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Assessing safety and immunogenicity of post-exposure prophylaxis following interchangeability of rabies vaccines in humans

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Rabies post exposure prophylaxis with cell culture vaccines by either intramuscular route or intradermal route spans over a period of one month. World Health Organization recommends completing post exposure prophylaxis against rabies with the same cell culture or embryonated egg rabies vaccine and with same route of administration and any deviation from this shall be an exception. In the present study, the safety and immunogenicity of rabies post-exposure prophylaxis was studied prospectively in 90 animal bite cases that had interchangeability of rabies vaccines either by route of administration or brand/type and such changes had occurred due to logistical/financial problems. Among them, 47 had change in route of administration from intramuscular to intradermal or vice versa and 43 had change in the brand/type of cell culture rabies vaccine. All of them had category III rabies exposure and received equine rabies immunoglobulin along with the rabies vaccine. None of the study subjects had any adverse reactions. The rabies virus neutralizing antibody titers was assessed by rapid fluorescent focus inhibition test and all the vaccinees had titers ≥ 0.5 IU per mL on day 14 which is considered as adequate for protection against rabies. Thus, the present study showed that, rabies post-exposure prophylaxis was safe and immunogenic despite changes in the route of administration and brand/type of rabies vaccine.

Introduction

Rabies is a viral zoonotic disease that occurs in over 100 countries throughout the world. It is transmitted to humans and other animals through close contact with saliva from infected animals i.e., bite, scratches, licks on broken skin and mucous membranes. Although a number of carnivorous animals serve as natural reservoirs, dogs are the main source of human infections and poses a potential threat to >3.3 billion people worldwide.¹ Timely and correct post exposure prophylaxis (PEP) for these animal bite victims is necessary to prevent rabies. Proper wound management and simultaneous administration of rabies immunoglobulin (RIG) combined with prompt administration of rabies vaccine is almost invariably effective in preventing rabies, even after high-risk exposure.²

Since their development more than 4 decades ago, purified cell culture and embryonated egg - based rabies vaccines (CCEEVs) have proved to be safe and effective in preventing rabies. These vaccines are intended for both pre- and post-exposure prophylaxis and have been administered to millions of people worldwide.³ However, the affordability to CCEEVs for intramuscular administration is a major constraint in many

developing countries. Therefore, in these countries where there are financial constraints, intradermal rabies vaccination (IDRV) has been implemented in Government hospitals which largely benefit the poor and needy.

In India, animal bites in humans are a major public health problem and an estimated 17.4 million animal bites occur annually which accounts to an incidence of 1.7%.⁴ The medical care to these animal bite victims is provided by both Government and private sectors. The animal bite victims often go to private hospitals/practitioners for PEP where rabies vaccine is administered by intramuscular route (IMRV) by Essen regimen i.e., 1 dose of vaccine is administered on days 0, 3, 7, 14, and 28. The bite victims have to pay for each dose of vaccination. Hence, due to high cost of CCEEVs, during the course of vaccination some switch over to the Government hospitals for further doses of rabies vaccination where intradermal route of rabies vaccination (IDRV) by updated Thai Red Cross regimen i.e., 0.1 mL of vaccine given at 2 sites on days 0, 3, 7, and 28 is given free of cost. Similarly, some of the animal bites victims who start rabies PEP by IDRV in Government hospital, following stock out of vaccine, due to poor logistics, go to private hospitals/ practitioners, where IMRV is provided for a "fees." Consequently in both the situations, there

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Table 1. Characteristics of animal bite victims

Characteristics	Group 1: Changes in the route of administration (n = 47)	Group 2: Changes in the brand/ type of vaccine (n = 43)
Age range (mean)	15–65 y (30.8)	15–65 y (32.4)
Sex: Male Female	27 (57.4%) 20 (42.6%)	27 (62.8%) 16 (37.2%)
Biting animal: Stray Pet	Dog (100%) 25 (53.2%) 22 (46.8%)	Dog (100%) 23 (53.3%) 21 (46.7%)
Provocation: Unprovoked Provoked	27 (63.8%) 17 (36.2%)	26 (60.5%) 17 (39.5%)
Site of bite: Lower limb Upper limb Trunk Head and Neck	25 (53.2%) 14 (29.8%) 6 (12.8%) 2 (4.2%)	24 (55.8%) 12 (27.9%) 5 (11.6%) 2 (4.7%)
Wound wash: Yes at home No	30 (63.8%) 17 (36.2%)	26 (60.5%) 17 (39.5%)
Categorization of wound: Cat III	47 (100%)	43 (100%)

will be changes in the route of administration of rabies vaccine and even the type/brand of vaccine.

The logistics of procurement, supply and consequent usage of rabies vaccines in Government hospitals is based on competitive pricing and bidding procedures. The market availability of rabies vaccines cannot guarantee that a particular brand/type of vaccine will be made available for PEP on a continual basis in Government hospitals. Therefore, interchangeability of brand/type of vaccine often occurs depending upon the brand/ type of rabies vaccine available at that time.

As rabies is almost always fatal, post exposure prophylaxis is life saving and has to be completed irrespective of route of administration and type/brand of vaccine available. Therefore, depending upon the availability of CCEEVs by whatever the route and type / brand, it is essential to complete PEP against rabies as per the scheduled course to save the lives of the animal bite victims. When it is impossible to complete PEP with the same CCEEV and by the same route of administration, another CCEEV and another route of administration may have to be used instead.¹ However, 2 studies conducted in this regard showed, an epidemiological effectiveness of interchangeability of brand of rabies vaccines⁵ and the other demonstrating adequate booster immunogenic response following changes in the route in previously vaccinated persons.⁶

However, no study has been done yet on vaccine safety and immunogenicity following changes in the route of vaccine administration (from intramuscular to intradermal and vice versa) or brand/ type of vaccine used (PCEC to PVRV and vice versa) during PEP.¹ In this regard, we studied the safety and immunogenicity of PEP following interchangeability of rabies vaccines by route of administration or type/ brand, and such changes had occurred in the usual course of PEP due to logistical/ financial problems.

Results

Ninety victims bitten by suspect rabid dogs were included in the study, among them 47 (Group 1) had changes in the route of administration of rabies vaccine and 43 (Group 2) had changes in the type/ brand of CCVs from PCECV to PVRV or vice versa. None of the study subjects had taken any pre- or post exposure prophylaxis in the past nor had any animal bites.

Group 1

Among the 47 subjects, who had changes in route of administration (24 from intramuscular to intradermal and 23 from intra - dermal to intramuscular), 27 were males and 20 females. The age distribution ranged from 15 to 65 y with the mean age of 30.8 y. Majority of dog bites (63.8%) were unprovoked, on the limbs (83%), and all were category III exposures. Wound wash was done and all the study subjects received total quantity of required equine rabies immunoglobulin (ERIG: Equirab) locally, into and around the wound/s (Table 1).

None of the study subjects reported any adverse drug reactions. The RVNA titers of all the vaccinees were ≥ 0.5 IU/mL on day 14, with the geometric mean concentration (GMC) of 14.83 and the range of 7.5–22.5. (Table 2)

All the study subjects were healthy and alive after 6 mo of completing PEP.

Group 2

Among the 43 animal bite victims, who had changes in type/ brand of vaccine (27 from PCEC: Rabipur to PVRV: Indirab and Abhayrab and 16 from PVRV: Indirab and Abhayrab to PCEC: Rabipur), 27 were males and 16 females. The age distribution ranged from 15 to 65 y with the mean age of 32.4 y. Majority (60.5%) of dog bites were unprovoked, on the limbs (83.7%) and all were category III exposures. Wound wash was done and all the study subjects received total quantity of required ERIG (Equirab) locally, into, and around the wound/s (Table 1).

None of the study subjects reported any adverse drug reactions either to rabies vaccine or ERIG. The RVNA titers of all the vaccinees were ≥ 0.5 IU/mL on day 14, with the geometric mean concentration (GMC) of 11.84 IU/mL and the range of 7.5–15.5 IU/mL. (Table 2).

All the study subjects were healthy and alive after 6 mo of completing PEP.

Discussion

CCEEVs have been administered to millions of people worldwide and have proved to be safe and effective in preventing rabies. But, there are various concerns in PEP especially in developing countries, such as: cost of rabies vaccines, purchase and supply of vaccines to the Government hospitals/ health centers, availability of vaccine stocks, and long course of vaccination. These factors come in the way of administering the same brand/ type and also route of vaccination. Therefore, in the course of PEP, many people cannot accept the entire treatment in the same hospital. Consequently, changes in the route of administration and replacing different vaccine happens.

Table 2. Rabies virus neutralizing antibody (RVNA) response on Day 14

RVNA (inIU/mL) response on Day 14	Group 1: Changes in the route of administration (n = 47)	Group 2: Changes in the brand/type of vaccine (n = 43)
GMC (IU/mL)	14.83	11.84
95% CI for GMC	Upper bound = 13.58 Lower bound = 15.63	Upper bound = 10.83 Lower bound = 12.94
GSD	1.18	1.33
Range	7.5–22.5	7.5–15.5
T value		4.531
P value		<0.01

All CCEEVs consist of inactivated rabies virus, that has been propagated in different cell substrates and the antigen is same in all these vaccines. Furthermore, all CCEEVs induce a prompt and high rabies-virus neutralizing antibody (RVNA) response to the viral G protein as per WHO specified minimum titer of ≥ 0.5 IU/mL of serum, as measured by the rapid fluorescent focus inhibition test (RFFIT) which indicates adequate seroconversion. Hence, an indirect assessment of vaccine efficacy can be made through immunogenicity studies. In healthy vaccinees, this level should be achieved in most of the individuals by day 14 of a post-exposure regimen, with or without simultaneous administration of RIG and irrespective of age.³

In India, where rabies is endemic, 4 types of rabies vaccines are available. The first 3 are the cell culture derived i.e., human diploid cell culture vaccine (HDCV), purified chick embryo cell vaccine (PCECV), and purified vero cell rabies vaccine (PVVR), and the fourth is the purified duck embryo vaccine (PDEV). Similarly, 2 brands of PCEC (Rabipur and Vaxirab N) and 3 brands of PVVR (Verorab, Abhayrab, and Indirab) are marketed in India. All these vaccines have been found to be highly immunogenic, safe, and efficacious.^{7–9} These vaccines are produced using approved strains of rabies viruses and are released after rigorous quality control testing from National drug authorities. Currently the vaccine strains used are PV 11, Pitman-Moore and Flury LEP. Whereas PV 11 and Pitman-Moore strains are the original derivatives of Pasteur virus (PV), the Flury LEP is derived from a human source and adapted to grow in chick eggs.¹⁰ Molecular studies have shown that these strains are genetically homologous. A recent study on genetic characterization of different vaccine strains used in 6 commercial vaccines has shown a close homology among each other, though the vaccines varied in their protein content and purity.¹¹

Keeping in view the close homology of different vaccine strains used in vaccine production, there should not be any major concern if a change in brand of vaccine occurs during a course of post-exposure prophylaxis. Further, it has also been shown that the rabies virus prevalent in India and other Asian countries belong to species 1 and all currently available rabies vaccines offer uniform protection against this strain. The rabies vaccines induce protection by mainly producing RVNA. It is also possible that cell mediated immune responses also play a role. Good levels of RVNA are produced both by IM and ID routes of vaccination and several studies have shown comparable RVNA responses by

these routes.¹² When the vaccine is administered by intramuscular route, the antigen gets absorbed into blood, picked up by circulating macrophages and dendritic cells which mature and process the antigen and then present this to T lymphocytes in all regional lymph nodes. A subset of T lymphocyte i.e., CD 4 cells will then initiate antibody response through conversion of B cells into plasma cells. The process is similar with intradermal administration except that the antigen inoculated into dermis is immediately picked up by resident dendritic cells (Langerhan's cells), processed and presented to regional lymph nodes through lymphatic system and again with the help of CD4 cells, B cells produce antibodies. Much smaller quantities of antigen are sufficient with ID route as there is no dilution as it happens in intramuscular administration.¹⁰

Considering the fact that both IM and ID routes of administration produce equally good RVNA titers, the antigenic stimulus and the immune mechanisms involved are the same, switching over from IM to ID route and vice versa need not be a major concern as far as protection against rabies is concerned. However, in such situations it is advisable to test the patient's blood samples to demonstrate adequate sero-conversion especially in cases where there is a confirmed rabid exposure or strong suspicion that the biting animal may be rabid. This will instill confidence in the treating physician and help the administrators to take decisions regarding vaccine procurement and supply logistics. In this study, confirmation of rabies in the biting animal could not be done due to practical and logistical difficulties.

The present study showed that, none of the study subjects had any adverse reactions following changes in route of administration or brand/type of anti rabies vaccine and our study has clearly shown that these deviations which have occurred in the usual course of rabies PEP have not adversely affected the immune responses. Even though, the GMCs between the 2 groups were statistically significant, it was not clinically relevant, as the RVNA titers among all the 90 bite victims in both the study groups were well above the WHO recommended protective titer of ≥ 0.5 IU/mL on day 14. This confirms that, there was an adequate protection against rabies among all the vaccinees who received post exposure prophylaxis, even when there were changes in the route of administration or brand/ type of CCVs. It was also seen that the RVNA titers among the study subjects were comparable with the geometric mean concentration (GMC) of RVNA titers among vaccinees in other studies conducted in

the same setting but PEP was completed with the same route and same brand/ type of cell culture vaccine.^{7,13-15}

In conclusion, PEP against rabies was safe and immunogenic, even following changes in the route of administration or type/ brand of anti rabies vaccine. Hence, in unavoidable circumstances, such changes in the route of administration or brand/ type of anti rabies vaccine may be allowed to ensure completion of the PEP, to save the lives of individuals exposed to rabies.

Materials and Methods

The study was conducted at 2 municipal corporation hospitals of Bangalore city. The study was initiated following clearance from the institutional ethics committee of Kempegowda Institute of Medical Sciences, Bangalore, India.

Subjects

The animal bite victims who came for rabies PEP were interviewed to find out whether they had received the rabies vaccine by different routes of administration i.e., intradermal to intramuscular or vice versa during the first 3 doses of vaccination on days 0, 3, and 7. Those who reported such changes in the route of administration of rabies vaccination, were included in the study and the case records (Out patient card of the hospital) of all these subjects were verified for confirmation of change in the route of vaccination from IM to ID or vice versa and to rule out any changes in the brand/ type of vaccines. (Group 1). The vaccines used were Rabipur, Verorab, Indirab, and Abhayrab.

Similarly, by studying the case records (Out patient card of the hospital), animal bite victims who had received rabies PEP following changes in the brand/type of intradermal rabies vaccines from PCEC (Rabipur) to PVRV (Indirab and Abhayrab) or vice versa without change in the route of administration during first 3 doses i.e., on days 0, 3, and 7 were also enlisted (Group 2).

Thorough and detailed enquiry was done among all the study subjects to rule out taking any rabies vaccine either as pre exposure prophylaxis (PrEP) or PEP and history of any animal bite in the past. Similarly, any concomitant medical conditions / treatments were ruled out.

All the bite victims were given PEP as per WHO recommendation. Following vaccination, all the subjects were observed for half an hour for possible immediate adverse drug reactions. At the end of half an hour, reactogenicity was recorded only if the subject spontaneously reported a problem to a question on general wellbeing i.e., unaided recall. The subjects were given a follow up card to indicate if they had any late adverse events and was recorded in the subsequent visits i.e., on Day 3, 7, 14, and 28.

All the study vaccines were from market batch and had the potency of >2.5 IU/mL.

All the study subjects who had interchangeability of rabies vaccines gave signed informed consent for serum analysis and follow up. Blood samples were drawn on day 14 for estimation of rabies virus neutralizing antibody (RVNA). Five mL of venous blood was drawn from each patient under aseptic precautions and the sera were separated and tested for RVNA by rapid fluorescent focus inhibition test (RFFIT) at the Department of Neurovirology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India which is a WHO collaborating center for reference and research on rabies.

Estimation of rabies virus neutralizing antibody (RVNA)

RFFIT was done as per WHO recommended procedure. The cell line used was BHK 21 (ATCC CCL 10) and 96 well tissue culture plates (Sigma) and BHK21 adapted CVS 11 strain of rabies virus. 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 uL of serum dilution 100 uL of CVS (100 FFD₅₀) was added and the plate was incubated at 37°C for 1 h. A confluent monolayer of BHK 21 cells were trypsinized and re-suspended in 10 mL of IMDM with 10% FCS (Sigma, cat No. F2442). Cell control and virus controls were also included. To each well of the 96 well plate 100 uL of cell suspension was added and the plate was incubated at 37°C in a CO₂ incubator (Sanyo). After 24 h the cells were fixed in cold acetone for 30 min and stained by direct FAT using commercially available rabies N conjugate (Light Diagnostics, Cat No. F199). 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.

All the study subjects in both the groups completed the course of vaccination.

All the study subjects were followed up for 6 mo to know their survival status.

All the biting dogs could not be traced or caught for laboratory examination due to practical and logistical difficulties.

Statistical analysis

The data were analyzed by computing percentage, range, and calculating geometric mean concentration (GMC).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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