National Institute of **EPIDEMIOLOGY**

Mulit-centric study on the use of intradermal administration of tissue culture Antirabies vaccines in india

Rationale :

Production of Nerve Tissue Rabies Vaccine (NTRV), commonly used for post-exposure treatment (PET) in India is discontinued. Tissue Culture Anti-rabies Vaccines (TCARV) and purified embryo vaccines are approved for use intra-muscular route in India. However, due to high cost, TCARVs are not being used for all post-exposure treatment (PET) purposes in the country. The use of TCARV in small doses given by intra-dermal route reduces the cost of treatment considerably compared to TCARV administered intra-musculary and many developing countries are using these vaccines intradermally as PET for animal bites. With this background, the Government of India asked the Indian Council of Medical Research to undertake a study to assess feasibility, safety and immunogenicity of indigenously manufactured TCARVs to be administered intra-dermally in healthy human volunteers.

Methods :

The study was carried out among healthy volunteers selected from five centres in the country. The TCARVs used for intradermal administration were Purified Vero cell Rabies vaccine (PVRV Abhayrab and Coonoor), Purified chicken embryo cell vaccine (PCEC Rabipur) and Purified duck embryo vaccine (PDEV Vaxirab) with a 2-2-2-0-1-1 regimen. Responses to intradermal TCARVs were compared with that of French PVRV (Aventis) administered intramuscularly on 0,3,7,14 and 28 days. Ten volunteers were recruited for each of the TCARV arm in each center as well as for control group receiving French PVRV. Vaccinated individuals were observed for immediate hypersensitivity reactions and their follow-up blood samples were collected on days 14, 28, 90 days and tested for anti-rabies antibody levels using Rapid Fluorescent Focus Inhibition Test at Pasteur Institute, Coonoor.

In order to assess the feasibility of introducing intra-dermal anti-rabies vaccination (IDRV) in government institutions, a survey was carried out to assess

a) Availability of different facilities (Physical, cold chain, manpower and injection supplies) at the anti-rabies vaccination clinics at the district hospitals
b) Animal bite load
c) Skill for Intra-dermal injection
d) Acceptability of IDRV among the patients receiving nerve tissue vaccine.

Results :

A total of 257 volunteers from five centres were recruited in the study after obtaining their consent. On the scruting of the data, it was observed that two centres in Delhi experienced several operational problems. Hence the data from 104 individuals from these 2 centres were not considered for the purpose of analysis. From the remaining 3 centres, day zero blood samples were available from 153 individuals. Twenty seven individuals were excluded from the analysis as their sera samples had a pre-vaccination antibody concentration of > 0.5 IU/ml. Six individuals were withdrawn from the trial for various reasons at different follow-ups; four by day 14 and two by day 90. All the vaccines administered intradermally were tolerated. No adverse drug reactions were reported from any of the vaccinated volunteers from the three participating centres and none of the volunteers was withdrawn from the trial on account of vaccine related reasons. Thus the primary analysis was restricted to 126 sero-negative individuals.

Details of the sera samples collected at different follow-up visits (with respect to seronegative individuals recruited at day 0) in different vaccine arms are give in Table 1.

Table 2 shows the proportion of volunteers sero-producted (antibody titre 0.5 IU/ml), geometric mean for antibody titres (GMT) and 95% CI according to different vaccines at different follow-ups. Proportions of individuals sero-protected on days 14, 28 and 90 for the French PVRV vaccine (standard) were 100%, 100% and 95.7% respectively with the GMT of 6.73, 10.08 and 4.65 IU/ml. The sero-protection rate and GMT dropped to 40.8% and 0.80 IU/ml by day 180. All the volunteers who received Abhayrab PVRV were sero-protected on days 14, 28 and 90. Results were similar for the PVRV from Coonoor.

Table 1 : Sera samples tested for anti-rabies antibodies at different follow-up visits according to different vaccines for day 0 sero-negatives for the three centres.

Vaccines	Day 0	Day 14	Day 28	Day 90	Day 180
French PVRV	25	24	24	23	22
Abhayrab	28	28	28	27	27
Coonoor	23	20	20	20	15
Rabipur	28	28	28	28	28
Vaxirab	22	22	22	22	19
Over all	126	122	122	120	111*

(* 8 samples from one participating centre are yet to be tested)

Table 2 : Sero-protection rate, Geometric mean titres of anti-rabies antibodies and its 5% confidence limits among the volunteers receiving different vaccines.

Vaccines	Day 14		Day 28		Day 90		Day 180	
	No. Sero-Protected/ No. Tested (%)	GMT (95% CI)	No. Sero-Protected/ No. Tested (%)	GMT (95% CI)	No. Sero-Protected/ No. Tested (%)	GMT (95% CI)	No. Sero-Protected/ No. Tested (%)	GMT (95% CI)
French PVRV	24/24 (100)	6.73 (3.64-12.42)	24/24 (100)	10.08 (5.77-17.62)	23/23 (100)	4.65 (2.45-8.81)	19/22 (86.4)	0.80 (0.47-1.37)
Abhayrab	28/28 (100)	7.25 (5.19-10.11)	28/28 (100)	11.04 (7.24-16.83)	27/27 (100)	9.10 (6.28-13.17)	26/27 (96.3)	3.31 (2.01-5.45)
Coonoor	20/20 (100)	8.57 (4.64-15.85)	20/20 (100)	6.73 (3.73-12.14)	19/20 (95)	2.12 (1.27-3.55)	14/15 (93.3)	1.80 (0.99-3.26)
Rabipur	27/28 (96.4)	3.26 (1.95-5.43)	28/28 (100)	4 (2.42-6.62)	28/28 (100)	2.83 (1.78-4.48)	28/28 (100)	3.36 (1.87-6.05)
Vaxirab	15/22 (68.2)	0.55 (0.31-0.97)	17/22 (77.3)	0.81 (0.4-1.63)	20/22 (90.9)	1.15 (0.71-1.84)	18/19 (94.7)	1.98 (1.08-3.63)

For volunteers receiving Rabipur PCECV, the responses were on the lower level but the sero-conversions achieved was 100%. For the volunteers who received Vaxirab PDEV the responses were very much on the lower side, both in terms of GMT values and the sero-conversions over all the three periods of observation. Responses to various vaccines in terms of the geometric means are shown graphically in Fig.1

The results of the study indicate that three TCARVs (Abhayrab PVRV, Coonoor PVRV and Rabipur PCECV) could be used for intradermal administration in India.

Fig.1: Geometric mean antibody titres (GMT) to different TCARVs