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Evaluation of a one week intradermal regimen for rabies post-exposure prophylaxis

Results of a randomized, open label, active-controlled trial in healthy adult volunteers in India

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The currently recommended intradermal regimen for post-exposure prophylaxis spreads over a month period which many times lead to low compliance from the patients. There is a need to introduce and evaluate short course regimens to overcome this problem. This study was conducted to evaluate the immunogenicity and safety of a "new one week intradermal regimen" for rabies post-exposure prophylaxis. A total of 80 healthy adult volunteers were enrolled and allocated randomly either to purified chick embryo cell (PCECV) rabies vaccine or purified verocell rabies vaccine (PVRV), 40 in each group. Each subject received intradermally one of the vaccines, using the one week regimen (4-4-4). Blood samples were collected on Days 0, 7, 14, 28, 180 and 365 for estimation of rabies virus neutralizing antibody (RVNA) concentration. The sera samples were analyzed by rapid fluorescent focus inhibition test (RFFIT). All subjects in both the groups had adequate RVNA concentration of ≥ 0.5 IU/mL from day 14 to till day 180 and the difference of geometric mean concentrations between the two groups was not significant ($p > 0.606$). Further to assess the immunological memory produced by this new regimen, a "single visit four site" intradermal booster vaccination was given to those who did not have adequate RVNA concentration on day 365. This resulted in a quick and enhanced RVNA concentration in these subjects thus denoting a successful anamnestic response. The incidence of adverse events was 8.3% in PCECV group and 1.6% in PVRV group ($p = 0.001$) and the regimen was well tolerated without any dropouts. In conclusion, the new "one week intradermal regimen" is immunogenic and safe for rabies post-exposure prophylaxis and needs to be further evaluated in persons exposed to rabies.

Introduction

Rabies is an acute and fatal viral encephalitis caused by a highly neurotropic single stranded negative sense RNA virus belonging to the genus Lyssa virus of family Rhabdoviridae. It is a zoonotic disease and nearly 95% of all human infections are due to exposure to rabid dogs. As per a World Health Organization (WHO) estimate, annually about 55,000 human rabies deaths occur globally and of these 31,000 are from Asia and 24,000 from Africa.[1] Rabies deaths can be prevented by effective post exposure prophylaxis (PEP) with potent rabies vaccines and immunoglobulins administered soon after the exposure. For developing countries in Asia and Africa, where rabies is endemic, the use of intradermal rabies vaccination (IDRV) is cost effective and many countries in Asia including India are now using IDRV for rabies prophylaxis. However, the currently used intradermal (ID) regimen (updated Thai Red Cross regimen, 2-2-2-0-2), as recommended by WHO is of one month duration, and requires four visits to the clinic. Because of this many animal bite victims exposed to rabies do not complete the full treatment and are still at risk of developing rabies. Most of the treatment failures have occurred because of non adherence to one or more PEP parameters including number of doses of vaccine.[2] To reduce the duration of rabies PEP by ID route, a preliminary study was done in Thailand which consisted of administration of 0.1 mL of purified vero cell rabies vaccine (PVRV) at four sites on days 0, 3 and 7 (4-4-4). The results of this "new one week" regimen was found to be encouraging,[3] and was reviewed in the last WHO expert consultation meeting on rabies held at Annecy, France in 2009. It was recommended to reassess this new regimen on the basis of a well designed study.[4]

In this background, the present study was undertaken with the objective of evaluating immunogenicity and safety of this "new one week" intradermal regimen using two WHO prequalified vaccines i.e., Rabipur (purified chick embryo cell rabies

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vaccine, PCECV) and Verorab (purified verocell rabies vaccine, PVRV) which are also recommended by WHO for administration by ID route.

Results

The socio-demographic characteristics of the two groups of subjects receiving two different vaccines were almost similar. The subjects belonged to middle age group, majority being men, with basic education, employed and from middle income group (**Table 1**).

Immunogenicity. None of the subjects had detectable rabies virus neutralizing antibody (RVNA) concentrations before receiving the first dose of vaccine, i.e., on day zero. The overall pattern of antibody response was similar in the two groups (**Table 2**). It was highest on day 14 and day 28 and then decreased by day 365. On day 7, only 4 (10.5%) and 8 (20.0%) subjects who had received PCECV and PVRV respectively had adequate RVNA concentration of ≥ 0.5 IU per mL which is considered as adequate for protection. However, all subjects had RVNA concentrations of ≥ 0.5 IU per mL from days 14 through 180. By day 365 about 78.9% of PCECV vaccinees and 62.5% of PVRV vaccinees had adequate levels of RVNA. However, there was no significant difference in the geometric mean concentrations (GMCs) of RVNA between the two groups of subjects who had received PCECV and PVRV from day 7 to day 365 ($p > 0.606$).

Longevity of the immune response and effect of booster dose. The present study also aimed to know whether the new one week regimen conferred an immune memory for one year. It was found that 8 (21.1%) subjects of PCECV (Rabipur) and 15 (37.5%) subjects of PVRV (Verorab) had inadequate RVNA response (< 0.5 IU per mL) on day 365. Consequently, these subjects (PCECV = 8; PVRV = 14) were given a dose of "single visit four site" (0.1 mL x 4 sites; two deltoid and two suprascapular) booster vaccination on day 436 ± 16 (day zero) and their serum samples taken on days 7 and 14 were tested for RVNA concentrations. It was satisfying to see that all the subjects produced enhanced RVNA concentration by day 7 itself (**Table 3**). This denotes that the new one week regimen produced an immune memory lasting for a year as shown by the quick anamnestic response by day 7 of booster vaccination. Also, there was no significant difference in the RVNA response to the two vaccines following booster vaccination ($p = 0.6$).

Table 1. Socio demographic characteristics of subjects

Socio demographic characteristics		PCECV group (n = 38)	PVRV group (n = 40)
Mean age (±SD) in yrs	Male	33.6 ± 8.5	31.4 ± 9.6
	Female	30.0 ± 8.4	32.9 ± 9.7
Sex	Male	25 (65.8)	24 (60.0)
	Female	13 (34.2)	16 (40.0)
Education	Higher Secondary and above	29 (76.3)	28 (70.0)
Occupation	Employed/working	38 (100)	38 (95.0)
Socio economic status	Middle income and above	30 (79.0)	33 (82.5)

Safety of IDRV regimen. Adverse reactions were reported more frequently in subjects who received PCECV (36.8%) compared with PVRV (17.5%) when administered by new one week intradermal (4-4-4) regimen. The adverse events (AE) to both the vaccines following each dose of vaccination were itching (41.3%), induration and pain (15.2%), fever (10.8%), erythema (8.7%), myalgia and lymphadenopathy (4.3%). The reported adverse reactions were mild (89%) to moderate (11%) in nature, self limiting and subsided with (28.3%) or without (71.7%) medication. The adverse events to PCECV (Rabipur) were more (total = 8.3%; local = 7.0%; systemic = 1.3%) when compared with PVRV (Verorab) (total = 1.6%; local = 1.0%; systemic = 0.6%). This difference was statistically significant for only local AEs ($p = 0.001$). However, none of the subjects dropped out of the study due to AEs.

Discussion

Though rabies is considered 100% fatal, it is preventable if the state of art modern prophylactic measures recommended by WHO are instituted soon after the exposure. With the advent of modern cell culture vaccines, which are highly potent and safe, the post-exposure vaccination for rabies underwent a dramatic change with almost painless injections, much reduced doses over the deltoid region and negligible side effects. The dosage schedule for modern rabies vaccines was initially evaluated based both on studies in healthy volunteers and the Iranian study.[5] The schedule was aimed at obtaining faster and long lasting antibody response of the IgG isotope and overcoming the possible suppressive effect of immunoglobulin if administered concomitantly. Though initially a six dose regimen was recommended by WHO, the sixth dose on day 90 was omitted by WHO in 2005. Consequently, the popular "Essen regimen" consisted of administering five doses of rabies vaccine by IM route on days 0, 3, 7, 14 and 28 or 30. However, recently based on an expert group recommendation the Advisory Committee on Immunization Practices, USA further shortened the Essen regimen from 5 doses to 4 doses by omitting the dose on day 28 and it is in vogue in USA since 2010.[6] However, as per the latest WHO recommendation, this shortened regimen should be administered only to healthy, fully immunocompetent exposed persons who receive wound care plus high quality rabies immunoglobulin plus WHO-prequalified rabies vaccines.[4]

Another paradigm shift occurred in 1992 when IDRV was recommended by WHO.[7] Subsequently different regimens were evaluated and finally the updated TRC regimen was recommended by WHO in 2005. In India, IDRV was recommended for use in the government sector in 2006 and presently 12 states are administering this regimen.[8] While administering the standard IM regimen and the ID regimen, one of the major concerns is the requirement of repeated clinic visits by the patients which increases the cost of travel, more time spent and leading to lot of inconvenience. This reduces the compliance of the patients which may prove fatal in definite rabid exposures. For instance

Table 2. Comparison of RVNA response in two groups of vaccinees following one week IDRV

Day of blood sample	Vaccine	No. of subjects	RVNA response (IU/mL)				t-value	p-value
			Range	GMC	95% CI			
					Lower bound	Upper bound		
7	PCECV	38	0.2–0.5	0.266	0.236	0.299	0.343	0.733
	PVRV	40	0.2–0.5	0.274	0.241	0.311		
14	PCECV	38	8.5–14.7	12.010	11.240	12.609	0.519	0.606
	PVRV	40	8.5–15.8	12.212	11.693	12.755		
28	PCECV	38	8.5–15.6	11.296	10.823	11.789	0.458	0.648
	PVRV	40	8.5–16.4	11.462	10.925	12.025		
180	PCECV	38	2.5–6.5	4.325	4.056	4.611	0.024	0.981
	PVRV	40	3.5–5.8	4.321	4.102	4.551		
365	PCECV	30	< 0.5–1.5	0.717	0.607	0.846	0.339	0.736
	PVRV	25	< 0.5–1.5	0.746	0.628	0.886		

Note: GMC, geometric mean concentration; CI, confidence Interval; PCECV, Purified chick embryo cell vaccine (Rabipur); PVRV, Purified vero cell rabies vaccine (Verorab).

Table 3. Rabies virus neutralizing antibody response following "single visit-4 sites" ID booster vaccination with PCECV and PVRV

Days	Vaccine	No. of subjects	Range of RVNA conc.	GMC	95% Confidence Interval for GMC		t-value	p-value (two-tailed)
					Lower Bound	Upper Bound		
Day 7	PCECV	8	2.5–5.5	3.81	3.13	4.64	0.515	0.612
	PVRV	14	2.5–5.7	3.60	3.11	4.17		
Day 14	PCECV	8	7.5–10.5	8.93	7.92	10.08	0.495	0.626
	PVRV	14	6.5–10.6	8.62	7.81	9.51		

GMC, geometric mean concentration; PCECV, purified chick embryo cell vaccine (Rabipur); PVRV, purified vero cell rabies vaccine (Verorab).

in Thailand about 5% patients do not come for the 4th dose on day 28.[3] In two recent studies from India where updated TRC, IDRV is given in government hospitals, the completion/compliance rate to full course or taking 4 doses of vaccine including the one on day 28 was found to be 38.5% in a rural clinic and 75.5% in an urban clinic.[9,10] Hence, any treatment failure resulting in rabies death, though due to lack of compliance on the part of the patient, may be linked to the efficacy of the ID regimen and this may adversely affect the implementation of ID regimen in future. This issue has been addressed several times in the expert meetings both at national and international levels but because of lack of substantial clinical evidence on the immunogenicity of the short course regimens, no recommendations were made to deviate from the presently recommended updated TRC ID regimen.

In a seminal study conducted previously in 1996, Thraenhart et al. first suggested that PEP schedules could be shortened by increasing initial injections, thus reducing the time to complete the series. He also found that there is an earlier humoral and cellular response compared with the intramuscular regimens.[11] Subsequent experiments done suggested that doubling the number of ID injections during the first few days of treatment produced higher initial (but not earlier) antibody concentrations.[12] This had encouraged the authors of the previous study to assess the immunogenicity of a new "one week PEP" schedule using PVRV (Verorab). As the results were encouraging, WHO in its last expert consultation on rabies held at Annecy, France, in October, 2009 advocated reassessing of this new regimen by a well designed study.[4]

Keeping this in mind, this randomized controlled trial (RCT) was conducted using two WHO prequalified vaccines, which are recommended for ID usage. The antirabies clinic of KIMS Hospital and Research Center, Bangalore, has been conducting several rabies vaccine trials since 1993 and has collaboration with Department of Neurovirology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, a WHO collaborating center for research and reference on rabies. Hence, the data of other clinical trials conducted on similar lines in this twin set up using WHO prequalified vaccines and recommended regimens as well as studies from other countries were used as "historical controls" to compare the immune response. The results showed that the immune response of this "new one week regimen" was comparable with other WHO recommended IM and ID regimens and using WHO prequalified vaccines.

Comparison of immune response (Table 4). The RVNA response of present ID regimen was comparable to RVNA response with updated TRC regimen, TRC regimen, 4 site intra dermal regimen and Essen IM regimens using PCECV and PVRV.[13-17] The only other study conducted on 4 site one week regimen is from Thailand by Shantavasinkul et al.[3] When we compare our results with this study it is found that while 100%

Table 4. Comparison of RVNA response to PCECV and PVRV administered by one week ID regimen (4-4-4) vs. WHO - prequalified vaccines administered by updated TRC/TRC, 4-site (ID), Essen (IM) regimen and one week regimen (Thailand)

Vaccine trials / studies	No. of subjects enrolled	RVNA response [GMC (IU/mL]				
		Day 7	Day 14	Day 28	Day 180	Day 365
Comparing studies using PCECV (Rabipur)						
Present study	38	0.27	12.01	11.30	4.33	0.72
TRC regimen[14]	58	0.34	28.5	10.9 (Day 30)	3.0 (Day 90)	-
TRC regimen[15]	55	-	4.3	9.0 (Day 30)	3.7	–
4 site regimen[16]	86	0.15	20.5	-	2.39 (Day 90)	-
Essen regimen[14]	37	0.29	12.3	18.5 (Day 30)	4.7 (Day 90)	-
Essen regimen[17]	50	-	6.88	16.48	3.45	-
Comparing studies using PVRV (Verorab)						
Present study	40	0.27	12.21	11.46	4.32	0.75
One week ID regimen (Thailand)[3]	45	0.10	18.58	8.61	1.41	1.17 (Day 360)
Updated TRC regimen[13]	63	-	3.26	7.70	3.57 (Day 90)	-
TRC regimen[14]	59	0.32	28.9	10.9 (Day 30)	2.7 (Day 90)	-
TRC regimen[15]	50	-	4.6	8.7 (Day 30)	3.6	-
4 site regimen[16]	87	0.08	26.1	-	2.75 (Day 90)	-
Essen regimen[13]	35	-	5.1	11.2	7.83 (Day 90)	-
Essen regimen[17]	48	-	6.65	16.43	3.71	-

Note: GMC, geometric mean concentration; PCECV, purified chick embryo cell vaccine (Rabipur); PVRV, purified vero cell rabies vaccine (Verorab); TRC: Thai Red Cross.

of subjects in our study had adequate titers till day 180 only 93.2% of subjects had protective titers in the Thailand study. At the end of one year 88.4% of subjects in the Thailand study and 62.5% in the PVRV group and 78.9% in the PCEC group in our study had titers greater than 0.5 IU/mL. However, this regimen produced a good immunological memory lasting for one year as revealed by a quick anamnestic response following a booster vaccination.

The incidence of adverse events to this new regimen using two different vaccines was quite comparable with the reported incidence from other studies.[13-17] However, all subjects in both the vaccine groups tolerated the vaccines and completed the full course of vaccination, thus indicating the acceptability of this new regimen. Indeed, a multiple site ID regimen consisting of 8 inoculations at different sites on day 0 was also well tolerated while it was practiced in the past.[18]

There are some limitations to this study. The sample size is small and was done in healthy adult volunteers. This is understandable as this is the first study conducted in India to assess the immunogenicity of this new short course regimen. Further, as this was a study in healthy volunteers, rabies immunoglobulins have not been administered due to ethical considerations. Also, the safety and tolerability to this regimen could not be fully assessed due to small sample size.

In conclusion, this study confirms the "new one week ID regimen" as immunogenic and safe and further clinical trials may be conducted on persons exposed to rabies, where it would be ethically possible to use rabies immunoglobulins. If the results are satisfactory it will reduce the duration of rabies PEP from the existing one month to one week. This would go a long way in improving the compliance of the patients to rabies prophylaxis and also reduces the overall expenditure of rabies PEP, thus helping to reduce the burden of rabies in endemic countries of Asia and Africa.

Subjects and Methods

This was a phase III, randomized, controlled trial (RCT) conducted at the Anti-Rabies Clinic, Kempegowda Institute of Medical Sciences (KIMS) Hospital and Research Centre, Bangalore, India. The study was conducted following its approval by institutional ethics committee (IEC No. 41 dated 11-7-2009) and in accordance with ICH-GCP norms.

Enrolment of subjects and vaccination. A signed informed consent was obtained from each study volunteer or subject. Eighty healthy adult volunteers were enrolled and allocated randomly either to PCECV or PVRV group (40 in each group). However, two subjects (one male and one female) belonging to PCECV group dropped out after day 0 due to personal and domestic reasons. The vaccines were purchased from the market [PCECV (Rabipur): Batch No. 1819, potency ≥ 2.5 IU per IM dose; expiry date 12/2013 and PVRV (Verorab): Batch no. E 0314-1; potency ≥ 2.5 IU per IM dose; expiry date 03/2012]. Each subject was vaccinated intradermally with either PCECV or PVRV using the one week regimen i.e., 4 doses of 0.1 ml (2 on deltoids and 2 on suprascapular region) given on days 0, 3 and 7.

Blood sampling and sera analysis. Blood samples were collected on Days 0 (before administration of first dose of vaccine), 7, 14, 28, 180 and 365 for estimation of RVNA concentrations. The sera samples were coded for blind processing and analyzed

by rapid fluorescent focus inhibition test (RFFIT) at WHO collaborating center for research and reference on rabies, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India.

Rapid fluorescent focus inhibition test (RFFIT). The test was done as per the procedure advocated by WHO (1996) with some modifications. Tissue culture plates were used instead of lab-tek chambers. The cell line used was BHK 21 cells (ATCC CCL 10). The virus used was challenge virus standard (CVS-11) obtained from Central Research Institute, Kasauli, Himachal Pradesh, India and adapted to grow in BHK 21 cells. The cell line was grown and maintained using minimum essential Medium-MEM (Sigma) with 5% fetal calf serum (Sigma).

Briefly, 2-fold dilutions of subject's heat inactivated serum was made in sterile MEM with 1% fetal calf serum in tissue culture plates followed by addition of 100 FFD 50 of CVS and the plate was incubated for 1 h at 37°C. Along with test, serum samples of the virus controls were also put up. After incubation, 100 μl of cell suspension was added and the plate was incubated at 37°C in a CO_2 incubator for 48 h and the cells were stained by fluorescent antibody technique (FAT) using polyclonal rabies nucleoprotein FITC conjugate (Chemicon Cat No. 5099). The plate was then observed under fluorescence microscope (Nikon Eclipse). The highest dilution of serum showing fluorescent foci in 50% of cells was noted. Along with test sample, a similar dilution of reference anti-rabies serum having known unitage of 30 IU/mL was tested (obtained from National Institute of Biological Standards, UK). The concentration of the test serum was expressed in IU/mL in comparison to reference serum.

Assessing safety of ID vaccination. To assess the safety of the vaccination regimen, all the subjects were observed for half an hour following the first dose of vaccination (on day zero) for possible immediate adverse events (AEs). At the end of half an hour, AE was recorded after soliciting from the subjects as well as physical examination of the subjects. All subjects were given a reminder slip indicating the date of the next dose of vaccination and blood sampling. Adverse events were again recorded during the visit of subjects for subsequent vaccinations on days 3 and 7 or afterwards when they came for blood sampling both by soliciting and physical examination. A standard four point scale viz. none, mild, moderate and severe was used to grade the severity of adverse events.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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This study was conducted from an unconditional financial grant of Rabies in Asia Foundation. The rabies vaccines used in the study were purchased from the market.

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