administered without incident.

Change in the composite pain grade following intervention

A composite pain grade was defined as a sum of all grades obtained in the following 5 categories: crying, irritability, facial expression, gagging, and distress. Table 4 presents a comparison of changes in the composite pain grade according to the timing of RV ingestion and number of injections. An increase in the composite pain grade indicated a positive pain response. The positive pain response of the experimental group tended to decrease than that of the comparison group at 30 s after vaccination ($p = 0.062$). Furthermore, at 180 s after vaccination, the positive pain response was significantly lower in the experimental group than in the comparison group.

Compared with the infants who received a single injection, the positive pain response significantly increased in the infants who received multiple injections at 30 s after vaccination. However, at 180 s after vaccination, the positive pain response did not differ significantly between the infants receiving multiple injections and those receiving a single injection.

Table 2. Demographic information of enrolled infants (N = 352).

Intervention Demographics	RV before injection n = 176	RV after injection n = 176	p value
Number of injection			0.362
Single	41 (23.3%)	34 (19.3%)	
Multiple	135 (76.7%)	142 (80.7%)	
Type of RV			0.910
Rotateq	59 (33.5%)	58 (33.0%)	
Rotarix	117 (66.5%)	118 (67.0%)	
Age (mo) (mean ± standard deviation)	2.24 ± 0.21	2.27 ± 0.26	0.232

Table 3. Comparison of pain scale between oral RV administration before and after injection.

Intervention Timing of observation	RV administration before injection n (%) of pain grade > 0	RV administration after injection n (%) of pain grade > 0	p value
0 sec before intervention			
Crying	13 (7.4%)	14 (8.0%)	0.841
Irritability	21 (11.9%)	17 (9.7%)	0.492
Facial expression	12 (6.8%)	12 (6.8%)	1.000
Gagging	2 (1.1%)	1 (0.6%)	0.624
Distress	17 (9.7%)	16 (9.1%)	0.855
30 sec after intervention			
Crying	102 (58.0%)	108 (61.4%)	0.514
Irritability	80 (45.5%)	104 (59.1%)	0.010
Facial expression	87 (49.4%)	109 (61.9%)	0.018
Gagging	4 (2.3%)	18 (10.2%)	0.002
Distress	92 (52.3%)	105 (59.7%)	0.163
180 sec after intervention			
Crying	7 (4.0%)	29 (16.5%)	<0.001
Irritability	4 (2.3%)	23 (13.1%)	<0.001
Facial expression	5 (2.8%)	23 (13.1%)	<0.001
Gagging	1 (0.6%)	2 (1.1%)	0.562
Distress	9 (5.1%)	31 (17.6%)	<0.001

Comparison of pain response by multivariate logistic regression analysis

A multivariate logistic regression analysis was used to compare the pain response between the experimental and comparison groups (Table 5). At 30 s after vaccination, pain responses of irritability, facial expression, and gagging were significantly lower in the experimental group than in the comparison group. Furthermore, at 180 s after vaccination, pain responses of crying, irritability, facial expression, and distress were significantly lower in the experimental group than in the comparison group.

Table 4. Changes in the composite pain grade after intervention.

Increase in the composite pain grade	30 s after intervention	p value	180 s after intervention	p value
Timing of RV administration		0.062		0.001
Before injection	100 (56.8%)		10 (5.7%)	
After injection	117 (66.5%)		29 (16.5%)	
Number of injections		0.027		0.170
Single	38 (50.7%)		5 (6.7)	
Multiple	179 (64.6%)		34 (12.3)	

Table 5. Comparison of the effectiveness of RV administration before and after injection on the risk of iatrogenic pain by using multivariate logistic regression analysis.

Pain response	Adjusted OR	95% CI	p
30 s after intervention			
Crying	0.869	0.563–1.342	0.527
Irritability	0.576	0.376–0.881	0.011
Facial expression	0.595	0.387–0.914	0.018
Gagging	0.197	0.065–0.596	0.004
Distress	0.738	0.480–1.134	0.165
180 s after intervention			
Crying	0.206	0.087–0.487	<0.001
Irritability	0.157	0.053–0.464	0.001
Facial expression	0.192	0.071–0.521	0.001
Gagging	0.501	0.044–5.662	0.577
Distress	0.240	0.110–0.526	<0.001

Discussion

In this randomized controlled trial (RCT), we investigated the effectiveness of oral RV administration in reducing injection-induced pain in infants at 6–12 weeks of age. We compared RV administration before injection with RV immediately after injection to determine pain responses. The results reveal that compared with RV administration after injection, RV administration before injection was more effective in reducing pain.

Several scoring systems have been developed to measure pain in infants. We used 5 major indices that parents are concerned with to measure pain response. These factors have been widely recognized as nonverbal pain indicators.[5] We analyzed these factors separately to prevent potential variations in a single index.[9] In addition, we recruited an independent observer blinded to the study purpose for minimizing possible pain assessment-related bias.

The mechanism through which RV administration affects pain responses has not yet been studied. However, some possible explanations can be provided. First, the RV is a sweet-tasting solution containing sucrose that acts as an analgesic effect to relieve pain from injection in young infants.[8,10,11] Many studies have confirmed that the oral administration of sweet-tasting solutions, such as oral sucrose or glucose, before painful procedures can reduce signs of pain in young infants.[12–17] This effect is attributable to the release of endogenous opioids that are activated by the sweet taste.[18] However, other studies have demonstrated little effect of sweet-tasting solutions on the relief of needle-induced pain.[19–22] In addition, a study proposed that sucrose reduces pain only during the young infant period but not after 4 mo of age;[23] this proposal is supported by our finding of a reduction in pain responses in 2-mo-old infants. Second, RV administration before injection may distract infants undergoing painful procedures. Distraction has been well documented as a useful method of reducing pain from injection.[24–26] Thus, we speculate that oral sweet-tasting solutions reduce clinical observational pain scores through not only pain relief but also distraction.[21]

Taddio *et al.* reported that RV administration before injection was as effective as a sucrose solution in reducing injection-induced pain.[8] Our study design differed from theirs. To the best of our knowledge, this is the first study to investigate the difference in RV administration before and after injection. The findings of our and their studies suggest that RV administration should be conducted before the administration of injectable vaccines to reduce pain.

Our study implied that RV administration before injection shortened the duration of crying and reduced the severity of gagging. Therefore, RV administration immediately after injection may increase the risk of spitting up. In addition, infants subjected to RV administration before injection were more relaxed, rested quietly, and were smiling. Taken together, these results provide evidence for the effect of RV administration on the relief of injection-induced pain.

In this study, most of the parents accepted the simultaneous administration of 2 injectable vaccines. However, we observed that compared with the administration of a single injectable vaccine, the simultaneous administration of 2 injectable vaccines was more painful. Moreover, the RV used in this study included Rotarix and Rotateq. Hence, whether the RV brand is associated with the reduction of injection-induced pain remains unclear. Therefore, we used multivariate logistic regression analysis to adjust the number of injections and the type of RV.

This study has some limitations. First, we selected a convenient sample of infants whose parents were willing to participate from a well-baby clinic. Nevertheless, we used multivariate logistic regression analysis to reduce recruitment bias. Second, parental behavior to comfort their babies might influence our results because the parents were aware that they were being observed. Nonetheless, we randomized the enrolled infants to minimize the possible bias from parents. The strengths of our study are as follows. First, this study was a RCT. Second, the sample size of our study is relatively large compared with those of previous RCTs.[8,19, 21]

The results of this study provide crucial implications for clinical practice. To date, guidelines regarding the sequence of the administration of oral RVs and other injectable vaccines are not available. Although it is recommended to administer RVs before injection, RCTs comparing the effectiveness of RV administration before and after injection on pain reduction are lacking. The current study is the first to report that pain reduction in infants receiving the RV before injection was superior to that in those receiving the RV after injection. In conclusion, our data suggest RV administration can serve as an alternative method for relieving injection-induced pain in infants.

Material and methods

Study design

The study was designed as a RCT. This prospective study involved exploratory research on the intervention of infant holding and examination of infant pain responses after regular vaccination. The flowchart of the study is presented in Fig. 1. We enrolled healthy infants who were administered a combination of oral rotavirus and injection vaccines at 6–12 weeks of age. We excluded infants who were admitted to the neonatal intensive care unit, had a gestational age of < 34 weeks, had a birth weight of < 2000 g, or had illnesses such as a significant congenital anomaly. The study was conducted in the well-baby clinic of Chang Gung Memorial Hospital between July 2014 and April 2015. The Institutional Review Board of Chang Gung Memorial Hospital approved the study protocol. Informed

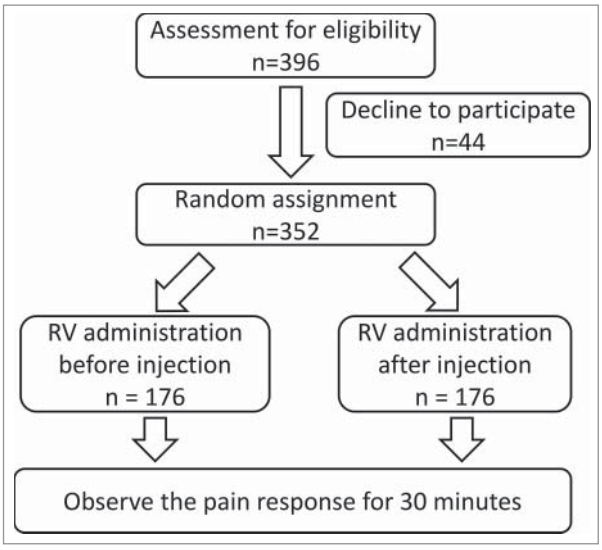

Figure 1. Flow-chart of study interventions and examinations.

consent was obtained from the parents of the enrolled infants. The sample size was determined using the G Power 3.1.2 program with a medium effect size of $\rho = 0.3$, power of 0.8, and α of 0.05 for a 2-tailed test.

Procedure

Vaccination was administered in a quiet room. Parents were asked not to talk to or comfort their babies during the procedure. In the experimental group, an oral RV was administered shortly before the injection of adjunct vaccine(s). In the comparison group, the oral RV was administered immediately after the injection of adjunct vaccine(s). The duration of RV administration after vaccine injection was very short (about 5 s). No additional intervention was conducted during the period of RV administration. Feeding was not allowed between 30 min before and 30 min after RV administration.

The injected vaccines were 13-valent pneumococcal conjugate vaccine (PCV13; Prevenar 13™; Pfizer, NY, USA) and DTPa-IPV/Hib (diphtheria toxoid, tetanus toxoid, acellular pertussis, polio, and *Haemophilus influenzae* type b; Pediacel™; Sanofi Pasteur, Lyon, France). The injection procedure, including skin cleaning, injection site, injection pressure, and total injection time, was standardized for all vaccinations to maintain consistency. Clinical nurses initially administered DTPa-IPV/Hib and then PCV13 in alternate thighs.[27] Each vaccine was administered into the vastus lateralis muscle on the front of the thigh by using a reported procedure. [28, 29] All nurses in charge of injection were trained and accredited by practicing the procedure at least 3 times before the commencement of the study.

Measures

We examined infant pain responses by evaluating the following 5 categories: (1) crying, (2) irritability, (3) facial expression, (4) gagging, and (5) distress (Table 1). For each infant, the minimal and maximal grades of each pain category were 0 and 2, respectively. The pain scale used in this study was modified from published assessment tools, including the CRIES observational assessment tool and the FLACC measurement tool.[5] A well-trained nurse performed the standardized observational pain scale measurements. This nurse was not involved in the intervention and was blinded to the study purpose. After vaccination, participants were immediately transferred to an isolated room for observation. Pain scale measurements were obtained at 0 s before vaccination and 30s, 180 s, and 30 min after vaccination for each infant.

Validity and reliability

The content validity of our pain scale was established by 3 experts. Their expertise included nursing education, vaccination, and clinical nursing. All experts had more than 20 y of work experience in their respective fields. After adjustments based on experts' advice, the pain scale was piloted in a group of 30 infants to estimate internal consistency by using Cronbach's α. The content validity index was 0.97 and Cronbach's α was 0.95, indicating adequate validity and reliability.

Statistical analyses

Statistics were performed using a commercially available program (SPSS 19.0 for Windows; SPSS Inc., Chicago, IL, USA). Categorical variables were analyzed using the chi-square test or Fisher's exact test when appropriate. For comparing groups with quantitative variables, the null hypothesis that there was no difference between groups was tested through one-way analysis of variance. A multivariate logistic regression model was used to assess the infant pain scale by adjusting for possible confounders, namely sex, number of injections, main caregiver, feeding type, and RV type. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated after adjustment for control variables. Significance was defined as $p < 0.05$.

Abbreviations

CI	confidence interval
OR	odds ratio
RCT	randomized controlled trial
RV	rotavirus vaccine

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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