

Safety of Rabies vaccine Human I.P. (Purified Vero Cell Rabies Vaccine) - Abhayrab vaccine, manufactured by Human Biologicals Institute, when administered in Category II animal exposure subjects by Intramuscular or Intradermal route.

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Abstract:

Background: Rabies is an enzootic and epizootic disease of worldwide importance. Globally each year, more than 15 million people require post exposure treatment. Rabies is a vaccine-preventable viral disease. Prevention of Rabies depends highly on availability and affordability of potent anti-rabies vaccine. Abhayrab vaccine (manufactured by Human Biologicals Institute) is a freeze dried, purified inactivated rabies vaccine containing inactivated Rabies Virus (L. Pasteur 2061/ Vero Strain propagated in Vero Cells) and has been found to be safe and efficacious for prophylaxis against human rabies since its launch. This study is a post marketing surveillance study carried out with the objective of assessing the safety of Abhayrab vaccine (reconstituted to 1 ml) when administered in Category II animal exposure subjects by Intramuscular or Intradermal route.

Methods: In an open label, two arm, single centric study, a total of 120 eligible subjects meeting the inclusion and exclusion criteria were enrolled into the study. Of them, 60 Subjects were enrolled in Arm A, where vaccine was administered by intramuscular route as per Essen regimen (One dose of 1ml administered in the deltoid region in adults and in the anterolateral aspect of thigh in children on days 0,3,7, 14 and 28) and 60 Subjects were enrolled in Arm B, where vaccine was administered by intradermal route as per Updated Thai Red cross regimen (Two doses of 0.1ml administered one on each deltoid region on days 0,3, 7 and 28). The safety data was evaluated throughout the study period from first dose of vaccination to till 7 days of last dose of vaccination in both the Arms.

Results: A total of 87 mild or moderate local and systemic adverse events were reported (including 33 in Arm A and 54 in Arm B) in the study. No serious adverse event was reported during the study period. Overall, Abhayrab vaccine when reconstituted to 1 ml was found to be safe when administered by intramuscular or intradermal route.

Keywords: PVRV, Abhayrab, 1ml reconstitution

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I. Introduction

Rabies is an infectious viral disease of the central nervous system that is almost always fatal and can occur virtually in all warm blooded animals including man. The virus is found in wild and some domestic animals, and is transmitted to other animals and to human through their saliva (following bites, scratches, licks on broken skin and mucous membrane). In India, dogs are responsible for about 97% of human rabies, followed by cats (2%), jackals, mongoose and others (1%). It is a neglected zoonotic disease which still causes significant mortality, mostly in the developing and third world countries.^{1, 2, 3}

Every year, more than 15 million people worldwide receive a post-bite vaccination. This is estimated to prevent hundreds of thousands of rabies deaths annually. Despite this, an estimated 59,000 people die from rabies across the world each year, with around 90% of these deaths occurring among children living in rural areas in Africa and Asia. In India alone, estimates range between 18,000 to 20,000 human deaths from rabies each year. It is endemic throughout India with the exception of Andaman & Nicobar and Lakshadweep Islands. In December 2015, countries from across the world met with WHO, the World Organization for Animal Health (OIE), the Food and Agriculture Organization of the United Nations (FAO) and the Global Alliance for Rabies Control (GARC), and agreed to end human deaths from dog-mediated rabies by 2030. Under the One Health Initiative, WHO, OIE, FAO, and GARC are working on simultaneous campaigns to eliminate canine rabies

through the vaccination of dogs, the treatment of human rabies exposures with wound washing and post-exposure prophylaxis, and the improvement of education about rabies prevention where it is needed most.^{4,5}

The mainstay in prevention of rabies is timely vaccination with a safe and potent anti-rabies vaccine. For intramuscular vaccination, the five-dose 'Essen' regimen is usually followed and for intradermal vaccination, the 'Updated Thai Red Cross' regimen (2-2-2-0-2) is followed.

Rabies vaccine Human I.P. (Purified VeroCell Rabies Vaccine) – Abhayrab vaccine manufactured by Human Biologicals Institute, has been found to be safe and efficacious since its launch. The vaccine is used for both intramuscular and intradermal vaccination. The present study is a post marketing surveillance study carried out with the objective of assessing the safety of Abhayrab vaccine (reconstituted to 1 ml) when administered in Category II animal exposure subjects by Intramuscular or Intradermal route.

II. Methods

2.1 Study Centre and Clinical Trial Registration

The study was conducted at Institute of Preventive Medicine, Hyderabad, Telangana State, India in the year 2016. The trial was registered with Clinical Trials Registry -India with CTRI number CTRI/2016/01/006482.

2.2 Ethics Committee approval and GCP

The study was approved by Institutional Ethics Committee, Directorate of Institute of Preventive Medicine, Public Health Labs & Food (H) Administration, Hyderabad. The study was conducted according to ICH-GCP, Schedule Y guidelines issued by the CDSCO and ICMR ethical guidelines.

2.3 Study Design and Sample size

The study was an Open label, Two arm, and Single centric study to assess the safety of Rabies Vaccine Human I.P. (Purified Vero Cell Rabies Vaccine) - Abhayrab vaccine reconstituted to 1 ml, administered through intramuscular and intradermal route in Category II animal exposure subjects. In this study one hundred twenty (120) subjects were recruited as per the Inclusion and Exclusion criteria. Sixty (60) subjects were assigned to Arm A where the subjects received Abhayrab vaccine by Intramuscular route as per Essen regimen and Sixty (60) subjects were assigned to Arm B where the subjects received Abhayrab vaccine by Intradermal route as per Updated Thai Red Cross regimen.

2.4 Inclusion and Exclusion Criteria

The Inclusion criterion for the study were: Subjects of age below 70 years with Category II Animal Exposure, Subjects to remain in the study area for the duration of the trial, Subject/ Subject's Legally Acceptable Representative providing written Informed Consent as per ICH – GCP guidelines prior to screening. The Exclusion criterion were: Subjects receiving immunosuppressive therapy (including steroids for any indication), allergy immunotherapy or having any known immunodeficient condition (e.g. AIDS, hypogammaglobinemia 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 with 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 finally 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 by their Medical History, General and Physical examination to rule out any underlying conditions by the Principal Investigator.

2.5 Vaccine, Vaccination Schedule and Dosage

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 with Thiomersal added as preservative. It is to be reconstituted with 1 ml diluent supplied. One Immunizing dose has a potency of ≥ 2.5 International Units (IU). The Abhayrab vaccine used in the study were of batch numbers 15URAB067 & 15URAB068.

In Arm A, one dose of 1 ml was administered by intramuscular route in the deltoid region in adults and in the anterolateral region in children on days 0, 3, 7, 14 and 28 as per Essen regimen.

In Arm B, two doses of 0.1 ml were administered intradermally, one on each deltoid region on days 0, 3, 7 and 28 as per Updated Thai Red Cross Regimen (2-2-2-0-2) (Day '0' being the day of first dose of vaccination).

2.6 Safety Evaluation

Following administration of each dose of the vaccine, all the subjects of both the arms were observed closely for 30 to 60 minutes at the study hospital for assessing and managing of any adverse events occurring soon after administering the vaccine. The Subject/Subject's Legally Acceptable Representative was provided with a diary card in a language which they understood, by the Investigator, to record the presence of local and general symptoms till the next scheduled visit. General physical examination was done during all the study visits.

Subjective assessment was done by the Investigator for any local and systemic adverse events resulting from the preceding immunization. Eligibility assessment was done for giving the next scheduled dose of the vaccine as per the inclusion and exclusion criterion during each visit. The subjects were followed up to 7 days after the last dose of vaccination in each arm.

The relationship to the Adverse event to the study vaccine were assessed as per World Health Organization's (WHO) Adverse event following immunization Causality Assessment Criteria. Grading of Adverse events was done as Mild, Moderate, and Severe.

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. Subject disposition were summarized, including the number of subjects withdrawn and discontinued the study. All subjects enrolled in the study were analyzed.

2.8 Subject withdrawal:

When a subject failed to appear for any visit, attempts were made to follow-up the subject/subject's legally acceptable representative to know the health status. The subjects/subject's legally acceptable representatives who decided to withdraw from the study were allowed to do so but attempts were made to convince the subject to at least complete the vaccination. However all the subjects who were at least vaccinated once were included for safety analysis and it was ascertained that the withdrawal was not due to an adverse event.

III. RESULTS

In this prospective open label two arm single centric study, one hundred and twenty (120) subjects were enrolled as per subject eligibility criterion. Sixty subjects were enrolled in Arm A where the vaccine was administered intramuscularly and 60 subjects were enrolled in Arm B where the vaccine was administered intradermally. In Arm A, 4 subjects discontinued the study and in Arm B, 5 subjects discontinued the study. Overall 111 (93%) subjects completed the study. However safety data of all the subjects who received at least one dose of vaccination were analyzed. There were no major protocol deviations or non-compliance.

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 120 subjects in the study, 107 (89.2%) subjects were males and 13 (10.8%) subjects were females. (TABLE 1)

The general and systemic examination data of all the enrolled subjects were collected on every visit for both the Arms and were analyzed. Physical examination was performed by the investigator, before each dose of vaccination and during each visit of the study for all the subjects enrolled. For the entire duration of the study period, the general health of all the subjects of both the arms 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 in both the arms.

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 in the study.

The adverse events reported in this study were categorized as local and systemic events.

Local Adverse Events: Out of 60 subjects in Arm A (Abhayrab administered through Intramuscular route), 18 (30%) subjects were having pain at the injection site. Out of 60 subjects in Arm B (Abhayrab administered through Intradermal route), 13 (21.7%) subjects were having pain at the injection site, 12 (20%) were having Local redness, and 8 (13.3%) were having Local itching.

Systemic Adverse Events: Out of 60 subjects in Arm A (Abhayrab administered through Intramuscular route), 7 (11.7%) subjects were having fever, 3 (5%) were having body pains, 1 (1.7%) was having backache, 3 (5%) were having headache and 1 (1.7%) was having tingling sensation in the lower limbs. Out of 60 subjects in Arm B (Abhayrab administered through Intradermal route), 7 (11.7%) subjects were having fever, 6 (10%) were having body pains, 6 (10%) were having headache, 1 (1.7%) was having joint pain and 1 (1.7%) was having dizziness (TABLE 2).

The causality assessment of most of the adverse events in both the Arms were classified as related and classified as certain, probable or possible except a few which were assessed as unlikely to the study vaccine by the Investigator. Similarly, all the local and systemic adverse events were of either mild or moderate severity only. There were no severe adverse events in the study in either arm.

IV. Tables

TABLE 1: Summary of Demographics

Parameter	Statistics	Arm A IM Route (n=60)	Arm B ID Route (n=60)	All (n=120)
Gender:				
Male	n (%)	56 (93.3%)	51 (85%)	107 (89.2%)
Female	n (%)	4 (6.7%)	9 (5%)	13 (10.8%)
Age (years)	n	60	60	120
	Mean	31.9	25.9	28.9
	SD	13.3	14.1	14
	Median	29	23	27
	Range (Min, Max)	(15,69)	(2,59)	(2,69)
	95% CI of the Mean	(28.5,35.3)	(22.3, 29.5)	(26.4, 31.4)

TABLE 2 : Summary of Adverse Events

Adverse Event	Arm A (Intramuscular Route) n (%)	Arm B (Intradermal Route) n (%)	Total n (%)
Local:			
Pain at the Injection site	18 (30%)	13 (21.7%)	31 (25.8%)
Local Redness	0	12 (20%)	12 (10%)
Local Itching	0	8 (13.3%)	8 (6.7%)
Systemic:			
Fever	7 (11.7%)	7 (11.7%)	14 (11.7%)
Body Pains	3 (5%)	6 (10%)	9 (7.5%)
Backache	1 (1.7%)	0	1 (0.8%)
Headache	3 (5%)	6 (10%)	9 (7.5)
Joint Pain	0	1 (1.7%)	1 (0.8%)
Tingling sensation on lower limbs	1 (1.7%)	0	1 (0.8%)
Dizziness	0	1 (1.7%)	1 (0.8%)

V. Discussion & Conclusion

In this open label study, safety evaluation was carried out for Abhayrab vaccine reconstituted to 1 mL, when administered by either intramuscular route or intradermal route in Category II animal exposure subjects in India. Out of 120 subjects who were enrolled in the study, 111 (93%) subjects completed the study as per protocol. The reason for discontinuation of the nine subjects (7%) was lost to follow up. The subjects who were withdrawn didn't have much impact on the study as the reason for their withdrawal was lost to follow up and

not for any adverse event.

A total of 87 mild or moderate local and systemic adverse events were reported (including 33 in Arm A and 54 in Arm B) in the study.

No serious adverse event was reported during the study period.

Among the local adverse events, in Arm A (Abhayrab vaccine reconstituted to 1 mL when administered by intramuscular route), 18 (30%) subjects were having pain at the injection site and was the only local adverse event observed. Whereas in Arm B (Abhayrab vaccine reconstituted to 1 mL when administered by intradermal route), pain at the injection site was the most common Local adverse event and was found in 13 (21.7%) subjects followed by local redness in 12 (20%) and local itching in 8 (13.3%) subjects.

The causality assessment of all the local adverse events in both the Arms were classified under certain, probable or possible by the Investigator.

The severity assessment of all the local adverse events showed that they were either mild or moderate only. No severe local adverse event was observed.

Among the Systemic adverse events, in Arm A (Abhayrab vaccine reconstituted to 1 mL when administered by intramuscular route), fever was the most common and was found in 7 (11.7%) of the subjects followed by body pains in 3 (5%), headache in 3 (5%), backache in 1 (1.7%) and tingling sensation in the lower limbs in 1 (1.7%) of the subjects. Whereas in Arm B (Abhayrab vaccine reconstituted to 1 mL when administered by intradermal route), fever was the most common and was found in 7 (11.7%) of the subjects followed by body pains in 6 (10%), headache in 6 (10%), joint pain in 1 (1.7%) and dizziness in 1 (1.7%) of the subjects.

The causality assessment of all the systemic adverse events in both the Arms were classified under possible except tingling sensation of both the lower limbs in the Arm A (Abhayrab vaccine reconstituted to 1 mL when administered by intramuscular route) and Joint pain in Arm B (Abhayrab vaccine reconstituted to 1 mL when administered by intradermal route) which were assessed as unlikely by the Investigator.

The severity assessment of all the systemic adverse events showed that they were either mild or moderate only. No severe systemic adverse event was observed.

Generally it is seen that in 35–45% of people vaccinated with rabies vaccine, minor, transient erythema, pain or swelling occurs at the site of injection, particularly after intradermal administration. Mild systemic adverse events, such as transient fever, headache, dizziness and gastrointestinal symptoms, have been observed in 5–15% of vaccinated people.⁶

Similar adverse events were encountered in various studies with Vero cell rabies vaccine administered intradermally or intramuscularly.^{7,8,9,10}

Overall it was concluded that Abhayrab vaccine reconstituted to 1 ml is safe when administered intramuscularly or intradermally in Category II animal exposure subjects in India.

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