Vaccine 32S (2014) A99–A103

Contents lists available at ScienceDirect

Vaccine

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

Intussusception in southern India: Comparison of retrospective analysis and active surveillance

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ARTICLE INFO

Article history:

Keywords:
Intussusception
Children
India
Active surveillance
Passive surveillance
Rotavirus vaccine

ABSTRACT

Surveillance for intussusception is a post marketing requirement for rotavirus vaccines following observation of a small increased risk of intussusception after rotavirus vaccination in some global settings. This study presents the clinical presentation and outcomes of children who presented with intussusception at a large tertiary care facility directly (non-surveillance) as retrospective analysis of a period where rotavirus vaccine was not in routine use, or as part of active surveillance in a phase III oral rotavirus vaccine trial.

Hospital records of children under 2 years of age treated for intussusception between 1 January 2010 and 31 August 2013 at the Christian Medical College Hospital, Vellore, India, were reviewed. Sixty-one cases of intussusception in children under two years of age presented at the hospital. An additional 16 cases of ultrasound diagnosed intussusception were identified through the active surveillance of a cohort of 1500 children participating in a rotavirus phase III trial in the same period.

In the nonsurveillance group, median age at presentation was 214 days (IQR 153–321) with 52 events (85.3%) occurring in the first year of life. Cases were seen year-round with no definitive evidence of seasonality. Thirty-one (50.8%) intussusceptions required surgical reduction, 26 (42.6%) had pneumatic reduction and 2 (3.3%) barium enema reduction. Two intussusceptions (3.3%) resolved spontaneously. There were no deaths, all children were discharged after recovery.

Active surveillance identified 16 children with a median age at event of 375 days (IQR 248–574). Nine (56%) children had small bowel or transient intussusception that resolved spontaneously. Seven intussusceptions were reduced radiologically; none required surgery.

In summary, there were significant differences between presentation and outcomes in cases of intussusception identified by passive and active surveillance, likely related to enhanced and early detection of intussusception through active monitoring in the trial. The WHO recommendation of sentinel hospital based surveillance for post-marketing surveillance after rotavirus vaccine introduction is likely to a better approach than active surveillance.

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1. Introduction

Rotavirus diarrhea contributes to an estimated 450,000 annual childhood deaths globally and is the most important cause of diarrheal mortality in the developing world [1]. Effective vaccines to prevent rotavirus diarrhea are licensed and available in several countries and offer a potent public health intervention in high mortality developing country settings [2]. Since 1999, when a tetravalent rhesus reassortant rotavirus vaccine (RotaShield, Wyeth Laboratories, Marietta, Pennsylvania) was linked to a 1 in 10,000 excess risk of intussusception following rotavirus immunization [3,4], concerns regarding intussusception have been associated with rotavirus vaccination. Currently licensed vaccines from Glaxo Smith Kline and Merck were evaluated in large safety studies that did not demonstrate increased risk of similar magnitude [5,6]. However postlicensure studies with both these vaccines, have identified a safety signal with 1–5 excess cases of intussusceptions in 100,000 immunized infants in different parts of the world [7–11]. While the risk benefit ratio of these vaccines remains

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http://dx.doi.org/10.1016/j.vaccine.2014.03.028
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overwhelmingly in favor of the vaccine [9,12], these concerns are likely to be key considerations in decision-making around introduction in a National Immunization Program (NIP).

When a new vaccine, especially one with a well-publicised, albeit rare, adverse event is introduced into a NIP, heightened awareness is likely to result in early reporting of events including self-limiting events which would not earlier have been documented. Interpreting post-introduction surveillance data of adverse events requires careful planning and an understanding of underlying event rates [13]. Intussusception, the commonest cause of acute intestinal obstruction in infants, involves the invagination of a bowel segment into another, and may occur in different segments of the small and large intestines. Large bowel intussusception, and the ileocecal type where the ileum invaginates through the ileocecal valve into the cecum often result in intestinal ischemia and intestinal obstruction requiring radiological or surgical intervention. On the other hand, transient small bowel intussusceptions (ileo-ileal) are common, generally asymptomatic or mildly symptomatic and usually resolve spontaneously [14].

Cases of pediatric intussusception that presented to a large tertiary care centre in southern India from January 2010 to August 2013 were retrospectively reviewed in 2013. This facility also served as the primary referral facility for intussusception cases identified through active surveillance during a phase III rotavirus vaccine trial which recruited 1500 children from April 2011 to November 2011 and followed them until they reached 2 years of age, with follow up ending in September 2013. The analysis of safety data in the phase III trial did not reveal any statistically significant difference in the incidence of intussusception meeting Brighton level 1 diagnostic certainty in vaccinees or placebo recipients [15]. We describe the presentation, management and outcomes of children with intussusception who presented routinely at the hospital (defined as non-surveillance intussusception cases collected by retrospective analysis) as well as those who were detected through an active surveillance program as a part of safety monitoring of the vaccine trial (defined as surveillance intussusception cases). This study may inform appropriate implementation and interpretation of intussusception surveillance post-licensure of rotavirus vaccines in similar developing country settings.

2. Materials and methods

2.1. Retrospective study

A retrospective review of all children 0–2 years of age with intussusceptions treated between 1st January 2010 and 31st August 2013 at Christian Medical College and Hospital (CMC), Vellore was undertaken. This hospital with 2695 beds caters to 1.9 million outpatients and 120,000 inpatients annually, is the largest healthcare facility in the region and is the sole provider of pediatric surgery services in Vellore district, which has a population of about four million people.

Cases were identified in a two-step process. Possible cases of intussusception were first identified by an electronic search of the radiology database and operation registers. Ultrasound reports of all children who had an ultrasound of the abdomen were searched for keywords related to intussusception. All children less than 2 years of age with an ultrasound diagnosis of intussusception requiring intervention were included in the study. The diagnosis of intussusception was then confirmed by reviewing the medical records, operation notes and other investigations and entered into a database by one of the investigators.

2.2. Active surveillance in a vaccine trial

Additionally, as part of safety surveillance of a phase III rotavirus vaccine trial, 1500 infants recruited between April and November 2011 at the age of 6 weeks were randomized in a 2:1 ratio of vaccine to placebo and were actively followed up with weekly contacts by field workers until they reached two years of age. All participants in this trial were provided mobile phones and access to a call center around the clock for the duration of follow up. They were also contacted weekly by field workers to check on the health status of the child. Any child with a history of blood in stools (any quantity including streaking), or continuous vomiting (> = 3 episodes in an hour) or any abdominal distension or abdominal lump was considered a case of suspected intussusception and was reviewed by a pediatrician in the study team or at the CMC hospital. The criteria for screening were agreed on by an expert group of pediatricians prior to development of the clinical trial protocol and were designed to be broad and sensitive, such that risk was minimized by ensuring that study investigators intensively followed up and arranged appropriate management for each child suspected to have intussusception. A screening ultrasonagram was performed by a trained sonologist on participants who had symptoms or signs confirmed on review by the study pediatrician. Those identified to have an intussusception, including transient intussusception, were reviewed by a pediatric surgeon and managed according to standard treatment algorithms and classified according to the Brighton criteria [16] by an off-site adjudication committee. Clinical data from hospital records of trial participants was abstracted by a pediatric surgeon and compared to data maintained at the clinical trial site by a second investigator.

Data were entered in Microsoft Excel and analyzed using Stata 11 (StataCorp, 2009). The incidence rate of symptomatic intussusception and those that were Brighton level 1 were calculated from the event rate in this cohort. Incidence rates and 95% CI were calculated assuming a Poisson distribution.

3. Results

3.1. Intussusceptions presenting through routine care identified on retrospective analysis

Apart from the 16 intussusceptions identified in the vaccine trial and described separately below, 61 children under two years of age had a diagnosis of intussusception made at CMC between January 2010 and August 2013. Thirty-one (50.8%) were referred from another hospital while 30 (49.2%) presented directly at CMC. The median time from onset of symptoms to arrival at the hospital was 48 h (range 6–240 h). The median age at presentation was 214 days (IQR 153–321) with 52 events (85.3%) occurring in the first year of life. As shown in Fig. 1, the age distribution was unimodal with a peak between 4 and 6 months of age. Males (42, 65.8%) were twice as likely to present with intussusception as females in this setting.

In all 61 intussusceptions evidence of intestinal invagination was present on ultrasonogram. The admission notes of two children were not traced in the records. The presenting symptoms for 59 of the 61 patients whose records were complete is presented in Table 1. Evidence of intestinal obstruction was noted in 27 cases (45.8%). Evidence of intestinal vascular compromise assessed by the passage of blood in stools or red currant jelly stools was present in 55 patients (93.2%).

Based on the Brighton Collaboration Intussusception Working Group criteria [16], 59 (96.7%) children met level 1 diagnostic certainty and 2 (3.3%) met level 2. Surgical intervention was required in 31 (50.8%) children. Sixteen (51.6%) of those children who had

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