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Comparison of safety and immunogenicity of 2 WHO prequalified rabies vaccines administered by one week, 4 site intra dermal regimen (4-4-4-0-0) in animal bite cases

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The currently advocated rabies post-exposure prophylaxis regimens are of one month duration with reduced patient compliance. WHO recommended research on shortened vaccination regimens which have a practical and economic advantage over the existing regimens. Hence, the present study was undertaken to assess the safety and immunogenicity of 2 WHO prequalified rabies vaccines administered by one week, 4 site intra dermal regimen (4-4-4-0-0) in animal bite cases. This study was a comparative, open label, phase III, randomized clinical trial conducted at Anti rabies clinic, KIMS Hospital, Bangalore, India. The study was registered in Clinical Trials Registry of India (CTRI) bearing the registration number CTRI/2012/12/003230. Ninety subjects with category II/III animal bites/exposures were enrolled. Equine rabies immunoglobulin was administered to all category III exposures. 0.1 mL of either purified chick embryo cell vaccine (Rabipur) or purified verocell rabies vaccine (Verorab) was administered intradermally into 4 sites on days 0, 3 and 7 to all the study subjects. Serum of subjects collected on day 0, 14, 90 and 365 were analyzed for rabies virus neutralizing antibody (RVNA) concentration. The incidence of ADR in Rabipur and Verorab group was 2.96% and 1.14% respectively. In Rabipur group, geometric mean concentration (95% confidence interval) of RVNA was 14.5 (13.50, 15.57), 11.78 (11.27, 12.31) and 5.95 (5.50, 6.44) IU/mL on days 14, 90 and 365 respectively; In Verorab group geometric mean concentration (95% confidence interval) of RVNA was 14.43 (13.41, 15.53), 11.93 (11.47, 12.40) and 5.67 (5.29, 6.08) IU/mL on days 14, 90 and 365 respectively. In conclusion, Rabipur and Verorab were found to be safe, immunogenic and comparable with each other, when administered using one week, 4 site intradermal regimen (4-4-4-0-0) in animal bite cases.

Introduction

Rabies is a viral zoonosis transmitted to animals and humans through close contact with saliva from infected animals through bites, scratches, licks on broken skin and mucous membranes. According to World Health Organization (WHO), globally 61,000 people die of rabies every year.[1] Although a number of carnivores and bat species serve as natural reservoirs, rabies in dogs is the source of 99% of human infections and poses a potential threat to more than 3.3 billion people worldwide.[2] Rabies is 100% fatal, but it is a preventable disease. Post-exposure prophylaxis (PEP) should be initiated as early as possible for people exposed to prevent rabies. PEP consists of local treatment of wounds, complete course of cell culture and embryonated egg-based vaccine (CCEEVs) of proven efficacy by intramuscular (IM) or intradermal (ID) route by approved regimens and administration of rabies immunoglobulin into and around the wounds in all category III exposures. Globally, more than 15 million people receive PEP annually which is estimated to prevent hundreds of thousands of rabies deaths.[2] To reduce the cost of treatment of animal bites, intra dermal rabies vaccination (IDRV) regimens that reduce the quantity and cost of vaccine was recommended by WHO Expert Committee on Rabies in its 8th report,1992 and was later implemented in countries like Sri Lanka, Thailand, Philippines and India as an alternative for IM regimen.[3] For administration by the intradermal route, cell culture rabies vaccines should meet the same WHO requirements for production and control as required for rabies vaccines delivered intramuscularly. In addition, the immunogenicity and safety of intradermally administered rabies vaccines should be demonstrated in appropriate clinical trials using the WHO recommended PEP regimen.[1]

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For developing countries in Asia and Africa where rabies is endemic, the use of IDRV is cost effective when compared to intramuscular route. However, the currently used updated Thai Red Cross (TRC) regimen is of one month duration and it requires 4 visits to the hospital. Due to the long duration of course many animal bite victims exposed to rabies do not complete the course of vaccination. Most of the treatment failures have occurred because of non-adherence to one or more PEP parameters including number of doses of vaccine.[4] To reduce the duration of rabies PEP by ID route, a preliminary study done in Thailand among healthy volunteers by administering 0.1 mL of purified verocell rabies vaccine at 4 sites on days 0, 3, 7 was found to be safe and immunogenic.[5] The WHO/Bill and Melinda Gates Foundation Consultation meeting on rabies held at Annecy, France in October, 2009 reviewed short course ID regimens and noted one week, 4 site ID regimen (4-4-4-0-0) requires 1.2 mL of rabies vaccines per course which is 0.4 mL more than that administered in 2 site updated TRC regimen (2-2-2-0-2). But one week, 4 site ID regimen reduces number of clinic visits from 4 to 3, thus reducing logistic cost and duration of PEP resulting in better compliance. Hence, WHO recommended to reassess this regimen as a possible alternative to the widely used 2 site updated TRC regimen on the basis of results from a well-designed 4 site ID regimen study in future.[6] Based on this WHO recommendation, a study was conducted in India among healthy volunteers in 2012 to evaluate the immunogenicity and safety of purified chick embryo cell vaccine (PCECV, Rabipur) and purified verocell rabies vaccine (PVRV, Verorab) using one week, 4 site intradermal regimen. The study concluded that PCECV and PVRV when administered intradermally using one week, 4 site ID regimen was safe and immunogenic for rabies PEP.[7] The recent WHO expert consultation on rabies held at Geneva in September, 2012 recommended more research on 4 site intradermal regimen with 0.1 mL per site (4-4-4-0-0) in association with rabies immunoglobulin, so as to reduce the expense of traveling to clinics which will improve patient compliance.[1]

In this background, this study was undertaken with the following objectives:

Primary objective: To assess and compare the immunogenicity of 2 WHO prequalified rabies vaccines administered intradermally using one week, 4 site (4-4-4-0-0) regimen in animal bite cases.

(1) Primary end point: To elicit adequate and protective rabies virus neutralizing antibody (RVNA) concentrations of $\geq$0.5 IU/mL on day 14 in study subjects.
(2) Secondary end point: To demonstrate adequate and protective RVNA concentrations of $\geq$0.5 IU/mL till day 365 in study subjects.

Secondary objective: To assess and compare the safety of 2 WHO prequalified rabies vaccines administered intradermally using one week, 4 site (4-4-4-0-0) regimen in animal bite cases.

Results

A total of 90 subjects exposed to suspect rabid animal were enrolled in the study and were randomized into 2 groups to receive either one of the WHO pre-qualified vaccines for intradermal administration i.e. Rabipur or Verorab. One subject in Verorab group was lost to follow up due to migration after receiving 2 doses of vaccine.

The socio demographic characteristics of the subjects in Rabipur and Verorab group were almost similar. The mean age of subjects was 32.3 $\pm$ 11.7 years and 31.1 $\pm$ 10.4 years in Rabipur and Verorab group respectively. There were 29 (64.4%) males and 16 (35.6%) females in Rabipur group and 28 (63.6%) males and 16 (36.4%) females in Verorab group. Majority of the subjects in both the groups have completed higher secondary education, employed and belonged to middle and high income group (**Table 1**).

43 (95.6%) had dog bite followed by 02 (4.4%) cat bite in Rabipur group and 39 (88.6%) had dog bite, 04 (9.1%) had cat bite and 01 (2.3%) had monkey bite in Verorab group. Most of the subjects in both the groups were exposed to stray animals whose vaccination status was not known. All the subjects were exposed to suspect rabid animal. 39 (86.7%) in Rabipur group and 37 (84.1%) in Verorab group had category III exposure. The common site of bite was lower limb in majority of the subjects (**Table 2**).

07 (15.6%) subjects in Rabipur group and 04 (9.1%) in Verorab group reported adverse drug reactions (ADRs) to rabies vaccine. The incidence of total adverse drug events (ADEs) was 2.96% in Rabipur group of which local ADEs was 2.22% and systemic ADEs was 0.74%. However, incidence of total ADEs

Table 1. Socio demographic characteristics of study subjects

Characteristics		Rabipur group (n = 45)	Verorab group (n = 44)
Mean Age ($\pm$SD) in Years		32.3 $\pm$ 11.7	31.1 $\pm$ 10.4
Sex	Male	29 (64.4)	28 (63.6)
	Female	16 (35.6)	16 (36.4)
Education	Higher Secondary and above	21 (46.7)	20 (45.5)
Occupation	Employed/working	33 (73.3)	32 (72.7)
Socio Economic Status	Middle and above	41 (91.1)	40 (90.9)

Note: Figures in parenthesis indicate percentages.

Table 2. Distribution of study subjects according to the details of exposure

Characteristics		Rabipur group (n = 45)	Verorab group (n = 44)
Biting animal	Dog	43 (95.6)	39 (88.6)
	Cat	02 (4.4)	04 (9.1)
	Monkey	-	01 (2.3)
Type of biting animal	Stray	29 (64.4)	22 (50.0)
Vaccination Status of biting animal	Not known	30 (66.6)	23 (52.3)
Classification of biting animal	Suspect rabid	45 (100)	44 (100)
Fate of biting animal	Available	28 (62.2)	31 (70.5)
Category of exposure	III	39 (86.7)	37 (84.1)
Site of bite	Lower limb	31 (68.9)	26 (59.1)

Note: Figures in parentheses indicate percentages.

was 1.14% in Verorab group of which local ADEs was 0.95% and systemic ADEs was 0.19%. The difference between proportions of total ADEs between the 2 vaccine groups was found to be statistically significant (Z-value = 2.101, P value <0.05) (**Table 3**). Out of total 22 ADEs, 17 (77.3%) were mild which did not require any medications and 05 (22.7%) were moderate and necessitated analgesics and antihistamines. In Rabipur group, out of total 16 ADEs, 87.5% were mild and 12.5% were moderate. In Verorab group, out of total 06 ADEs, 50% each were mild and moderate. However, none of the subjects in both the vaccine groups dropped out due to ADRs.

The geometric mean RVNA concentration (95% confidence interval) in Rabipur group was 14.50 IU/mL (13.50, 15.57) on day 14, 11.78 IU/mL (11.27, 12.31) on day 90 and 5.95 IU/mL (5.50, 6.44) on day 365. In Verorab group, geometric mean RVNA concentration (95% confidence interval) was 14.43 IU/mL (13.41, 15.53), 11.93 IU/mL (11.47, 12.40) and 5.67 IU/mL (5.29, 6.08) on days 14, 90 and 365 respectively. However, there was no demonstrable RVNA titers on day 0 in any of the study subjects indicating no prior anti rabies vaccination as per criteria for enrolment. 100% of the subjects tested for RVNA had adequate RVNA concentration of ≥ 0.5 IU/mL from day 14 onwards till day 365 as per WHO criteria indicative of protection against rabies. The GMC values of both the vaccine groups were compared using t- test for independent sample means and the P value was >0.05 on days 14, 90 and 365 indicating no statistical significant difference between the GMC values of Rabipur and Verorab group (**Table 4**). All the 89 (100%) subjects who completed the course of vaccination were alive and healthy on day 365.

Effect of Equine rabies immunoglobulin (ERIG) on RVNA response

To find out the effect of ERIG on antibody production by the study vaccines if any, geometric mean RVNA concentration on days 14, 90 and 365 in subjects with category III exposures were compared with those subjects with category II exposures. The analysis of variance (ANOVA) performed on 4 groups viz. PCECV alone, PCECV + ERIG, PVRV alone, PVRV + ERIG on all the 3 different days of blood sampling (Days 14, 90 and 365) were found to be statistically not significant which shows that both the vaccines (Rabipur and Verorab) with or without ERIG had similar Geometric mean RVNA concentration.

Discussion

After the development of modern anti rabies CCEEVs, PEP for rabies became more safe, effective and millions of people have been administered these vaccines in several parts of the world. For many years the conventional intramuscular regimen consisting of 5 doses spread over a period of 1 month was in practice. High cost, inadequate supply and increased demand for modern rabies vaccines especially in the Government hospitals in rabies endemic countries of Asia and Africa was a major limiting factor for wider intramuscular usage. To reduce the cost of PEP for animal bites, IDRV was recommended by WHO Expert Committee on Rabies in its 8th report in 1992.[3] Intradermal administration of cell culture vaccines is an equally safe, immunogenic, cost effective and ethical alternative to intramuscular rabies vaccination. The advantage of IDRV is administration of small quantities of vaccine ($1/5^{th}$ with 0.5 mL vaccine or $1/10^{th}$ with 1 mL vaccine) making IDRV more economical and cost effective for developing countries. Different intradermal regimens such as Oxford regimen (8-0-4-0-1-1), Thai Red Cross regimen (2-2-2-0-1-1), 4 site ID regimen (4-0-2-0-1-1) and updated TRC regimen (2-2-2-0-2) were evaluated for safety, immunogenicity and efficacy. The updated TRC regimen was developed and evaluated

Table 3. Comparison of adverse drug events of study vaccines

Type of adverse drug events*	Rabipur group (n = 45)	Verorab group (n = 44)
Local		
Itching	04 (0.74)	01 (0.19)
Erythema	06 (1.11)	02 (0.38)
Pain	02 (0.37)	02 (0.38)
Systemic		
Fever	02 (0.37)	—
Myalgia	02 (0.37)	—
Regional Lymphadenopathy	—	01 (0.19)
Total	16/540** (2.96)	06/528*** (1.14)
Z – value	2.101	
p –value	<0.05	

Note: Figures in parenthesis indicate percentages.
*Multiple responses;
**45 subjects × 3 doses × 4 sites;
***44 subjects × 3 doses × 4 sites.

Table 4. Comparison of geometric mean RVNA concentration following administration of Rabipur or Verorab using one week, 4 site ID regimen in animal bite cases

Day of blood sample	Vaccine	No. of subjects	Range (IU/mL)	GMC (IU/mL)	95% CI		t-value	P value
					Lower Bound	Upper Bound		
14	Rabipur	45	4.5–16.5	14.50	13.50	15.57	0.095	0.924
	Verorab	44	4.5–16.5	14.43	13.41	15.53		
90	Rabipur	42	6.5–14.5	11.78	11.27	12.31	0.432	0.667
	Verorab	43	10.5–14.5	11.93	11.47	12.40		
365	Rabipur	32	4.5–8.5	5.95	5.50	6.44	0.933	0.354
	Verorab	38	4.5–7.5	5.67	5.29	6.08		

Note: GMC- Geometric Mean Concentration; CI- Confidence Interval.

to omit the dose on day 90 for which compliance was very low. The dose on day 90 was replaced by giving 2 doses of vaccine on day 28 instead of one. [8-17]

WHO Expert Consultation on Rabies (1st Report, 2005 and 2nd Report 2013) has approved the use of updated TRC regimen (2-2-2-0-2) spread over a period of one month and is currently in use in many Asian countries. However, dropout rate is as high as 60% for last dose of vaccination with updated TRC regimen.[18] To improve the patient compliance for complete vaccination, WHO recommended research on shorter regimens which may be an alternative to updated TRC regimen.[1,6] Studies done in Thailand and India among healthy volunteers using one week, 4 site intradermal regimen, the rabies vaccines were proved to be safe and immunogenic.[5,7] The improved compliance and cost effectiveness of this regimen along with advantages and disadvantages of other PEP regimens is very well discussed by Hampson et.al.[19]

This was a pioneering study on animal bite cases, where only adults between 18 to 55 years of age were enrolled as study subjects. The safety and immunogenicity of present study was compared with other studies conducted with WHO prequalified vaccines with Essen, updated TRC and one week, 4 site regimen ('Historical control') at Kempegowda Institute of Medical Sciences (KIMS), Bangalore, India and RVNA analyzed at WHO collaborating center for reference and research on Rabies, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India.

The incidence of local and systemic ADEs of the study vaccines administered with one week, 4 site intradermal regimen was comparable to other studies done at KIMS, Bangalore, India.[7,16,17,20]

The immune response elicited in this study on day 14 was comparable with studies done using updated TRC regimen, Essen regimen and one week, 4 site intradermal regimen.[7,16,17,20] Similarly, the immune response in the present study on day 90 was comparable with Essen regimen.[20] All the study subjects in both the groups of vaccines on day 365 had adequate RVNA concentration of $\geq$0.5 IU/mL, whereas the previous study from India showed that the RVNA concentration was <0.5 IU/mL among 21.1% subjects in Rabipur group and 37.5% subjects in Verorab group.[7] The concomitant administration of ERIG in all category III exposures in the study did not suppress the immune response to rabies vaccines.

Both the TRC intradermal regimen and Essen intramuscular regimen have shown long lasting immune response up to 5–21 years with primary course of vaccination.[21] However, the longevity of the shortened one week, 4 site regimen and subsequent response to booster doses needs to be studied particularly in Asian countries where re-exposures are not uncommon.

There were some limitations in the study like; confirmation of rabies in the biting animals was not possible due to practical difficulty in catching the stray animals and sacrificing them for laboratory examination. Similarly, safety and immunogenicity of rabies vaccines by this new one week, 4 site intradermal regimen was not done in children, pregnant and lactating women.

In conclusion, both Rabipur and Verorab were safe, immunogenic and comparable with each other when administered using one week, 4 site intradermal regimen in animal bite cases and also with respect to other rabies vaccine regimens which are in practice. There was no incidence of rabies in any of the subjects who were administered with one week, 4 site regimen. The subjects are currently under follow up to assess the longevity of immune response.

Material and Methods

The study was conducted at the Anti-Rabies Clinic, KIMS Hospital and Research Center, Bangalore, India. The study was initiated after getting approval from the KIMS institutional Ethics Committee and registering in Clinical Trials Registry of India (CTRI) bearing the registration number CTRI/2012/12/003230. The study was done in accordance with ICH-GCP guidelines.

Enrolment of subjects and vaccination

The study was a Randomized (1:1), active controlled, parallel assigned, comparative, open label, phase III clinical trial conducted between January 2013 and June 2014. The subjects who fulfilled standard inclusion and exclusion criteria for rabies vaccine trial (**Table 5**) was asked to read and understand the study information sheet provided in their own language and if subject agreed to participate in the study, written informed consent was taken. Enquiry regarding animal bite and anti-rabies vaccination in the past and history about concurrent illness and medications was also obtained.

Table 5. Inclusion and Exclusion criteria for enrolling subjects in the study

	Inclusion Criteria		Exclusion Criteria
1	Subjects aged 18 years and below 55 years of age	1	Subject who has received any type of rabies vaccination in the past.
2	Subjects with either category II or category III exposures to rabies	2	Pregnancy and lactation
3	Subjects willing to sign informed consent	3	Subject has received rabies immunoglobulin (human/equine) in the past
4	Subjects available for one year follow-up period and willing to give blood samples on recommended days	4	Subject is suffering from chronic diseases like diabetes mellitus, hypertension and tuberculosis
5	Subject with animal bite cases reported within 72 hours of exposure	5	Subject on steroids, anticancer drugs and radiation therapy or any other immunosuppressant or immune compromised
		6	Subject is on concomitant antimalarial drugs
		7	Subject with history of allergy to any ingredient of the vaccine
		8	Subject in other clinical trial in the past 3 months

A total of 90 animal bite cases in the age group of 18 to 55 years with category II and III exposures were enrolled and were randomly administered marketed batch of either Rabipur (1 mL, Batch No: 2416, Mfg. date Feb 2012, Exp.date Jan 2016, potency 6.9 IU/dose and Batch No.2524, Mfg. date Aug 2012, Exp. date July 2016, potency 7.5 IU/dose) or Verorab (0.5 mL, Batch No H1106, Mfg. date Mar 2011, Exp. date Feb 2014, potency 7.0 IU/dose) intradermally using one week, 4 site regimen (4-4-4-0-0). The potency of the vaccines were obtained from the manufacturers after completion of the study. The ID vaccine administration involved injection of 0.1 mL of reconstituted vaccine per ID site on 4 such ID sites per visit (one on each deltoid and one on each suprascapular area) on days 0, 3, and 7 where day 0 was the day of first dose of administration of vaccine. Subjects with category III exposures were administered ERIG (Equirab) into and around all the bite wounds on day 0 as per WHO guidelines with the dosage of 40 IU/kg body weight.

Assessment of safety

Following anti rabies vaccination, all the subjects were observed for 30 minutes for possible immediate local/systemic ADRs and recorded if any. The subjects were provided follow up card for mentioning any delayed local/systemic ADRs.

Assessment of immunogenicity

The average incubation period of human rabies is 1 to 3 months, occasional cases of human rabies has been reported even up to one year. Hence, to know whether protective rabies antibodies persists up to one year, sera of vaccinated subjects were analyzed up to day 365.

5 mL of venous blood was collected from subjects on days 0,14,90 and 365, sera separated, coded and analyzed for RVNA by Rapid Fluorescent Focus Inhibition Test (RFFIT) at NIMHANS, Bangalore, India.

Estimation of RVNA concentration

RFFIT was done as per WHO recommended procedure with some modifications. The cell line used was BHK 21 (ATCC CCL 10) and micro neutralization test was done in 96 well tissue culture plates (Sigma) and BHK21 adapted CVS 13 strain of rabies virus obtained from Central Research Institute, Kasauli, Himachal Pradesh, India. The reference serum used was an in house serum calibrated against 2nd international reference standard having a titer of 30 IU/mL (obtained from National Institute of Biological standards, UK). Briefly, doubling dilutions of serum samples and reference serum (after heat inactivation at 56°C for 30 min in a water bath) in duplicate were made in 96 well plates using IMDM (Sigma Cat No.17633). To each 100 μl of serum dilution 100 μl of CVS (100 FFD_{50}) was added and the plate was incubated at 37°C for 1 hour. A confluent monolayer of BHK 21 cells were trypsinized and re-suspended in 10 ml of IMDM with 10% FCS (Sigma, Cat No. F2442). To each well of the 96 well plate, 100 μl of cell suspension was added and the plate was incubated at 37°C in a CO2 incubator (Sanyo, Japan). Normal cell control and virus controls were also included. After 24 hours, the cells were fixed in cold acetone for 30 minutes and stained by direct FAT using commercially available rabies N conjugate (Light diagnostics USA, Cat No. F5100). The plates were then observed under an inverted fluorescence microscope (Nikon Eclipse). The highest dilution of serum showing 50% inhibition of fluorescence foci was taken as end point dilution. The titer was converted to IU/mL in comparison with reference serum.

Data analysis and statistical inferences

The data collected in the study was analyzed statistically by computing percentages, GMC, Range, 95% Confidence Interval for GMC, t- test, ANOVA and P value. The difference in proportion of ADRs between the vaccine groups was assessed by Z test.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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