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Safety Profile of Rotavac: An Observational Prospective Study

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Abstract: **Rotavirus vaccination (ROTAVAC®) was included in the rainbow of the Universal Immunization Program (UIP) of Punjab, India in 2019. This is a single centre observational prospective study conducted in Government Civil Hospital in Punjab, India.**

Endpoints: This study has two endpoints; Primary, to detect and study the adverse events (AE) arising after ROTAVAC® vaccine administration to infants and Secondary, to create awareness to promote the reporting of adverse events following immunization (AEFI) by Health Care Practitioners (HCPs).

Results: In this study, 47% of the subjects receiving ROTAVAC® vaccine experienced AEFIs. Overall, most of the AEFIs reported were non-serious and resolved completely in less than a day. Most of the AEFIs were consistent with the known safety profile of ROTAVAC® vaccine. There was no statistically significant difference between the different demographics and AEFI incidence. All the 30 HCPs who were interviewed had limited knowledge regarding reporting of AEFI and had rarely reported any AEFI. The mean score prior to imparting health education was 4.07±1.17, and the score after educating them increased to 7.27±1.05, depicting a statistically significant difference ($W=465.000$, $p<0.005$).

Conclusion: ROTAVAC® vaccine was found to be safe in Punjab, India where the vaccine was launched recently. There were no new safety concerns identified with ROTAVAC®. The study also highlights the importance of conducting knowledge sharing sessions for HCPs at immunization clinics to improve adverse event detection and reporting.

Keywords**: Rotavirus, Rotavac, intussusception, adverse events, adverse events following immunization, safety profile.**

I. INTRODUCTION

Diarrheal disease is one of the leading cause of child mortality in the world [1]. Infectious diarrhoea is caused by a variety of agents like bacteria, parasites, and viruses [1]. Among these, Rotavirus is the most important cause of severe diarrhea among children. The World Health Organization (WHO) estimates that globally 527,000 deaths occur each year among children as a result of rotavirus infection [2]. In India, diarrheal diseases are the third most common cause of death among infants and young children, after pneumonia followed by prematurity & low birth weight. It is responsible for 13% of deaths in children less than 5 years of age and approximately 34% of these deaths are due to rotavirus infection [3]. Thus, Rotavirus infection is a heavy burden on the healthcare system of a country because of its associated high mortality.

While there are effective antibacterial and antiparasitic drugs available for treating some intestinal infections, there is no approved pharmacotherapy for rotavirus infection. The management of rotavirus infection is symptomatic with an emphasis on the treatment of dehydration [4]. If untreated, the dehydration can be fatal for children [4]. In most of the cases, treatment involves the use of oral rehydration therapy. If the infection is serious enough to warrant hospitalization, then fluids are given by parenteral route, intravenous therapy or nasogastric intubation.

Vaccination has been accepted as an important method of protecting children from serious illness and complications of Vaccine-Preventable disease, all over the world. A vaccine to prevent Rotavirus gastroenteritis was first licensed in 1998 in the United States (US). This was a rhesus-based tetravalent rotavirus vaccine (RRV-TV, Rotashield). However, RRV-TV was withdrawn from the U.S. market within 1 year of its introduction because of its association with intussusception. After a gap of eight years, manufacturers were able to introduce new vaccines that were shown to be more safe and effective in children: RotaTeq® containing five rotavirus strains produced by reassortment, is a live, oral pentavalent vaccine and Rotarix® containing one rotavirus strain of G1P[8] specificity is a monovalent, human, live attenuated rotavirus vaccine. In India, ROTAVAC® is manufactured indigenously by Bharat Biotech International Limited, based on natural bovine- human reassortant rotavirus strain, 116E. It was licensed for use in India in 2014. This vaccine is a live attenuated, monovalent vaccine containing a G9P [11] human strain isolated from an Indian child. The vaccine is considered safe and has been recommended by WHO in its list of essential medicines [5]. Many other rotavirus vaccines are under different stages of development. More than 100 countries have licensed a vaccine against rotavirus in their EPI (Expanded Programme on Immunization) schedule, and more than 80 countries have introduced routine rotavirus vaccination.

In India, ROTAVAC® was launched in a phased manner in the Universal Immunization Program (UIP) by the Government of India (GOI). It was launched in 4 states in 2016 and later expanded to 7 more states. Thus, a total of 11 states were covered by the end of 2018. Since then, 17 more states have been covered under the immunization programme of India [6]. It was launched in the state of Punjab in August 2019.

To detect rare Adverse Events following Immunization (AEFI) like intussusception, it is essential to monitor the safety profile of Rotavirus vaccines. ROTAVAC® was launched in India in 2016, after a trial of around 4500 infants, whereas prior to the launch of RotaTeq®, a trial of 70,000 subjects was conducted in 11 countries. Therefore, rare AEFIs like intussusception cannot be ruled out in the Indian population with the use of ROTAVAC®. Also, monitoring of safety profile of a vaccine is a continuous process, but so far only a few studies like Kar et al. have evaluated its safety profile in some Indian states. Since ROTAVAC® was launched in Punjab very recently, it is important to understand the safety profile of the vaccine in this region. To the best of my knowledge, no such study has been conducted in Punjab region so far. Therefore, this study aims to identify the different AEFI occurring after administration of ROTAVAC®.

Collection and evaluation of AEFI by solicited and unsolicited methods help in studying the safety profile of a drug. This aspect is a part of Pharmacovigilance (PV) or drug safety. The Pharmacovigilance programme of India (PvPI) was started by the Government of India in 2010 [7]. Since then, a hierarchy of centres was established for robust ADR monitoring system. However, the practical knowledge of PV among HCPs is relatively less. Therefore, this study also aims to educate healthcare professionals regarding the importance of AEFI reporting.

II. METHODOLOGY

A. ***Study design:*** This is a single centre observational prospective study conducted in a Government Civil Hospital in Punjab, India.

B. ***Study population:***

Inclusion criteria

- Infants attending immunization clinic for routine vaccination for 1st, 2nd or 3rd dose.
- Male or Female
- Age: 6 weeks to 8 months
- Parents willing to provide informed consent and participate in the study were selected on first come first serve basis.

Exclusion criteria

- Evidence of any underlying illness in the infant
- Parents unwilling to provide informed consent
- Parents unwilling to follow up for the study

C. ***Study treatment:*** ROTAVAC®, a live attenuated, monovalent vaccine is currently administered as the rotavirus vaccine in EPI schedule of India. It is given by mouth in 3 dose series at ages 6, 10 and 14 weeks of age. It is not administered to children older than 8 months of age.

D. ***Study endpoints:***

- Primary endpoint: Safety and tolerability of ROTAVAC® vaccine.
- Secondary endpoint: Increasing awareness of AEFI identification and reporting among HCPs in the study site.

E. ***Study Conduct and Patient Safety:*** The study was conducted from 1st January, 2020 to 31st March, 2020 in the immunization clinic of Government Civil Hospital, Mohali, Punjab. Informed consent was obtained from the parents/caregivers of the infants attending the vaccination clinic. Informed consent was also taken from the health care professionals at the vaccination clinic for participation in the study.

A pre-designed, structured questionnaire was prepared to solicit socio-demographic and relevant clinical information. The questionnaire was administered on the day of the vaccination at the study site and on days 0, 1, 7, 14 and 30 telephonically.

In case of an AEFI, parents/caregivers were counselled and if required, were referred to appropriate health care facility for its management.

A second pre-designed, structured questionnaire was used to collect information from healthcare professionals working in these clinics regarding their level of awareness about AEFI reporting. After an initial assessment, a knowledge-sharing session was conducted for the HCPs to instruct regarding pharmacovigilance and importance of reporting of such events. The questionnaire was then readministered to the HCPs on a different date to measure the difference in awareness after the knowledge sharing session.

F. ***Statistical analysis:*** Data is presented using appropriate descriptive statistics. Chi square/Fisher's exact test was used to explore the association across categorical variables. The difference of scores of HCPs before and after imparting knowledge was assessed using Paired samples T Test/Wilcoxon signed rank test. The data was analyzed using IBM® SPSS® v20.0.0. Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 was used for coding of AE. Medical judgement where applicable was used for grading of AEFI. Causality assessment of AEFIs was performed using WHO's new causality assessment algorithm by checking the eligibility and using the checklist and algorithm. Finally, the AEFIs were categorized as per the causality assessment classification. A p value of <0.05 was considered statistically significant for the purpose of this study.

G. ***Ethical consideration:*** In this study, a written consent was taken from the parents of infants and HCPs. No intervention was done on infants or HCPs.

The study was conducted after getting ethics approval from University of Siena, Italy and after obtaining informed consent from the parents/caregivers. The study was conducted according to the Declaration of Helsinki (2013).

All patients attending the immunization clinic of Civil Hospital, Mohali, India from 1st January, 2020 to 31st January, 2020 were screened for the study. A total of 308 parents came to the immunization clinic, 56 refused to give informed consent. Hence, 252 infants in the age group of 6 to 14 weeks were enrolled in the study and followed up for a period of one month.

III. RESULTS

AEFI

139 AEFIs were observed in 133 infants. The verbatim of subject's complaints was coded using MedDRA v23.0. The five most common PTs were:

- pyrexia, 21.8%
- crying, 7.5%
- injection site erythema 4.7%
- irritability, 4.3%
- vomiting, 4.3%.

Seriousness of AEFI

Out of 252 infants, only 2 (approx. 1%) infants had a serious AEFI. One had diarrhea which occurred on third day post vaccination, and second had vomiting which occurred on same day and lasted for a few hours. Both recovered after appropriate medical intervention.131 (approx. 52%) infants had a non-serious AEFI and 119 (approx. 47.2%) infants did not suffer from any AEFI.

Severity of AEFI

126 (90.6 %) AEFIs were mild, 11 (7.9%) were of moderate severity and 2 (0.7%) were severe in nature.

AEFI on 30th day post vaccination

On 30th day after rotavirus vaccine administration, 12 infants (5.0%) reported an AEFI, while the rest (n=240, 95.0%) were healthy and did not suffer from any AEFI.

Causality Assessment

93 (67%) of the events had consistent causal association,46 (33%) AEFIs had an inconsistent causal association, and no case had indeterminate association to ROTAVAC® immunization. None of the reactions were unclassifiable (Table 1).

TABLE I: Causality assessment of ROTAVAC® AEFI with Preferred Terms.

Type	Causality assessment, n (%)	Preferred Term (PT)
I. Cases with adequate information	139 (100%)	
Consistent with causal association to immunization	93 (67.0%)	Pyrexia 44, Crying 16, Vomiting 8, Rash 7, Infantile spitting up 6, Irritability 5, Diarrhea 4, Cough 3
Indeterminate	0	
Inconsistent with causal association to immunization (coincidental)	46 (33.0%)	Injection site erythema 12, Pyrexia 11, Irritability 6, Diarrhea 5, Crying 3, Rhinorrhea 3, Vomiting 3, Cough 2, Rash 1
II. Cases without adequate information	0	

Association of AEFI with different socio-demographic and clinical variables

The association of various socio-demographic and clinical variables such as birth weight, gender, place of delivery etc. with incidence of AEFI is presented in Table 2. None of the variables showed a statistically significant association with the presence of AEFI (p>0.05).

TABLE II: Association of AEFI with variables

Variables		No. of infants with AEFI		P value
		Yes (n=133)	No(n=119)	
Birth Weight	LBW	20	11	0.16*
	Normal Weight	113	108	
Gender	Male	66	68	0.23*
	Female	67	51	
Mother's working status	Working	19	23	0.28*
	Homemaker	114	96	
Place of Birth	Tertiary hospital	116	104	0.97*
	Home	17	15	
Type of Birth	Normal	75	81	0.06*
	Caesarian	58	38	
Place of residence	Rural	24	17	0.42*
	Urban	109	102	

Breastfed	Yes	116	105	0.81*
	No	17	14	
Gestational age	Normal	126	106	0.10*
	Preterm	7	13	
Literacy of father	Literate	130	114	0.48**
	Illiterate	3	5	
Literacy of mother	Literate	120	110	0.54*
	Illiterate	13	9	
Religion	Hindu	78	63	0.65**
	Sikh	50	51	
	Christian	0	1	
Socio-economic Class	Lower	0	2	0.07**
	Upper Lower	34	31	
	Lower Middle	93	72	
	Upper Middle	6	12	
	Upper	0	2	

*Chi-square test, **Fischer's exact test

Pharmacovigilance education to HCPs

Thirty HCPs associated with the immunization clinic agreed to participate in a knowledge sharing session for pharmacovigilance with a pre- and post- session assessment.

Health care professionals were administered a questionnaire prior to and after PV education. The mean score prior to imparting health education was 4.07±1.17, with median (IQR) score of 4 (2) and the score after educating them increased to 7.27±1.05, with median (IQR) score also increasing to 7(1).

The difference in the median related pair of scores was explored using Related Samples Wilcoxon Signed Rank test which depicted a statistically significant difference. (W=465.000, p<0.005). The graph below depicts the scores achieved by the health care professionals before and after imparting them knowledge about pharmacovigilance (Figure 1).

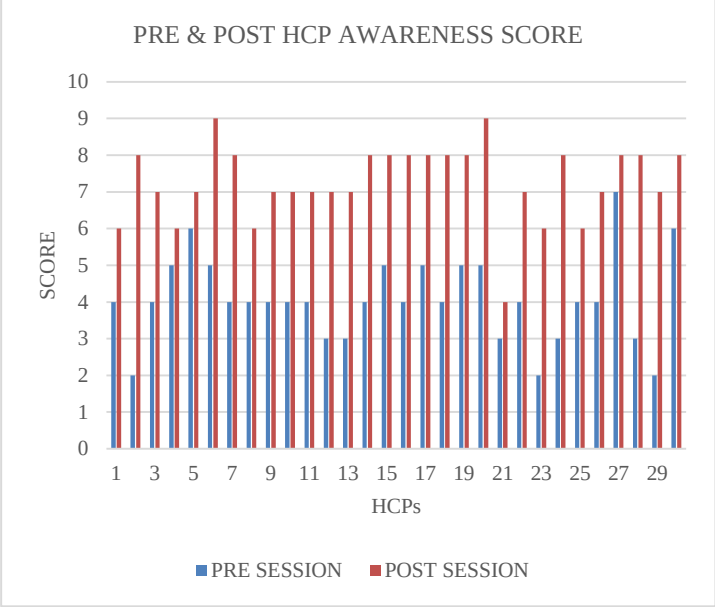

Fig. 1: Pre and post pharmacovigilance session score of HCPs (Maximum score=9).

IV. DISCUSSION

Reporting of AEFIs is crucial to detect vaccine-associated risks and leads to subsequent formulation of risk management to prevent or mitigate the risk. This ensures patient safety, appropriate risk management of vaccines and reduces healthcare overload and associated healthcare expenditure.

WHO recommends to monitor for any significant AEFI of unexplained cause occurring within 30 days after a vaccination [8].

Causality assessment is an important tool that can help in addressing the safety concerns of a vaccine. If these concerns are not addressed, it may lead to the vaccine being withdrawn from the market (163). In this study, causality assessment of the AEFIs was performed for association with ROTAVAC® vaccine. 93 (67%) of the AEFI showed a consistent causal association, 46 (33%) had an inconsistent causal association, and no AEFI had an indeterminate causal association with ROTAVAC®. Most of the consistent events are also known to be caused by administration of concomitant vaccines (OPV, IPV, PCV and Pentavac) however the role of ROTAVAC® vaccine cannot be ruled out. Infantile spitting up was considered consistent as the event was caused by oral administration of ROTAVAC® whereas injection site erythema was considered inconsistent as it was caused due to administration of concomitant injectable vaccines. To our knowledge, the causal association of ROTAVAC® with the AEFI was not reported by any earlier study.

Overall, most of the AEFIs reported were non-serious and resolved completely in less than a day. The AEFIs were consistent with the known safety profile of ROTAVAC® vaccine.

There seems to be inconclusive evidence with respect to the risk of intussusception with the various rotavirus vaccines. Although this study did not show any risk of intussusception in infants receiving ROTAVAC® vaccine, the small sample size of the study limits any confirmation of lack of risk of intussusception with ROTAVAC®. Larger studies better powered to detect rare events like intussusception are required to confirm the safety of ROTAVAC® vaccine with respect to intussusception.

It is important to note that the WHO underlines the importance of rotavirus vaccination, inspite of the risk of intussusception, in its position paper, on Rotavirus vaccines published in January 2013 with the following statement:

"..... the benefits of rotavirus vaccination against severe diarrhoea and death from rotavirus infection far exceeds the risk of intussusception [9]. "

30 HCPs were given the predesigned, structured questionnaire before and after imparting knowledge regarding AEFI reporting. The mean score prior to imparting pharmacovigilance education was 4.07±1.17, with maximum score of 9, and the score after educating them increased to 7.27±1.05. The difference in scores was statistically significant ($p<0.05$). This indicates the benefit of imparting appropriate pharmacovigilance education to HCPs. The HCPs understood the importance of AEFI reporting, however, they felt the process was difficult to follow because of time constraints.

Although there is a robust pharmacovigilance program in India (PvPI), this study highlights that there is a lack of knowledge regarding AEFI reporting among HCPs in Punjab. Therefore, wider efforts to educate and inform the HCPs regarding pharmacovigilance and AEFI reporting are required.

Strengths and limitations: To our knowledge, this is the first effort that generated AEFI data after ROTAVAC® administration in children in the state of Punjab. The study shows that the vaccine is safe in the population studied and no new safety concerns for the vaccine were identified.

Moreover, this study evaluated the pharmacovigilance knowledge among the HCPs at the study site and also addressed the knowledge gap via a knowledge sharing session. This small but significant effort underlines the importance of conducting knowledge sharing sessions with HCPs to further the practice of AEFI reporting.

This study has some limitations, which are as follows:

- Firstly, the study population it represents is mostly urban (73%), so it is not a true representation of the larger Indian population which lives in rural areas. The study results therefore may not be generalizable to the population residing in rural settings.

- Secondly, as per the design of the study, AEFIs were actively solicited. Therefore, there could be a possibility of over-reporting of AEFIs, as parents tend to report more AEFIs, when asked. Without the solicitation they may not have reported some of the AEFIs. The incidence of AEFIs reported in this study may not be a true representation of the general reporting of AEFIs by caregivers or HCPs.

- Thirdly, the sample size of the population is small. So, the findings of our study cannot be generalized to a large population. A larger sample of the population could not be studied due to time constraints. Hence, there is limited significance of the evaluation of association of the different variables to the incidence of AEFIs.

- Fourthly, most of the consistent AEFI are also known to be caused by administration of concomitant vaccines (OPV, IPV, PCV and Pentavac), hence the role of ROTAVAC® vaccine could not be fully established.

- Fifthly, the data regarding the AEFI occurring on separate Rotavac doses was not available.

V. CONCLUSION

ROTAVAC® vaccine was found to be safe in a small study sample in Punjab, India where the vaccine was launched recently. There were no new safety concerns identified with ROTAVAC®. However, since the vaccine is relatively new in the region, the HCPs have to be vigilant in identifying and reporting any rare safety concerns with the vaccine. To this effect, the study evaluated and educated the HCPs in the tertiary level hospital, to strengthen AEFI reporting from the study site. This will help in monitoring the safety profile of newer vaccines being launched in the region.

VI. RECOMMENDATIONS

Larger multicentric studies should be conducted in the region to confirm the safety of ROTAVAC® vaccine, demonstrated in this study. This will generate more confidence in use of ROTAVAC® vaccine and help in reducing the rotavirus induced diarrheal burden which would then reflect in a decreased infant mortality rate in the country.

HCPs at all healthcare levels including primary healthcare centers should be educated and encouraged to report AEFIs. Pharmacovigilance workshops and knowledge sharing sessions for HCPs will be helpful to emphasize the importance of AEFI reporting. Proper infrastructure, support and knowledge of pharmacovigilance centers should be provided to facilitate smooth reporting of AEFIs.

Parents of infants should be counselled appropriately regarding detection and reporting of AEFIs. This will ensure timely detection of AEFI and help in appropriate management of the infants.

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