Original Article

Rotavirus vaccination is a protective factor for adverse outcomes in primary intussusception: a single-center retrospective study

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Background: The clinical features and prognosis of intussusception in children vaccinated against rotavirus were undefined. Hence, we conducted the study to explore the clinical characteristics and outcomes of primary intussusception patients who received rotavirus vaccine.

Methods: A single-center retrospective study was performed in 327 primary intussusception patients between January 2019 and December 2021. Of these, 168 were vaccinated against rotavirus and 159 were not, the latter serving as the control group. Data on patients' clinical characteristics, commonly used inflammatory biomarkers, treatment, and outcomes were collected and evaluated.

Results: Most of the vaccination group received pentavalent rotavirus vaccine produced by Merck, USA (89.88%). There were no differences in demographic characteristics, time from onset to hospital attendance, clinical symptoms and signs between the vaccination group and the control group. The success rate of air enema reduction in the vaccination group was higher than that in the control group (98.21% *vs*. 88.68%, q=0.01). The vaccination group had lower rates of surgery and complication (1.79% *vs*. 11.32%, q=0.008; 2.98% *vs*. 12.58%, q=0.006). Both platelet-lymphocyte ratio (PLR) and C-reactive protein (CRP) levels were lower in the vaccinated group (q=0.02, q=0.004). Higher CRP level [odds ratio (OR): 1.635; 95% confidence interval (CI): 1.248–2.143; P=0.006] and the longer time from onset to hospital attendance (OR: 3.040; 95% CI: 2.418–12.133; P=0.01) were associated with increased adverse events. Rotavirus vaccination (OR: 0.527; 95% CI: 0.103–0.751; P=0.02) was associated with a reduction in the probability of adverse events.

Conclusions: Adverse events such as surgery and complications were lower in the vaccination group. Rotavirus vaccination was an independent protective factor for adverse events in patients with primary intussusception.

Keywords: Primary intussusception; surgery; complication; rotavirus vaccination; children

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Introduction

Intussusception is one of the most common causes of acute bowel obstruction in infants and young children, with abdominal mass, bloody stool, and abdominal pain as the classic triad of clinical presentation (1). Ileocolic intussusception is the most common type, and approximately 90% of cases are idiopathic (1,2). Air enema reduction is the first-line treatment for intussusception, with success rates ranging from 60% to 90% (1). Surgery is needed when air enema fails, or when intestinal perforation and necrosis are suspected. It has been demonstrated that longer duration of symptoms, bloody stool and younger age were risk factors for enema failure (3).

For most intussusception cases, the cause is unknown. Some cases are caused by anatomical lead points. Studies (4-6) have linked gastroenteritis with an increased risk of intussusception. Rotavirus is the most common pathogen causing acute gastroenteritis. Rotavirus vaccine has been widely used in the prevention and control of rotavirus-associated gastroenteritis (7). Since 1999, when the first-generation rotavirus vaccine (RotaShield, Wyeth Laboratories, Marietta, Pennsylvania) was linked to a risk of intussusception following immunization (8), whether rotavirus vaccination increased the incidence of intussusception has attracted great attention (9-11).

The second-generation rotavirus vaccines [Rotateq (RV5) and Rotarix (RV1)] are recommended as a routine vaccine by the World Health Organisation (WHO) (12). RV5 produced by Merck, USA and the Lanzhou lamb rotavirus vaccine (LLR) produced by Lanzhou Institute of Biological Products in China was launched in China in 2000 and 2018 respectively. LLR is a single rotavirus strain G10P[15], and can stimulate the body to produce immunity to group A rotaviruses. LLR is mainly used in children between the age of 2 months and 3 years. It is taken orally once a year. RV5 is a multi-strain bovine-human reassortant, and can express the VP7 protein (G1, G2, G3, G4, G6) and the VP4 protein (P7[5], P1A[8]). RV5 is used to prevent rotavirus gastroenteritis in young children caused by serotypes G1, G2, G3, G4, and G9 (13). RV5 is administered orally with a total of three doses. The first dose is administered at 6–12 weeks of age. The interval of each dose is 4-10 weeks. The third dose should be administered no later than 32 weeks of age. A recent study (14) suggested that including RV5 in the national immunization programs (NIP) would reduce 62.6% of the total rotavirus gastroenteritis cases and 72.6% of the deaths. LLR through the NIP would avert 20.3% of rotavirus gastroenteritis cases and 22.4% of deaths. These results implied lower efficacy of LLR. Both LLR and RV5 are self-funded. RV5 is more expensive than LLR in China (900 RMB for three doses *vs.* 576 RMB for three doses). They can be available at preventive health care facilities. Parents choose to vaccinate their children voluntarily and pay for the vaccination.

Previous studies (8,12,15) have linked rotavirus vaccination to a small increased risk of intussusception. However, a growing number of studies have found that the incidence of intussusception does not increase after the introduction of rotavirus vaccine (2,7,16-18). Increasing evidence (19) suggested an overall reduction in intussusception in the first 12 months of life when early, high rotavirus vaccine coverage was achieved. Rotavirus vaccine coverage in Chengdu from 2019 to 2021 was 38.44%, 40.02% and 39.13%, respectively (Data provided by Chengdu Center for Disease Control and Prevention).

Highlight box

Key findings

- Rotavirus vaccination was an independent protective factor for adverse events in patients with primary intussusception.

What is known and what is new?

- A growing number of studies have found that the incidence of intussusception does not increase after the introduction of rotavirus vaccine. However, the clinical features and prognosis of intussusception in children vaccinated against rotavirus remain largely undefined.
- This study explored the clinical characteristics and outcomes of primary intussusception patients who received rotavirus vaccine. We found that rotavirus vaccination was associated with better outcomes and lower rates of surgery and complications.

What is the implication, and what should change now?

- Rotavirus vaccination was an independent protective factor for adverse events in patients with primary intussusception. Adverse events such as surgery and complications were lower in the vaccination group.

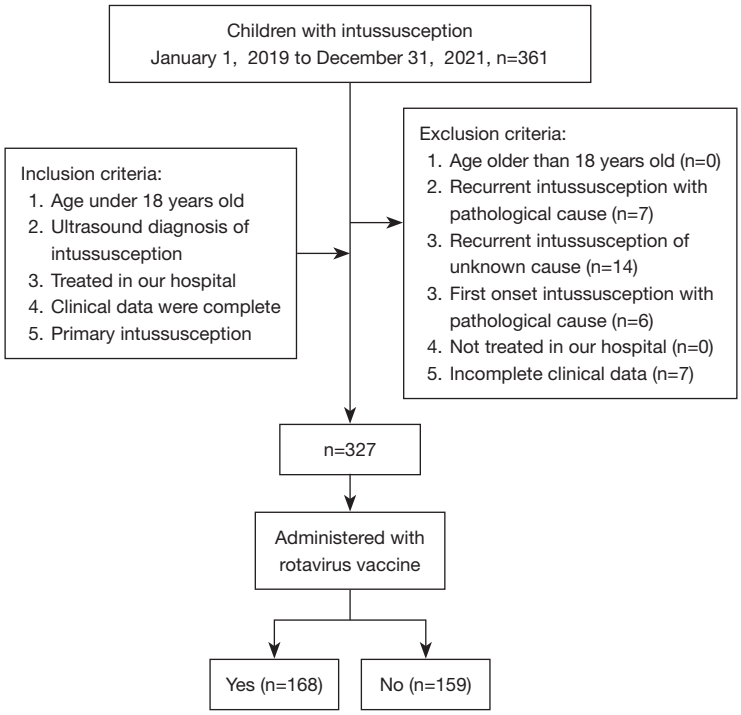

Figure 1 The flow chart of the cohort study.

The clinical features and prognosis of intussusception in children vaccinated against rotavirus remain largely undefined. Hence, we conducted the study to elucidate the clinical characteristics and outcomes of primary intussusception children with rotavirus vaccination. We present this article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-109/rc).

Methods

Study design and participants

This study was a single-center retrospective study. Children diagnosed with idiopathic intussusception for the first time without pathologic lead points were defined as primary intussusception (20,21). We focused on primary intussusception, as it was the most common type. We reviewed the medical records of pediatric patients (<18 years of age) with primary intussusception admitted to the Chengdu Women's and Children's Central Hospital (Sichuan, China), during the 3-year period from January 2019 to December 2021. Inclusion criteria were as follows: (I) age under 18 years old; (II) ultrasound diagnosis of intussusception. Ultrasound results were reviewed by senior pediatric ultrasound physicians (an attending physician and an associate chief physician); (III) treated in our hospital; (IV) clinical data were complete; (V) first occurrence of primary intussusception. Exclusion criteria were as follows: (I) age older than 18 years old; (II) recurrent intussusception; (III) intussusception with pathological cause; (IV) not treated in our hospital; (V) incomplete clinical data. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of the Chengdu Women's and Children's Central Hospital [No. 2019 (6)], and written informed consent was obtained from the parents or legal guardians of the children.

The flow chart is shown in *Figure 1*. A total of 361 cases of intussusception were recorded over the 3-year period. Clinical data were incomplete in 7 (1.94%) cases. Pathological causes were found in 13 (3.60%) cases (7 intestinal polyps, 4 Meckel's diverticulum, 2 intestinal duplicates). There were 21 (5.82%) cases of recurrent intussusception, of which 7 (1.94%) cases were patients with pathological intussusception mentioned above, and the cause of recurrence was unknown in the remaining 14 (3.88%) cases. Recurrent intussusception was defined as a subsequent intussusception after successful non-surgical or surgical

reduction of prior episode. Recurrent intussusception was a special group with complicated causes, mechanisms and outcomes. It has been reported that the longest interval between recurrence can be more than 5 years (22). This study excluded recurrent intussusception with low incidence and focused on idiopathic intussusception that occurred for the first time. At last, 327 primary intussusception patients were enrolled in this study. We divided the cohort into two groups based on whether they were vaccinated against rotavirus. The unvaccinated group was set up as the control group (n=159), and the clinical features and outcomes between the groups were compared.

In clinical practice of our hospital, the management of patients with intussusception followed the following standard protocol. Air enema reduction was firstly attempted, and if reduction failed, the patient was immediately transferred to manual surgical reduction. If intestinal necrosis was found during the operation, necrotic intestinal segment resection and anastomosis were required. For some patients with high suspicion of intestinal necrosis and perforation, such as peritonitis, surgery was first selected.

Two dedicated research staffs collected the data on patients' sociodemography and clinical characteristics. Age, gender, place of residence, season, symptoms, signs, intussusception location, commonly used inflammatory biomarkers at visit [neutrophils, lymphocytes, platelets, C-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR)], treatment, outcome were collected. Rotavirus vaccination information was collected from the Chengdu Center for Disease Control and Prevention. All data entry was double-checked. These data were used to analyze the clinical features of primary intussusception patients with rotavirus vaccination. We also analyzed the predictors of intussusception adverse events, hoping to provide guidance for clinical practice.

Definition

Abdominal pain was determined by subjective description in older children, especially those over 3 years old. In infants younger than 3 years old who could not express abdominal pain, abdominal pain was determined by medical history described by crying uneasiness and accompanying pale face, refusal to eat, and painful expressions. Complications were defined as the occurrence of intestinal necrosis, intestinal resection, and dehydration. Adverse events were defined as air enema failure, the need for surgical reduction, and the occurrence of complications.

Statistical analysis

Statistical analysis was performed using SPSS software version 23.0 (IBM Corp., Armonk, NY, USA). When the sample size was ≤50, Shapiro-Wilk test was used for normality test. When the sample size was >50, Kolmogorov-Smirnov test was applied for normality analysis. The normally distributed continuous variable was presented as mean ± standard deviation (SD). The continuous variable that was not normally distributed was presented as median (interquartile range, IQR). Unpaired two-tailed *t*-test was used to compare continuous variables of normal distributions. Mann-Whitney *U* test was employed for the comparison of continuous variables with non-normal distributions. Categorical variables were presented as absolute numbers and percentages using Chi-squared test or Fisher's Exact tests. Multivariable logistic regression analysis was used to identify the independent predictive factors. Results were expressed as odds ratios (ORs) with 95% confidence interval (CI). The P value was corrected by Benjamini & Hochberg (BH), and the result was expressed as q value. When $q<0.05$, values were considered statistically significant.

Results

Demographic characteristics

From January 2019 to December 2021, 327 primary intussusception patients were enrolled. Of these, 168 (51.38%) were vaccinated against rotavirus (vaccination group). Most of the vaccination group received RV5 (n=151, 89.88%) and very few received LLR (n=17, 10.12%). 79 patients received only one dose of vaccine (RV5, n=71; LLR, n=8), 70 patients received two doses of vaccine (RV5, n=63; LLR, n=7) and 19 patients received three doses of vaccine (RV5, n=17; LLR, n=2). A total of three intussusception cases occurred within 28 days of vaccination. Patients with primary intussusception who did not receive rotavirus vaccine were set up as the control group.

Demographic characteristics are summarized in *Table 1*. Most of the patients were under 3 years old. The youngest patient was of age of 5 months and the oldest was of age of 59 months. The median age of the vaccination group was 31 months, with most patients >12–36 m (n=88, 52.38%), similar to the control group. In the vaccination group, there

Table 1 Demographic characteristics of all patients with primary intussusception

Characteristics	Total (n=327)	Administered with rotavirus vaccine		P value	q value
		Yes (n=168)	No (n=159)		
Age (m), n (%)					
5–12	34 (10.40)	19 (11.31)	15 (9.43)	0.83[a]	0.83
>12–36	175 (53.52)	88 (52.38)	87 (54.72)		
>36	118 (36.09)	61 (36.31)	57 (35.85)		
Median [IQR]	32 [21–42]	31 [22–43]	33 [21–41]	0.67[b]	0.73
Gender, male, n (%)	199 (60.86)	101 (60.12)	98 (61.64)	0.78[a]	0.81
Season, n (%)					
Spring	86 (26.30)	48 (28.57)	38 (23.90)	0.11[a]	0.41
Summer	73 (22.32)	34 (20.24)	39 (24.53)		
Autumn	66 (20.18)	27 (16.07)	39 (24.53)		
Winter	102 (31.19)	59 (35.12)	43 (27.04)		
Place of residence, urban, n (%)	154 (47.09)	82 (48.81)	72 (45.28)	0.52[a]	0.73
The dose of rotavirus vaccine, n (%)					
0 dose of rotavirus vaccine	159 (48.62)	–	–	–	–
1 dose of RV5 vaccine	71 (21.71)	71 (42.26)	–	–	–
2 doses of RV5 vaccine	63 (19.27)	63 (37.50)	–	–	–
3 doses of RV5 vaccine	17 (5.20)	17 (10.12)	–	–	–
1 dose of LLR vaccine	8 (2.45)	8 (4.76)	–	–	–
2 doses of LLR vaccine	7 (2.14)	7 (4.17)	–	–	–
3 doses of LLR vaccine	2 (0.61)	2 (1.19)	–	–	–

[a], Chi-squared test was applied; [b], Mann-Whitney U test was applied. q value, the result after false discovery rate correction of the P value. m, months; IQR, interquartile range; RV5, the pentavalent rotavirus vaccine; LLR, the Lanzhou lamb rotavirus vaccine.

were more patients admitted in winter (n=59, 35.12%) and fewer in autumn (n=27, 16.07%). There were more male patients in the vaccination group (n=101, 60.12%). The proportion of patients in urban (n=82, 48.81%) was similar to that in non-urban areas. The demographic characteristics of the vaccination group were consistent with those of the control group, such as age, gender, season and regional distribution. No statistical differences were found.

Clinical characteristics

Table 2 summarizes the clinical characteristics. All patients were diagnosed with intussusception by ultrasound. Ileocolic intussusception was the most common type (82.57%). Most patients (n=292, 89.30%) were clinically reviewed by a doctor within 48 hours. Vomiting and abdominal pain were the most common clinical manifestations (61.47%, 52.91%), while bloody stool was less common (10.70%). The classic triad of intussusception (abdominal pain, bloody stool, and a palpable mass) was uncommon in this study, accounting for only 1.83%. Abdominal mass was documented in 38.23% patients. Few patients had fever (6.73%), diarrhea (5.50%), and abdominal distension (2.75%). There were no significant differences in time from onset to hospital attendance, clinical symptoms and signs, site of intussusception between the vaccination group and the control group.

All the patients of the vaccination group were given air enema reduction. We find that the success rate of air enema reduction in the vaccination group was much higher than

Table 2 Clinical characteristics of patients with administered rotavirus vaccine or not

Characteristics	Total (n=327)	Administered with rotavirus vaccine		P value	q value
		Yes (n=168)	No (n=159)		
Time from onset to hospital attendance (h), n (%)					
Median [IQR]	25 [18–35]	24 [17–36]	26 [18–36]	0.57[b]	0.72
<48	292 (89.30)	154 (91.67)	138 (86.79)	0.15[a]	0.43
Symptom, n (%)					
Fever	22 (6.73)	10 (5.95)	12 (7.55)	0.56[a]	0.74
Vomiting	201 (61.47)	108 (64.29)	93 (58.49)	0.28[a]	0.50
Diarrhea	18 (5.50)	7 (4.17)	11 (6.92)	0.25[a]	0.52
Bloody stool	35 (10.70)	14 (8.33)	21 (13.21)	0.15[a]	0.38
Abdominal pain	173 (52.91)	91 (54.17)	82 (51.57)	0.64[a]	0.73
Classical triad	6 (1.83)	2 (1.19)	4 (2.52)	0.37[c]	0.58
Sign, n (%)					
Abdominal distension	9 (2.75)	6 (3.57)	3 (1.89)	0.35[a]	0.59
Abdominal mass	125 (38.23)	62 (36.90)	63 (39.62)	0.61[a]	0.73
Location, ileocolic intussusception, n (%)	270 (82.57)	144 (85.71)	126 (79.25)	0.12[a]	0.38
Air enema reduction, success rate, n (%)	306 (93.58)	165 (98.21)	141 (88.68)	0.001[a]	0.01
Surgery, n (%)	21 (6.42)	3 (1.79)	18 (11.32)	0.001[a]	0.008
Complications, n (%)	25 (7.65)	5 (2.98)	20 (12.58)	0.001[a]	0.006
Intestinal necrosis and resection, n (%)	2 (0.61)	0 (0.00)	2 (1.26)	–	
Intestinal necrosis and resection+ dehydration, n (%)	3 (0.92)	0 (0.00)	3 (1.89)	–	
Dehydration, n (%)	20 (6.12)	5 (2.98)	15 (9.43)	–	

[a], Chi-squared test was applied; [b], Mann-Whitney U test was applied; [c], Fisher's Exact test was applied. q value, the result after false discovery rate correction of the P value. h, hours; IQR, interquartile range.

the control group (98.21% *vs.* 88.68%, q=0.01). Three patients of the vaccination group and 13 patients of the control group who failed air enema received timely surgical treatment and intraoperative manual reduction, and all of them were successfully reduced without intestinal necrosis or resection. In addition, five patients in the control group with severe intussusception had poor general conditions, abdominal pain and distension, excessive bloody stool, and high suspicion of intestinal necrosis. Thus, air enema reduction was not performed and direct surgical treatment was selected. Intestinal necrosis was confirmed during the operation, and necrotic intestinal resection and enterostomy were performed. The vaccination group had a lower surgical rate (1.79% *vs.* 11.32%, q=0.008), and no intestinal necrosis and resection occurred.

Complications were also lower in the vaccination group (2.98% *vs.* 12.58%, q=0.006). Only five patients in the vaccination group developed complications, all of which were dehydration due to vomiting, diarrhea and reduced intake. A total of 20 patients in the control group had complications, including two cases of necrotic enterectomy, 15 cases of dehydration, three cases of necrotic enterectomy combined with dehydration. No death was observed in this study. Inflammatory biomarkers play an important role in predicting intestinal inflammation. As shown in *Table 3*, both PLR and CRP levels were lower in the vaccinated group (q=0.02, q=0.004). Vaccinated children were less prone to inflammation. While there were no statistical differences in other inflammatory markers such as neutrophils, lymphocytes, platelets and NLR between the

Table 3 Inflammatory biomarkers at hospital attendance

Category	Total (n=327)	Administered with rotavirus vaccine		P value[d]	q value
		Yes (n=168)	No (n=159)		
Neutrophil (10^9/L)	2.45±1.21	2.38±1.19	2.53±1.22	0.26	0.51
Lymphocyte (10^9/L)	5.90±2.04	5.85±1.66	6.07±2.32	0.16	0.37
Platelet (10^9/L)	355.62±141.32	341.62±139.73	368.87±141.96	0.08	0.34
CRP (g/L)	8.20±7.49	6.66±4.50	9.82±9.44	<0.001	0.004
NLR	0.49±0.38	0.50±0.41	0.47±0.35	0.41	0.61
PLR	69.78±37.46	63.80±34.78	75.45±39.10	0.005	0.02

Data are presented as mean ± SD. [d], unpaired two-tailed *t*-test was applied. q value, the result after false discovery rate correction of the P value. SD, standard deviation; CRP, C-reactive protein; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio.

Table 4 Clinical features of patients with adverse events

Variable	Adverse events		P value	q value
	Yes (n=41)	No (n=286)		
Age (months), median [IQR]	25 [9–42]	33 [23–42]	0.01[b]	0.03
Gender, male, n (%)	30 (73.17)	169 (59.09)	0.08[a]	0.14
Place of residence, urban, n (%)	16 (39.02)	138 (48.25)	0.32[a]	0.40
Time from onset to hospital attendance (h), mean ± SD	39.34±10.52	17.83±8.47	<0.001[d]	<0.001
Fever, n (%)	6 (14.63)	16 (5.59)	0.04[a]	0.10
Vomiting, n (%)	27 (65.85)	174 (60.84)	0.07[a]	0.13
Diarrhea, n (%)	7 (17.07)	11 (3.85)	0.003[a]	0.01
Bloody stool, n (%)	20 (48.78)	15 (5.24)	<0.001[a]	0.02
Abdominal pain, n (%)	14 (34.15)	159 (55.59)	0.01[a]	0.04
Abdominal distension, n (%)	2 (4.88)	7 (2.45)	0.70[a]	0.74
Abdominal mass, n (%)	17 (41.46)	108 (37.76)	0.73[a]	0.73
Ileocolic intussusception, n (%)	30 (73.17)	240 (83.92)	0.12[a]	0.19
Rotavirus vaccination, n (%)	6 (14.63)	162 (56.64)	<0.001[a]	0.009

[a], Chi-squared test was applied; [b], Mann-Whitney U test was applied; [d], unpaired two-tailed *t*-test was applied. q value, the result after false discovery rate correction of the P value. IQR, interquartile range; SD, standard deviation.

two groups.

Rotavirus vaccination is a protective factor for adverse events

The clinical features and inflammatory biomarkers of the adverse events group are summarized in *Tables 4*,*5*. The patients suffered from adverse events were younger than those without adverse events (median age: 25 *vs.* 33 months, q=0.03). The adverse events group had a longer time from onset to hospital attendance (39.34±10.52 *vs.* 17.83±8.47 hours, q<0.001). As expected, patients with adverse events were more likely to have diarrhea (17.07% *vs.* 3.85%), and bloody stool (48.78% *vs.* 5.24%). The CRP level was higher in adverse events group (21.61±13.71 *vs.* 6.27±2.85, q=0.006), suggesting a more severe inflammatory response. Other inflammation markers (neutrophils, lymphocytes, platelets, PLR, NLR) were not statistically different between

Table 5 Inflammatory biomarkers of patients with adverse events

Variable	Adverse events		P value[d]	q value
	Yes (n=41)	No (n=286)		
Neutrophil (10^9/L)	2.77±1.30	2.40±1.19	0.07	0.14
Lymphocyte (10^9/L)	5.97±2.47	5.66±1.97	0.37	0.44
Platelet (10^9/L)	378.07±163.41	352.41±137.89	0.28	0.38
CRP (g/L)	21.61±13.71	6.27±2.85	<0.001	0.006
NLR	0.56±0.54	0.47±0.35	0.17	0.24
PLR	74.18±44.43	69.15±36.40	0.49	0.55

Data are presented as mean ± SD. [d], unpaired two-tailed *t*-test was applied. q value, the result after false discovery rate correction of the P value; SD, standard deviation; CRP, C-reactive protein; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio.

Table 6 Independent predictors of adverse events in primary intussusception

Variable	Multicollinearity analysis		Multivariable logistic regression				
	Tolerance	VIF	β	S.E.	Wald χ^2	P value	OR (95% CI)
Age	0.923	1.084	0.063	0.037	2.831	0.09	1.165 (0.890–2.146)
Time from onset to hospital attendance	0.799	1.252	1.112	1.013	1.205	0.01	3.040 (2.418–12.133)
Diarrhea	0.907	1.103	–0.154	1.336	0.013	0.91	0.857 (0.163–2.752)
Abdominal pain	0.937	1.067	–1.549	0.765	7.309	0.27	0.721 (0.138–2.899)
Rotavirus vaccination	0.901	1.109	–1.175	0.632	9.607	0.02	0.527 (0.103–0.751)
CRP	0.846	1.182	0.492	0.138	12.691	0.006	1.635 (1.248–2.143)

VIF, variance inflation factor; S.E., standard error; OR, odds ratio; CI, confidence interval; CRP, C-reactive protein.

the two groups. Abdominal pain was less common in the adverse events group (34.15% *vs.* 55.59%). Notably, the rotavirus vaccination rate was lower in the adverse events group (14.63% *vs.* 56.64%). This suggested that rotavirus vaccination may be a protective factor for adverse events.

Bloody stool usually indicates long-term intestinal obstruction ischemia and necrosis. It has been widely accepted as an important manifestation of late intussusception. Therefore, it is not suitable as a predictor of adverse events. We excluded bloody stool and included the remaining six variables with q<0.10 (age, time from onset to hospital attendance, diarrhea, abdominal pain, rotavirus vaccination, CRP) into logistics regression analysis (*Table 6*). In order to determine whether there was collinearity, we conducted a multicollinearity analysis, and the results are shown in *Table 6*. These variables did not have collinearity problems.

The results demonstrated that higher CRP level (OR: 1.635; 95% CI: 1.248–2.143; P=0.006) and the longer time from onset to hospital attendance (OR: 3.040; 95% CI: 2.418–12.133; P=0.01) were associated with increased adverse events. Rotavirus vaccination (OR: 0.527; 95% CI: 0.103–0.751; P=0.02) was found to reduce the probability of adverse events. This further suggested that rotavirus vaccination was an independent protective factor against adverse events in patients with primary intussusception.

Discussion

The rotavirus vaccination rate in children with intussusception in this study was higher than that reported in India (51.38% *vs.* 24.1%) (23). A growing number of studies have found that the introduction of rotavirus vaccine does not increase the incidence of intussusception (2,7,16-18,24). Wang *et al.* (25) included 15 randomized controlled studies from different countries for the latest meta-analysis and found that rotavirus vaccination did not increase the incidence of intussusception, and there was no

significant difference in the incidence of intussusception by subgroup analysis of different vaccine brands and types. More importantly, data from Korea and Japan (26,27) showed that the incidence of intussusception in children decreased after rotavirus vaccine introduction, suggesting that rotavirus vaccination may also have a protective effect.

We analyzed the clinical features of children with primary intussusception who received rotavirus vaccine. The included patients in this study were older with a median age of 32 months. In the Indian multicenter study (23) and another study (28) in Zhejiang, China, most patients were younger than 1 year old. In addition, a study (29) from Shandong, China, reported that the peak age of intussusception was 3 to 4 years old. There were huge differences in different regions. These differences may be related to the environment, diet, genetic background and so on in different regions (30). There were no statistical differences in demographic characteristics between the vaccination group and the control group. Vomiting and abdominal pain were the most common manifestations of primary intussusception, but bloody stool was rare in this study, and the classic triad of intussusception was even rarer. There were no significant differences in time from onset to hospital attendance, clinical symptoms and signs between the vaccination group and the control group.

Complete blood count and CRP are simple and inexpensive but contains important follow-up parameters for many diseases. PLR and NLR are easily calculable indexes that correlate with the prognosis of many diseases. We found that both PLR and CRP levels were lower in the vaccinated group, suggesting vaccinated children were less prone to inflammation. Rotavirus vaccination is an important and effective strategy for the prevention and control of rotavirus infection. A Turkish study (31) of rotavirus gastroenteritis also found lower PLR and less inflammatory responses in rotavirus vaccinated children. These results suggested that vaccination may reduce the severity of inflammation.

Intussusception can lead to bowel ischemia and necrosis, so resection of necrotic intestinal may be required. Early air enema is still the first choice for intussusception treatment. A study of 121 intussusception cases in Nigeria (32) showed that 53 (43.8%) had bowel resection. In the study of Chen *et al.* (33), 115 intussusception patients underwent surgery, 47 patients (40.9%) underwent intestinal resection. While, in our study of 327 primary intussusception cases, only 21 (6.42%) cases underwent surgery, and five cases had intestinal resection, which was much lower. Compared with the multi-center report in India (23), the successful enema reduction rate was much higher in this study (93.58% *vs.* 83.8%), and surgical patients were also fewer (6.42% *vs.* 16.2%). The reason may be that most of the patients in our study received timely and effective treatment, thus improving the success rate. This suggested the importance of early diagnosis and treatment. Our facility is one of the largest tertiary children's hospitals in China. We have experienced clinical and ultrasound doctors, and can accurately diagnose intussusception through simple, non-invasive ultrasound in the early stage. This also suggested the importance of experienced ultrasonic examination in the early diagnosis of intussusception.

It is worth noting that the success rate of air enema reduction in the vaccination group was much higher than the control group (98.21% *vs.* 88.68%, q=0.01). Meanwhile, the vaccination group also had a lower surgical rate (1.79% *vs.* 11.32%, q=0.008), and no intestinal necrosis and resection occurred. Complications such as necrotic enterectomy and dehydration were also lower in the vaccination group (2.98% *vs.* 12.58%, q=0.006). The exact mechanisms underlying these differences are unclear. A study (34) found that intussusception patients with adenovirus infection exhibited a lower rate of surgical intervention (7.4%) than uninfected controls (17.2%). From these similar outcomes and lower levels of inflammation markers in vaccinated children, we hypothesized that the virus-associated intestinal protective immune response may promote intestinal function, reduce inflammation and facilitate intestinal peristalsis unwinding after intussusception. More studies are needed to further confirm these results and assumptions.

Previous studies (1,3,35) found that longer duration of symptoms and bloody stool were associated with failed enema reduction, increased surgery and complications. Another meta-analysis (1) confirmed that age younger than 1 year, presence of fever and vomiting were risk factors for enema reduction failure. In this study, adverse events were defined as failure of air enema requiring surgical reduction, resection of intestinal necrosis and dehydration. Consistent with previous findings, we found that longer time from onset to hospital attendance was a risk factor for adverse events. It may be due to prolonged intestinal obstruction, mucosal ischemia leading to adverse events (28). An Indian study (36) presented the retrospective outcomes of intussusception children when rotavirus vaccine was not in routine use, and the prospective outcomes of intussusception children in a phase III oral rotavirus vaccine trial. Prospective cases did not require surgery and had a better prognosis. This suggested that vaccinated

intussusception children who received active monitoring and management may have a better prognosis. Health care providers need to fully inform parents of the risk and management of intussusception during vaccine consultation, so that these children can visit the hospital in a shorter time when intussusception occurs. This plays an important role in improving prognosis.

Higher CRP level was also proved to be associated with increased adverse events. Similarly, another study found that intussusception patients requiring surgical reduction presented higher levels of NLR and CRP, and high NLR level might anticipate the need for surgery (37). Systemic inflammation was recognized as the hallmark of intestinal complications. Elevated inflammatory biomarkers may indicate intestinal necrosis and perforation in intussusception (33). To our surprise, rotavirus vaccination was found to reduce the probability of adverse events. The possible mechanism may be that vaccinated patients had less inflammatory responses. Increasing evidence (19) suggested an overall reduction in intussusception in the first 12 months of life when early, high rotavirus vaccine coverage was achieved. These results may also suggest that the reassortant/attenuated vaccine strains induce a lower generalized inflammatory response and have high effectiveness. Further studies are needed to confirm these assumptions.

There were several limitations in our study. First, this was a retrospective study with data obtained from a single institution in China. Large sample data from multiple centers were not included. Sampling error may be possible. This study excluded recurrent intussusception with low incidence and focused on idiopathic intussusception that occurred for the first time. Bias therefore could not be avoided. Therefore, our cohort cannot represent the real situation of the whole population, and the conclusions may not be generalized. Second, clinical characteristics of intussusception patients with different rotavirus vaccine subtypes or different vaccine doses were not analyzed. Third, these intussusception patients were unable to provide accurate information about their past gastroenteritis history and rotavirus surveillance. We did not have data on the prevalence of gastroenteritis and rotavirus infection in vaccinated and unvaccinated children. We were unable to compare clinical differences in intussusception children with the vaccine strain versus the wild strain.

Conclusions

Our retrospective study revealed that rotavirus vaccination was associated with better outcomes and lower rates of surgery and complications in children with primary intussusception. Rotavirus vaccination is an independent protective factor for adverse events. Longer time from onset to hospital attendance and high CRP level might anticipate adverse events.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-109/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-109/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of the Chengdu Women's and Children's Central Hospital [No. 2019 (6)], and written informed consent was obtained from the parents or legal guardians of the children.

References

1. Kim PH, Hwang J, Yoon HM, et al. Predictors of failed enema reduction in children with intussusception: a systematic review and meta-analysis. Eur Radiol 2021;31:8081-97.
2. Groome MJ, Tate JE, Arnold M, et al. Evaluation of Intussusception After Oral Monovalent Rotavirus Vaccination in South Africa. Clin Infect Dis 2020;70:1606-12.
3. Huang HY, Lin XK, Guo SK, et al. Haemostatic indexes for predicting intestinal necrosis in children with intussusception. ANZ J Surg 2021;91:1485-90.
4. Muhsen K, Kassem E, Efraim S, et al. Incidence and risk factors for intussusception among children in northern Israel from 1992 to 2009: a retrospective study. BMC Pediatr 2014;14:218.
5. Willame C, Cheuvart B, Aris E, et al. Association between rotavirus gastroenteritis and intussusception: suggested evidence from a retrospective study in claims databases in the United States. Hum Vaccin Immunother 2021;17:269-77.
6. Fotso Kamdem A, Vidal C, Pazart L, et al. A case-control study of risk factors for intussusception among infants in eastern France after the introduction of the rotavirus vaccine. Vaccine 2019;37:4587-93.
7. Sun ZW, Fu Y, Lu HL, et al. Association of Rotavirus Vaccines With Reduction in Rotavirus Gastroenteritis in Children Younger Than 5 Years: A Systematic Review and Meta-analysis of Randomized Clinical Trials and Observational Studies. JAMA Pediatr 2021;175:e210347.
8. Escolano S, Hill C, Tubert-Bitter P. Intussusception risk after RotaTeq vaccination: evaluation from worldwide spontaneous reporting data using a self-controlled case series approach. Vaccine 2015;33:1017-20.
9. Clark AD, Hasso-Agopsowicz M, Kraus MW, et al. Update on the global epidemiology of intussusception: a systematic review of incidence rates, age distributions and case-fatality ratios among children aged <5 years, before the introduction of rotavirus vaccination. Int J Epidemiol 2019;48:1316-26.
10. Bruun T, Watle SSV, Tveteraas IH, et al. Intussusception among Norwegian children: What to expect after introduction of rotavirus vaccination? Vaccine 2019;37:5717-23.
11. Fathima P, Moore HC, Blyth CC, et al. Association between rotavirus vaccination and intussusception in Australian children: A record linkage study. Paediatr Perinat Epidemiol 2020;34:583-9.
12. Kassim P, Eslick GD. Risk of intussusception following rotavirus vaccination: An evidence based meta-analysis of cohort and case-control studies. Vaccine 2017;35:4276-86.
13. Vetter V, Gardner RC, Debrus S, et al. Established and new rotavirus vaccines: a comprehensive review for healthcare professionals. Hum Vaccin Immunother 2022;18:1870395.
14. Wang J, Zhang H, Zhang H, et al. Public health impact and cost-effectiveness of rotavirus vaccination in China: Comparison between private market provision and national immunization programs. Hum Vaccin Immunother 2022;18:2090162.
15. Haber P, Parashar UD, Haber M, et al. Intussusception after monovalent rotavirus vaccine-United States, Vaccine Adverse Event Reporting System (VAERS), 2008-2014. Vaccine 2015;33:4873-7.
16. Lu HL, Ding Y, Goyal H, et al. Association Between Rotavirus Vaccination and Risk of Intussusception Among Neonates and Infants: A Systematic Review and Meta-analysis. JAMA Netw Open 2019;2:e1912458.
17. Roose A, Keita AM, Tapia MD, et al. Incidence of Intussusception in Bamako, Mali, Before and After the Introduction of Rotavirus Vaccine. J Pediatric Infect Dis Soc 2022;11:404-7.
18. Tate JE, Mwenda JM, Keita AM, et al. Evaluation of Intussusception Following Pentavalent Rotavirus Vaccine (RotaTeq) Administration in 5 African Countries. Clin Infect Dis 2024;78:210-6.
19. Cohen R, Martinón-Torres F, Posiuniene I, et al. The Value of Rotavirus Vaccination in Europe: A Call for Action. Infect Dis Ther 2023;12:9-29.
20. Zhang T, Cui L, Geng X, et al. Epidemiology study of pediatric primary intussusception aged ≤24 months in pre-rotavirus vaccine era of Jinan, China. Vaccine 2019;37:1436-42.
21. Wei CH, Fu YW, Wang NL, et al. Laparoscopy versus open surgery for idiopathic intussusception in children. Surg Endosc 2015;29:668-72.
22. Chen X, Chen Q, Wang X, et al. Clinical characteristics of recurrent intussusception: A single-center retrospective study. J Pediatr Surg 2021;56:1831-4.
23. Das MK, Arora NK, Mathai J, et al. Profile and Epidemiology of Intussusception in Children Under-Two

Years of Age: A Prospective Surveillance. Indian J Pediatr 2021;88:1187-94.
24. Reddy SN, Nair NP, Tate JE, et al. Intussusception after Rotavirus Vaccine Introduction in India. N Engl J Med 2020;383:1932-40.
25. Wang G, Zhang K, Zhang R, et al. Impact of vaccination with different types of rotavirus vaccines on the incidence of intussusception: a randomized controlled meta-analysis. Front Pediatr 2023;11:1239423.
26. Fukuda Y, Akane Y, Honjo S, et al. Characteristics of intussusception among children in Hokkaido, Japan, during the pre- and post-rotavirus vaccine eras (2007-2016). Acta Paediatr 2023;112:868-75.
27. Cho HK, Hwang SH, Nam HN, et al. Incidence of intussusception before and after the introduction of rotavirus vaccine in Korea. PLoS One 2020;15:e0238185.
28. Hu J, Liu M, Yu X, et al. Clinical Characteristics of Intussusception with Surgical Reduction: a Single-Center Experience with 568 Cases. J Gastrointest Surg 2019;23:2255-62.
29. Sun Z, Song G, Lian D, et al. Process Management of Intussusception in Children: A Retrospective Analysis in China. Pediatr Emerg Care 2022;38:321-5.
30. Guo WL, Geng J, Zhan Y, et al. Forecasting and predicting intussusception in children younger than 48 months in Suzhou using a seasonal autoregressive integrated moving average model. BMJ Open 2019;9:e024712.
31. Okuyan O, Elgormus Y, Sayili U, et al. The Effect of Virus-Specific Vaccination on Laboratory Infection Markers of Children with Acute Rotavirus-Associated Acute Gastroenteritis. Vaccines (Basel) 2023;11:580.
32. Ajao AE, Lawal TA, Ogundoyin OO, et al. Clinical predictors and outcome of bowel resection in paediatric intussusception. Afr Health Sci 2020;20:1463-70.
33. Chen B, Cao J, Yan C, et al. A promising new predictive factor for detecting bowel resection in childhood intussusception: the lymphocyte-C-reactive protein ratio. BMC Pediatr 2021;21:577.
34. Tseng WY, Chao HC, Chen CC, et al. Adenovirus infection is a risk factor for recurrent intussusception in pediatric patients. Pediatr Neonatol 2023;64:428-34.
35. Younes A, Lee S, Lee JI, et al. Factors Associated with Failure of Pneumatic Reduction in Children with Ileocolic Intussusception. Children (Basel) 2021;8:136.
36. Jehangir S, John J, Rajkumar S, et al. Intussusception in southern India: comparison of retrospective analysis and active surveillance. Vaccine 2014;32 Suppl 1:A99-103.
37. Delgado-Miguel C, García A, Delgado B, et al. Neutrophil-to-Lymphocyte Ratio as a Predictor of the Need for Surgical Treatment in Children's Intussusception. Eur J Pediatr Surg 2023;33:422-7.

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