Asian Biomedicine Vol. 5 No. 5 October 2011; 589-593 **DOI: 10.5372/1905-7415.0505.078**

Review article

Time interval for booster vaccination following re-exposure to rabies in previously vaccinated subjects

Mysore Kalappa Sudarshan, Haradanhalli Shankaraiah Ravish, Doddabele Hanumanthappa Ashwath Narayana

Department of Community Medicine, Kempegowda Institute of Medical Sciences, Bangalore 560070, India

Background: In rabies endemic areas, re-exposures to rabies are quite common and the incidence could be up to 15%. The recent guidelines of World Health Organization do not specify the duration of protection provided by previous pre- or post exposure prophylaxis. This often puts the treating physician in a dilemma in such cases of re-exposure.

Objective: Study the time interval between primary and booster vaccination in individuals who have taken previously a full course of either pre- or post exposure prophylaxis and are now re-exposed to rabies.

Methods: The data obtained through a literature search using Pubmed and advanced Google search along with data from in house clinical trials were used for analysis. Sixty-six vaccine cohorts spanning more than 27 years from 1983 to 2010 from six countries were studied. The duration of protection offered by previous vaccination was assessed by using a surrogate marker of adequate ($\geq$ 0.5 IU per mL) rabies virus neutralizing antibody levels in the individuals vaccinated either by pre-exposure or post exposure regimens received by intramuscular or intradermal routes.

Results: The proportions of 2,795 subjects who had received prior post-exposure immunization and produced rabies virus neutralizing antibody levels of less than 0.5 IU per mL were 0.07% and 0.14% at the end of the first and third month post primary vaccination. All 577 subjects with previous pre-exposure vaccination had antibody responses above 0.5 IU per mL at the end of the first and third month post primary vaccination.

Conclusion: We concluded that it may be safe for up to three months after previous pre- or post exposure vaccination to not administer boosters to healthy subjects who have been re-exposed to rabies.

Keywords: Booster vaccination, post exposure prophylaxis, pre-exposure vaccination, rabies, re-exposure

In rabies endemic areas, re-exposure to rabies is common with an incidence up to 15% [1]. As rabies is 100% fatal, it is very important to provide timely and correct post exposure prophylaxis (PEP) in such cases. The PEP includes immediate wound cleansing, rabies immunoglobulin injected into and around wounds and rabies vaccination. However, the recent guidelines of World Health Organization (WHO) do not specify the duration of protection provided by previous vaccination i.e. pre-exposure (PrEP) or post exposure prophylaxis (PEP) [2]. Most established Asian animal bite clinics use the arbitrary cut-off of either three or six months post reliable vaccination when boosters are not deemed to be required [36]. This practice has, however, not been defined in WHO guidelines and creates a dilemma for many attending physicians who are confronted by a potential exposure. This study was conducted to study antibody kinetics in previously vaccinated subjects.

Correspondence to: Mysore Kalappa Sudarshan, Department of Community Medicine, Kempegowda Institute of Medical Sciences, Bangalore 560 070, India. E-mail: mksudarshan@gmail.com

Materials and method

Articles published in peer reviewed national and international journals that could be accessed from Pubmed and Google Scholar were reviewed [3, 5-22]. In-house data of rabies vaccine trials was also perused [4, 23-35]. We focused on the number of patients that had vaccine and who produced an inadequate rabies virus neutralizing antibody (RVNA) concentration < 0.5 IU per mL to a full course of

vaccination given either intramuscularly (IM) or intradermaly (ID), with or without rabies immunoglobulin (RIG) during the first six months. Wherever possible, the RVNA response was studied up to day 365 post vaccination.

Sixty-six vaccine cohorts from six countries (France, Germany, India, Thailand, United Kingdom, and USA) were available. They included 44 cohorts from published studies and 22 cohorts from in house vaccine trials. The span of coverage of the data was about 27 years extending from 1983 to 2010. The vaccines used included human diploid cell vaccine (HDCV), purified chick embryo cell vaccine (PCEC), purified vero cell rabies vaccine (PVRV), and purified duck embryo vaccine (PDEV). These were administered PrEP and PEP and by IM and ID regimens. The vaccines were given with RIGs either equine (21 cohorts) or human (8 cohorts) in PEP regimens. The PEP IM regimen used was the "Gold Standard" intramuscular Essen (1-1-1-1-1) or intradermally the "Thai Red Cross" (TRC) (2-2-2-0-1-1), "updated TRC" (2-2-2-0-2) and "Oxford" (8-0-4-0-2-1) schedules.

Results

Antibody response to PEP immunisation

Vaccinees who produced a neutralizing antibody concentration of less than the optimal level of 0.5 IU per mL to a full course of vaccination by intramuscularly (IM) or intradermally (ID) with or without rabies immunoglobulin (RIG) were 0.07% and 0.14% at the end of the first and third month post primary vaccination respectively as shown in **Table 1**. All subjects retained detectable titers for up to one year.

Antibody response to PrEP vaccination

Vaccinees with a history of pre-exposure vaccination, all had neutralizing antibody levels above 0.5 IU per mL one and three month later **(Table 2)**. All subjects retained detectable titers for up to one year.

Table 1. Antibody response to PEP immunization

Route of administration of vaccine	Enrolment/ Recruitment		RIGs used		Patients with inadequate antibody response					References
	Cohorts	Subjects/ Patients	Cohorts	Subjects/ Patients	Day 28	Day 90	Day 180	Day 365	Total	
Intramuscular	23	1314	12	636	0/1238	0/1051	3/670	9/99	12	3,4,5
Intradermal	32	1481	17	690	2/1268	4/1366	3/719	37/558	46	4,5,6,7,8,9
Total	55	2795	29	1326	2/2506	4/2417	6/1389	46/657	58	-

The numerator is the number of Vaccinees with inadequate antibody response, RVNA concentration < 0.5 IU per mL, and the denominator, number of sera samples tested for RVNA.

Table 2. Antibody response to PrEP vaccination

Route of administration of vaccine	Enrolment/ Recruitment		Patients with inadequate antibody response					References
	Cohorts	Subjects/Patients	Day 28	Day 90	Day 180	Day 365	Total	
Intramuscular	8	518	0/263	0/33	4 (D135)/37	8+4 (D450)/209	16	10,11
Intradermal	3	59	0/59	0/59	0/33	0/59	-	3
Total	11	577	0/322	0/92	4 (D135)/70	8+4 (D450)/268	16	11

The numerator is the number of Vaccinees with inadequate antibody response, RVNA concentration <0.5 IU per mL, and the denominator, number of sera samples tested for RVNA.

Discussion

Based on previous studies, we understand that the neutralizing antibody response to PEP and PrEP is usually close to 100% by days 14 and 28. This indeed is a WHO requirement for acceptance of any new tissue culture vaccine. These titers then gradually decline but remain detectable for decades and will rapidly respond to booster injections in virtually all normal hosts. We also assume that an antibody titer above 0.5 IU per mL is important during the first month after a re-exposure. We also believe that, if the antibody level is under the WHO recommended minimum level of 0.5 IU per mL during this initial critical time period, this constitutes a risk factor if no booster response is elicited. It is reassuring to note that virtually all subjects in this large PEP and PrEP groups have antibody levels above 0.5 IU per mL up to the end of the third month.

Conclusion

Thailand and Philippines issued local guidelines that mandate boosters six month after the previous PEP or PrEP in subjects who experienced a new rabies exposure. In Sri Lanka, it is twelve months [1]. Data collected in this study, confirm the practice of using three months cutoff point in normal hosts. The final decision, however, cannot be taken from the attending physician who bears the ultimate responsibility for the patient. A position statement by the next WHO expert committee may well be overdue.

The authors have no conflict of interest to report.

References

1. Goswami A. Rabies re-exposure realities. APCRI Journal. 2007; 7:19-23.
2. World Health Organisation. Rabies vaccines: WHO position paper, Weekly Epidemiological Record. 2010; 85:309-20.
3. Charanasri U, Kingnate D, Meesomboon V, Samuthananon P, Chaeychomsri W. Intradermal simulated rabies postexposure prophylaxis using purified chick embryo rabies vaccine. J Med Assoc Thai. 1992; 75:639-42.
4. Sudarshan MK, Bhardwaj S, Mehta JM, Parasuramalu BG, Mahendra BJ, Gangaboraiah. Clinical evaluation of safety and efficacy of PCEC rabies vaccine (Kaketsuken) in post- exposure treatment. Indian J. Maternal and Child Health. 1996; 7:49-52.
5. Warell MJ, Warrell DA, Suntharasamai P, Nicholson KG, Chanthavanich P, Viravan C et al. Multisite intradermal rabies vaccination: Improved economical regimens. Lancet. 1984; 1: 874-6.
6. Warell MJ, Nicholson KG, Warrell DA, Suntharasamai P, Chanthavanich P, Viravan C et al. Economical multiple-site intradermal immunization with human diploid cell strain vaccine is effective for post-exposure rabies prophylaxis. The Lancet. 1985; 1:1059-62.
7. Warell MJ, Warrell DA, Suntharasamai P, Viravan C, Sinhaseni A, Udomsakdi D et al. An economical regimen of human diploid cell strain anti-rabies vaccine for post- exposure prophylaxis. The Lancet. 1983: 301-4.
8. Suntharasamai P, Chaiprasithikul P, Wasi C, Supanaranond W, Auewarakul P, Chanthavanich P et al. A simplified and economical intradermal regimen of purified chick embryo cell rabies vaccine for postexposure prophylaxis. Vaccine. 1994; 12:508-12.
9. Beran J, Honegr K, Banzhoff A, Malerczyk C. Potency requirements of rabies vaccines administered intradermally using the thai red cross regimen: investigation of the immunogenicity of serially diluted purified chick embryo cell rabies vaccine. Vaccine. 2005; 23:3902-7.
10. Strady A, Lang J, Lienard M, Blondeau C, Jaussaud R, Plotkin SA. Antibody persistence following preexposure regimens of cell culture rabies vaccines: 10- year follow-up and proposal for a new booster policy. JID. 1998; 177:1290-5.
11. Ajjan N, Pilet Ch. Comparative study of the safety and protective value in pre-exposure use of rabies vaccine cultivated on human diploid cells (HDCV) and of the new vaccine grown on vero cells. Vaccine. 1989; 7:125-8.
12. Fishbein DR, Pacer RE, Holmes DF, Ley AB, Yager P, Tong TC. Rabies post-exposure prophylaxis with human diploid cell rabies vaccine: a dose-response study. J Infect Dis. 1987; 156:50-5.
13. Madhusudana SN, Premanand N. Response to purified chick embryo cell rabies vaccine administered intradermally for post-exposure prophylaxis. The National Medical Journal of India. 1997; 10:115-6.
14. Ubol S, Phanuphak P. An effective economical intradermal regimen of human diploid cell rabies vaccination for post-exposure treatment. Clin Exp Immunol. 1986; 63:491-7.
15. Briggs DJ, Banzhoff A, Nicolay U, Sirikwin S, Dumavibhat B, Tongswas S. Antibody response of patients after postexposure rabies vaccination with small intradermal doses of purified chick embryo cell

vaccine or purified vero cell rabies vaccine. Bulletin of the World Health Organization. 2000; 78:693-8.
16. Madhusudana SN, Prem Anand N, Shamsundar R. Evaluation of two intradermal vaccination regimens using purified chick embryo cell vaccine for post-exposure prophylaxis of rabies. The National Medical Journal of India. 2001; 14:145-7.
17. Madhusudana SN, Saha SM, Sood M, Saxena SN. Multisite intradermal vaccination using tissue culture vaccine as an economical prophylactic regimen against rabies. Indian J Med Res. 1987:1-4.
18. Madhusudana SN. Pre-exposure immunization with cell culture rabies vaccines by intradermal route: A longitudinal study of the immune responses and effect of yearly booster dose. Journal of Basic & applied Biomedicine. 1997; 5:19-23.
19. Madhusudana SN, Prem Anand N, Shamsundar R. Economical multi-site intradermal regimen with purified chick embryo cell vaccine prevents rabies in people bitten by confirmed rabid animals. International journal of Infectious Diseases. 2002; 6:15-9.
20. Sehgal S, Bhardwaj M, Bhatia R. Clinical evaluation of purified chick embryo cell anti rabies vaccine in healthy volunteers. J. Com. Dis. 1988; 20:247-52.
21. Bernard KW, Mallonee J, Wright JC, Reid FL, Makintubee S, Parker RA. Preexposure immunization with intradermal human diploid cell rabies vaccine. JAMA. 1987; 1:437-45.
22. Chutivongse S, Wilde H, Supich C, Baer GM, Fishbein DB. Post exposure prophylaxis for rabies with antiserum and intradermal vaccination. The Lancet. 1990; 335:896-8.
23. Sudarshan MK, Bhardwaj S, Mahendra BJ, Sharma H, Sanjay TV, Ashwath Narayana DH et al. An Immunnogenicity, safety and post marketing surveillance of a novel adsorbed human diploid cell rabies vaccine in Indian subjects. Human Vaccines. 2008; 4:275-9.
24. Sudarshan MK, Madhusudhana SN, Mahendra BJ. Post exposure prophylaxis with purified verocell rabies vaccine during pregnancy–safety and immunogenicity. J.Commun. Dis. 1999; 31:229-36.
25. Sudarshan MK, Mahendra BJ, Madhusudhana SN, Ashwath Narayana DH. Administration of purified verocell rabies vaccine during pregnancy: Results of a controlled clinical trial. J. of Obst. & Gyn. of India. 2002; 52:48-52.
26. Madhusudana SN, Sanjay TV, Mahendra BJ, Sudarshan MK, Ashwath Narayana DH, Anandgiri et al. Comparison of safety and immunogenicity of purified chick embryo cell rabies vaccine (PCEC) and purified vero cell rabies vaccine (PVRV) using the thai red cross intradermal regimen at a dose of 0.1ml. Human Vaccines. 2006; 2:200-4.
27. Sudarshan MK, Mahendra BJ, Madhusudhana SN, Ashwath Narayana DH, Jayakumary M, Gangaboraiah. Post exposure rabies prophylaxis with purified verocell rabies vaccine: A study of immune response in pregnant women and their matched controls. Indian Journal of Public Health. 1999; 43:76-8.
28. Madhusudana SN, Sanjay TV, Mahendra BJ, Suja MS. Simulated post-exposure rabies vaccination with purified chick embryo cell vaccine using a modified thai red cross regimen. International Journal of Infectious Diseases. 2004; 8:175-9.
29. A report on "A clinical evaluation of safety and immunogenicity of purified chick embryo cell rabies vaccine (PCECV), administered intradermally using updated Thai Red Cross regimen in animal bite cases. 2007, Novartis Vaccines, India.
30. A report on "A comparative, multi center Phase III, randomized (1:1) double blind study to evaluate the safety and immunogenicity of PVRV (Indirab vs. reference vaccine) administered intradermally using simulated updated Thai Red cross regimen in healthy volunteers. 2009, Bharath Biotech International Ltd, Hyderabad, India.
31. A report on "A comparative phase III, randomized (1:1) single blind study to evaluate the safety and immunogenicity of rabies vaccines (Indirab vs reference vaccine) reconstituted with 1 mL diluent each, administered intradermally using simulated post exposure updated Thai Red Cross regimen in healthy volunteers". 2009, Bharath Biotech International Ltd, Hyderabad, India.
32. Mahendra BJ, Madhusudhana SN, Ashwath Narayana DH, Sampath G, Datta SS, Gangaboraiah et al. A comparative study on the immunogenicity, safety and tolerance of purified duck embryo vaccine manufactured in India and Switzerland: A randomized simulated post-exposure study in healthy volunteers. Vaccine. 2007; 25:8405-9.
33. Ashwath Narayana DH, Madhusudhana SN, Sampath G, Sathpathy DM, Mankeshwar R, Ravish HS et al. A comparative study on the safety and immunogenicity of purified duck embryo vaccine with purified chick embryo cell vaccine and purified verocell rabies vaccine. Vaccine. 2010; 28:148-51.
34. Sampath G, Madhusudhana SN, Sudarshan MK, Ashwath Narayana DH, Mahendra BJ, Ullas TP et al.

Immunogenicity and safety study of Indirab: A vero cell based chromatographically purified human rabies vaccine. Vaccine. 2010; 28:4086-90.

35. Mahendra BJ, Madhusudana SN, Sampath G, Datta SS, Ashwath Narayana DH, Venkatesh GM et al. Immunogenicity, safety and tolerance of a purified duck embryo vaccine (PDEV, VAXIRAB) for rabies post-exposure prophylaxis: Results of a multicentric study in India. Human vaccines. 2010; 6:721-4.
36. In a conversation with H. Wilde, MD and T. Hemachudha, MD, March 2011.