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A Post Marketing Surveillance Study To Evaluate The Safety Of Abhayrab Vaccine, A Purified Vero Cell Rabies Vaccine Manufactured Byhuman Biologicals Institute, When Administered By Intradermalroute In Category Iianimal Exposure Subjects In India.

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Abstract:
Background:*Rabies is a viral disease which is almost always fatal. It is a neglected zoonotic disease which still causes significant mortality, mostly in the developing and third world countries. The mainstay in prevention of rabies is timely vaccination with a safe and potent anti-rabies vaccine. Abhayrab Vaccine, a purified Vero cell rabies vaccine (PVRV) manufactured by Human Biologicals Institute, has proved its safety and efficacy since its launch. The objective of this post marketing surveillance study is to further evaluate the safety of the Abhayrab vaccine when administered by Intradermal route in Category II animal exposure subjects in India.*
Methods*: In an open label single arm single centric study, a total of 101 subjects meeting the eligibility criteria were enrolled in the study. Abhayrab Vaccine was reconstituted to 1 ml and two doses of 0.1ml wereadministered intradermally, one on each deltoid region on days 0, 3, 7 and 28 as per Updated Thai Red Crossregimen. The safety data was collected and evaluated throughout the study period from the time of first dose of vaccination till 7 days of the last dose of vaccination.*
Results*: A total of 88 mild or moderate local and systemic adverse events were reported in the study. No Serious adverse event was recorded during the study period. Overall it was concluded that Abhayrab vaccine issafe when administered by Intradermal route in Category II animal exposure subjects in India.*
Keywords:*PVRV, Abhayrab,Intradermal, 1ml reconstitution*

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I. Introduction

Rabies, is an acute, highly fatal viral disease of the central nervous system, caused by Lyssavirus type1. The disease affects both domestic and wild animals, and is spread to people through close contact with infectious material, usually saliva, via bites or scratches and licks on broken skin. Though it is a vaccine-preventable disease, it occurs in more than 150 countries and territories. Rabies is a neglected disease of poor and vulnerable populations whose deaths are rarely reported. It occurs mainly in remote communities where measures to prevent animal to human transmission have not been implemented.Although dogs are the source of the vast majority of human rabies deaths, particularly in Africa and Asia, bats are the main cause of infection in the Americas.Low awareness of the need to seek health care after an animal bite claims the lives of more than 55, 000 people each year, mostly in Asia and Africa. Rabies is one of the oldest recognized diseases affecting humans and one of the most important zoonotic diseases in India. India is endemic for rabies accounting for 36% of the world's deaths. Rabies is present throughout the country, exception the islands of Lakshadweep, Andaman & Nicobar. True burden of rabies in India is not fully known; although as per available information, it causes 18 000-20 000 deaths every year. About 30-60% of reported rabies cases and deaths in India occur in children under the age of 15 years as bites that occur in children often go unrecognized and unreported.[1, 2, 3, 4]

The cost of cell culture rabies vaccines for intramuscular administration limits their widespread use in many areas where canine rabies is prevalent and both availability and/or affordability of rabies biologicals are limited. WHO has been promoting the use of economical post-exposure prophylaxis (PEP) regimens administered by the intradermal route for many years where more than 80% of the people exposed to rabies cannot afford intramuscular regimens in Africa and Asia.Intradermal administration of these vaccines offers an

equally safe and immunogenic alternative that requires only 1–2 vials of vaccine to complete a full course of PEP, thereby reducing the volume used and the direct cost of vaccine by at least 60% depending of the vaccine type compared with standard intramuscular vaccination.[5].Every year, more than 15 million people worldwide receive a post exposure vaccination.

Abhayrab vaccine since its launch has been found to be safe and efficacious.The objective of this post marketing surveillance study is to further evaluate the safety of the Abhayrab vaccine when administered by Intradermal routein Category II animal exposure subjects in India.

II. Methods

2.1 Ethics

The study was carried out at Institute of Preventive Medicine, Hyderabad after obtaining approval from the DCGIas well as by the Institutional Ethics Committee, Directorate of Institute of Preventive Medicine, Public Health Labs & Food (H) Administration, Hyderabad. The trial was registered with Clinical Trial Registry India (www.ctri.nic.in) with CTRI number CTRI/2016/01/006477.The study was conducted according to ICH-GCP guidelines issued by the CDSCO, ICMR Ethical guidelines. The study followed the principles laid down by Declaration of Helsinki.

2.2 Sample Size and Study duration

In this study one hundred and one (101) subjects were recruited.The study duration was about 7 weeks, First subject was enrolled on 30th March 2016 and last completed follow up was on 18th May 2016.

2.3 Inclusion and Exclusion criteria

The inclusion criteria for the study weresubjects with Category II animal exposure and aged below 70 years and were willing to remain in the study area for the duration of the trial, Subject/subject's legally acceptable representative who provided written informed consent for participation in the study, prior to screening.

The exclusion criterion weresubjects receiving immunosuppressive therapy (including steroids for any indication), allergy immunotherapy or having any known immunodeficient condition (e.g. AIDS, hypogammaglobulinemia etc.) or malignancy,Subjects treated with anti-malarial drug (e.g. chloroquine) in the previous 2 months or requiring antimalarial treatment during the study period,Subjects suffering from acute febrile illness or allergic reactions including allergy to antibiotics,Subjects with history of or occurrence of seizures at the time of vaccination,Planned participation in another clinical trial during the trial period. Subjects who had participated in any other clinical trial within the previous 3 months,Subjects who had clinical evidence of significant neurological, hematological, hepatic, renal, cardiac, respiratory disease or metabolic illness,Pregnant or nursing women,Subjects with known hypersensitivity to the vaccine or any component of the vaccine,Subjects with history of drug or alcohol abuse,Subjects who received blood and/or plasma transfusion within the previous 3 months and any condition which, in the opinion of the investigator, would have posed a health risk to the participant or interfere with the evaluation of the vaccine.Prior to administration of Anti rabies vaccine each subject was evaluated byhis/her Medical History, General and Vital examination, Physical examination to rule out any underlying conditions by the Principal Investigator.

2.4 Vaccine

Abhayrab vaccine is a freeze dried, purified inactivated rabies vaccine manufactured by Human Biologicals Institute. It contains inactivated Rabies Virus (L. Pasteur 2061/ Vero Strain propagated in Vero Cells) and withThiomersal added as preservative. It is to be reconstituted with 1 ml diluent supplied. One Immunizing dose has a potency of $\geq$ 2.5 International Units (IU).

The Abhayrab vaccine used in the study were of batch number AYB 105/14.

2.5 Vaccination Schedule and Dosage

Abhayrab vaccine was reconstituted with 1 mL of the diluent supplied and Subjects were administered with two doses of 0.1 mL intradermally, one on each deltoid region on days0,3,7 and 28 (Day '0' being the day of first dose ofvaccination)as per Updated Thai Red Cross Regimen (2-2-2-0-2).

2.6 Safety Evaluation

Following administration of each dose of the vaccine, subjects were observed closely for 30 to 60 minutes at the study hospital for observing occurrence of any local reactions andsystemic events. Subject/Subject's LegallyAcceptableRepresentativewereprovidedwithadiarycard,torecordthepresenceoflocalandgeneralsymptomsti ll the next scheduledvisit.Physical examination was performed by the investigator, before and during each visit

of the study for all the subjects enrolled. The general and systemic examination data of all the enrolled subjects were collected on every visit and were analyzed. The variables for general examination were pulse rate, systolic blood pressure, diastolic blood pressure, respiration rate, and body temperature. Subjective assessment with respect to the seriousness, causality and severity was done for all local and systemic adverse events that occurred postvaccination by the Investigator.

2.7 Statistical Methods

Reported solicited and unsolicited adverse events were summarized, using frequencies and percentages, by event severity and event relationship to the study vaccine during the study duration. Any non-serious and serious adverse events were listed for analysis. Frequency and percentage of subjects with at least one adverse event after each dose of vaccination and during the study follow up period were calculated. Demographics and baseline characteristics were summarized descriptively. For continuous data descriptive statistics like Mean, Median, Standard Deviation and range (minimum, maximum) were generated. For categorical data, Frequencies and Percentages were calculated. Subject disposition were summarized, including the number of subjects withdrawn and discontinued the study. All subjects enrolled in the study were analyzed for safety.

III. Results

In this prospective open label single centric study, overallone hundred and one (101) subjects were screened, all the one hundred and one (101) subjects were eligible and gave informed consent. The study was for the duration of 7 weeks i.e. from 30thMarch 2016 (date of first subject recruitment)to 18thMay 2016(date of last subject last follow up visit).There were no major protocol deviations or non-compliance.Out of 101 subjects, 96 (95%) subjects completed the study as per the protocol. The reason for discontinuation of the five subjects (5%) was lost to follow up.However, all the subjects enrolled into the study were analyzed for safety.

Subjects aged below 70 years were recruited in the study.The least age recruited was two years and maximum age was 69 years.Out of 101 subjects enrolled into the study,75 (74.3%) subjects were males and 26 (25.7%) subjects were females (TABLE1).

For the entire duration of the study period, the general health of all subjects who participated in this trial was found to be good. There was no statistically significant difference in vital parameters before and after administration of the vaccine by intradermal route.

Safety evaluation was done by observing and recording the adverse events observed by the physician or reported by the subjects during each visit and during the first 30 minutes to one hour after vaccination. The events which were reported by the subjects in the diary card during the follow up period were also considered for evaluation of safety.

No Serious Adverse Event (SAE) was reported during the study period. The adverse events reported in this study were categorized as local and systemic events.

Local Adverse Events: Out of 101 subjects in the study, 26 (25.7%) subjects experienced pain at the injection site, 23 (22.7%) subjects experienced erythema at the injection site, 16 (15.8%) experienced itching at the injection site.

Systemic Adverse Events: Out of 101 subjects in the study, 10 (9.9 %) subjects had fever, 3(3%) had headache, 6 (5.9 %) had body pains, 2 (2%) had joint pains,2 (2 %) had dizziness(TABLE 2).

The causality assessments of the reported local and systemic adverse events are listed in TABLE 3. All the adverse events were found to be related to the study vaccine.

All the adverse events were of mild or moderate severity only. No severe adverse events were found in the study (TABLE 4).

No concomitant medications were used in the study.

IV. Tables

TABLE 1: Summary of Demographics

Parameter	Statistics	Abhayrab (n=101)
Gender:		
Male	**n (%)**	75 (74.3%)
Female	**n (%)**	26 (25.7%)
Age (years)	**n**	101
	Mean	24.8
	SD	16.0
	Median	23
	Range (Min, Max)	(2,69)
	95% CI of the Mean	(21.6, 28)

TABLE 2: Summary of Adverse Events

Adverse Event	n (%)
Local:	
Pain	26 (25.7%)
Erythema	23 (22.7%)
Itching	16 (15.8%)
Systemic:	
Fever	10 (9.9%)
Headache	3 (3%)
Body Pains	6 (5.9%)
Joint Pain	2 (2%)
Dizziness	2 (2%)

TABLE 3: Causality Assessment

Adverse Event	Relationship to the vaccine				
	Certain	Probable	Possible	Unlikely	Unrelated
Local:					
Pain	2	0	24	0	0
Erythema	4	19	0	0	0
Itching	2	14	0	0	0
Systemic:					
Fever	0	0	10	0	0
Headache	0	0	3	0	0
Body Pains	0	0	6	0	0
Joint Pain	0	0	2	0	0
Dizziness	0	0	2	0	0

TABLE 4: Severity Assessment

Adverse Event	Severity of the Adverse Event		
	Mild n (%)	Moderate n (%)	Severe n (%)
Local			
Pain	24 (23.8%)	2 (2%)	0 (0%)
Erythema	19 ((18.8%)	4 (4%)	0 (0%)
Itching	14 (13.9%)	2 (2%)	0 (0%)
Systemic			
Fever	10 (9.9%)	0 (0%)	0 (0%)
Headache	3 (3%)	0 (0%)	0 (0%)
Body Pains	6 (5.9%)	0 (0%)	0 (0%)
Joint Pain	2 (2%)	0 (0%)	0 (0%)
Dizziness	2 (2%)	0 (0%)	0 (0%)

V. Discussion & Conclusion:

In this prospective study, safety evaluation was carried out for Abhayrab vaccine reconstituted to 1 ml when administered intradermally in Category II animal exposure subjects.Out of 101 subjects (75 male and 26 female) enrolled in the study, 96 (95 %) subjects completed the study as per the protocol. The reason for discontinuation of five (5%) subjects was Loss-to follow up and not because of any adverse event.
A total of 88 mild or moderate local and systemic adverse events were reported in the study.

No serious adverse event occurred during the study period.
Among the local reactions, pain at the injection site was the most common and was found in 26 (25.7%) subjects followed by erythema at the injection site in 23 (22.7%) subjects and itching at the injection site in 16 (15.8%) subjects.
The causality assessment of local pain was classified either under 'certain' or 'possible' and for that of local erythema and itching were classified either under 'certain' or 'probable' by the Investigator.
Most of the local adverse events were mild except few which were assessed as moderate. No severe local adverse event was observed.
Among the systemic reactions, fever was the most common adverse event and was found in 10 (9.9%) subjects followed by body pains in 6 (5.9%) subjects, headache in 3 (3%) subjects, joint pains in 2 (2%) subjects and dizziness in 2 (2%) subjects.
The causality assessment of all the systemic adverse events were classified under 'possible' by the Investigator.
All the systemic adverse events were assessed as mild by the Investigator. No moderate or severe systemic adverse event was observed.
Overall it was concluded from this Post Marketing Surveillance study that Abhayrab vaccine is safe when administered by Intradermal route in Category II animal exposure subjects in India.

Acknowledgments

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