

The Alternative Intradermal Regimens for Rabies Postexposure Treatment

Chantapong Wasi, M.D.*

Paramet Chaiprasithikul, M.Sc.*

Prawan Suntharasamai, M.D.**

Prasert Auewarakul, M.D., Dr. med.*

Prasert Thongcharoen, M.D., Dr. med.*

Rabies is a fatal disease transmitted by the bites of animals especially dogs. The disease had been recognized long long time ago, however rabies in animals and human beings are still with us in the modern era.

Success in rabies prevention after exposed to rabid animals were demonstrated by rabies vaccination since 1885. Nearly a century, the nervous tissue rabies vaccines were used worldwide. The first generation duck embryo vaccine was developed in 1957. However, these old vaccines had low potency, low immunogenicity with some adverse reactions and vaccine failure were reported (1-3).

The breakthrough in human rabies vaccine started in 1967, when cell culture adapted rabies vaccine was established. The human diploid cell rabies vaccine (HDCV) was licensed first, then the purified chick embryo cell culture rabies vaccine (PCEC), purified vero cell rabies vaccine (PVRV) and purified duck embryo rabies vaccine (PDEV) (4). These second generation vaccines show high efficacy in rabies postexposure treatment.

Although the good rabies vaccines are in hand, human rabies deaths still occur especially in developing countries where rabies are epizootic and the cost of vaccinations are unaffordable. Reduced cost of rabies vaccination should be the solution in these countries (5,6).

To moderate the short supply of vaccines and budget as well as encourage the rabies postexposure

victims visit the nearby clinic as soon as possible; the Ministry of Public Health, Thailand recommended the economical regimen as the alternative to the conventional scheme in 1994 (7).

The efficacy of the small doses given intradermally have been monitored closely towards the goal of no human rabies death in Thailand in 1996 (8).

Rabies situation in Thailand

From 1980 to 1995, the number of human rabies death declined year by year (Table 1) (8,9). At the end of 1992, the nervous tissue vaccines were replaced totally by the purified cell culture and duck embryo vaccines.

The number of postexposure vaccinees were double increased (Table 2) (8,9).

The positivity rate of rabies in animals sent to laboratory diagnosis declined from 65 percent in 1980 to 45 percent in 1990s as shown in Table 3. Rabies were found in dog, cat, cattle, pig, sheep, goat, horse, monkey, rodent and other wild-life animals (Table 4) (8,9).

The new rabies act was issued in 1992. The pet dog must have the rabies vaccination yearly. The dog population in the whole country was estimated and 20 percent of them (2 million dogs) have been vaccinated annually. The target of giving rabies vaccination to 8 million dogs has been set and be approached by the community participation strategy (8).

*Department of Microbiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700,

**Vaccine Trial Centre, Faculty of Tropical Medicine, Mahidol University, Bangkok 10400, Thailand.

Received for publication : November 10, 1995.

Reprint request : Chantapong Wasi, M.D., Department of Microbiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

Key words : Rabies, postexposure treatment, intradermal regimen, vaccination, diagnosis.

Table 1. Reported cases of human rabies in Thailand, 1980-1995.

Year	N	Rate/100,000
1980	370	0.78
1981	339	0.71
1982	300	0.61
1983	288	0.58
1984	228	0.45
1985	210	0.41
1986	179	0.34
1987	212	0.39
1988	213	0.39
1989	212	0.38
1990*	185	0.33
1991	171	0.28
1992*	113	0.19
1993	93	0.16
1994	71	0.12
1995**	36	

Source : Division of Epidemiology, Ministry of Public Health.

* Semple Vaccine used until December 1990,
SMBV until December 1992.

** Figure at September 1995.

Human rabies death after postexposure treatment

It is the real tragedy revealed that to the best of our knowledge, with good efficacious treatment, rabies is still unpreventable in some cases as shown in Table 5 (8-11). In the previous series reported before 1988 (12), we blamed the delayed vaccination, not appropriate wound care and no rabies immune globulin. In this series from 1988 to 1994, twelve cases were investigated. Of these, three cases were males at fortys, resided outside Bangkok, received no rabies immune globulin although exposed to rabid dogs at severe degree. One teenage boy bitten at leg, received suckling mouse brain in the early 1993 and expired after long incubation period of 202 days.

The other seven cases were children, bitten at face, head with multiple bites except one case. The incubation period in all case was shorter than 2 weeks. How could we save these poor children? If HRIG was given instead of ERIG or none, would they survive? Two cases were given cell culture vaccines two sites ID on days 0, 3 (and 7 in one case). If we gave 8 sites ID, would they survive?

Conventional and alternative post exposure rabies immunization regimens in Thailand

For rabies postexposure prophylaxis, purified cell culture or purified duck embryo of potency higher than 2.5

Table 2. Number of rabies post-exposure cases receiving vaccine, 1980-1994.

Year	N	Rate/100,000
1980	63,939	135.54
1981	60,457	127.31
1982	61,276	126.37
1983	58,477	118.23
1984	74,086	147.01
1985	76,900	148.80
1986	79,977	151.91
1987	84,178	157.03
1988	79,454	145.70
1989	81,905	147.48
1990	88,312	156.87
1991	96,641	170.56
1992	116,222	201.11
1993	133,946	229.51
1994	148,112	250.81

Source : Division of Epidemiology, Ministry of Public Health.

Table 3. Positivity rate of rabies laboratory diagnosis in animals, 1980-1995.

Year	No. Tested	No. Positive	Percent
1980	9,510	6,156	64.73
1981	9,952	6,209	62.39
1982	10,833	6,684	61.70
1983	12,159	7,261	59.72
1984	11,516	6,516	56.58
1985	13,563	7,885	58.14
1986	15,558	8,646	55.57
1987	15,937	8,779	55.15
1988	16,341	8,489	51.95
1989	15,300	7,501	49.03
1990	13,934	6,535	46.89
1991	12,149	5,263	43.32
1992	10,489	4,643	44.27
1993	9,576	4,263	44.52
1994	8,113	3,781	46.60
1995*	2,516	1,232	48.97

Source : Division of Epidemiology, Ministry of Public Health.

* Until September 15, 1995.

IU per dose should be applied by the conventional full dose intramuscularly or alternative regimen of small doses intradermally.

For intramuscular schedule, one dose of vaccine should be administered on days 0, 3, 7, 14 and 28 or 30. The injection site must be at deltoid region or in small children into the anterolateral area of the thigh muscle. Vaccine should never be administered to the gluteal region.

Table 4. Rabies diagnosis in animal, 1990-1994.

Animal	1990	1991	1992	1993	1994*
Total	6,535/13,934 (46.89)	5,263/12,149 (43.32)	4,643/10,489 (44.27)	4,263/9,576 (44.52)	3,781/8,113 (46.60)
Dog	6,172/12,340 (50.02)	4,972/10,769 (46.17)	4,430/9,446 (46.90)	4,023/8,493 (47.37)	3,561/7,178 (49.61)
Cat	267/1,199 (22.27)	208/1,064 (19.55)	152/802 (18.95)	165/833 (19.81)	132/708 (18.64)
Cattle	65/100	54/88	44/70	54/95	66/99
Pig	5/16	8/19	3/16	4/15	4/7
Sheep, Goat	0/1	1/3	1/3	2/3	1/1
Horse	0/0	1/1	1/2	2/2	0/3
Non Human Primate	8/61	8/49	7/32	6/40	6/33
Rodent	8/152	7/142	2/100	1/82	2/69
Wild-Life	10/65	4/32	3/18	6/16	9/15

Source : Division of Epidemiology, Ministry of Public Health.

* Data analysis is under processing.

Table 5. Rabies death after post-exposure treatment in Thailand, 1988-1994 (9, 10).

No.	Yr.	Sex	Age	Residence	Exposure*	IP/day	Vaccine
1.	1988	M	6	Bangkok	face-single,	12	PVRV × 3 ERIG 800 IU
2.	1989	M	9	Cha-Cherng Sao	face, head, arm, 12 sites	25	TCV × 4
3.	1989	M	8	Petchaboon	mouth 2 sites	14	PCEC × 3
4.	1990	F	3	Samutsakorn	face 5 sites	20	PVRV ID 2 × 2
5.	1991	M	45	Pathum thani	rt. finger 3 sites	30	TCV × 4
6.	1993	M	41		head, cheek, eyebrow, It, hand	13	PVRV × 3
7.	1993	F	3		cheek	13	PCEC × 3
8.	1993	M	7		cheek, ear	13	PCEC × 3
9.	1993	F	12		cheek, nose	11 m* 1st vac: 10m	PCEC × 5
10.	1993	M	13		It. leg	202	SMBV × 16
11.	1994	M	44	Nakornratsima	rt. thumb	30	PVRV × 4 1st vac. D4
12.	1994	F	2½	Cholburi	cheek, ear nose, mouth 5 sites	10	PCEC ID 2 × 3 ERIG 400 IU

* All cases were bitten by dogs, severe exposure.

The alternative intradermal regimen was given one dose of 0.1 ml at each of two sites at deltoid regions on days 0, 3, 7 and one dose (0.1 ml) at one site on days 28 and 90. Separate syringe and needles must be used.

The intradermal injection should only be administered by staff who has been well trained. After reconstituted, the vaccine vial should be stored at 4-8°C and used within 8 hours, since the vaccine potency would be

deteriorated and contamination might occur.

Combined immunoglobulin-vaccine treatment is considered as the best specific treatment available for postexposure prophylaxis in humans, although experience indicates that vaccine alone is sufficient for mild to moderate degree of exposure (13). Immunoglobulin should be given in a dose of 20 IU/kg body weight for HRIG and 40 IU/kg for ERIG. The RIG should be instilled and injected around the wounds as much as possible and given the amount left IM at different site of vaccine injection. The first dose of vaccine and RIG should be given as early as possible. Skin test for sensitivity to ERIG must be determined before administered although the negative or positive test result might not predict the event. The physicians have to prepare to deal with anaphylactic shock reaction.

Treatment should be started as early as possible after exposure, but in no case should it be denied to exposed person whatever time interval has elapsed.

In persons who had history of pre- or postexposure vaccination with purified vaccine, no RIG is needed. Give only one dose of vaccine IM or 0.1 ml ID if the last injection was given within 6 months, and two doses on days 0 and 3 if the last infection was given beyond 6 months.

Since HRIG or even ERIG is not always available, pre-exposure immunization for people at high risk including children in enzootic area should be promoted.

The controversial issues in the ID regimens

Although the effectiveness of the 2-2-2-0-1-1 intradermal regimen has been demonstrated in postexposure categories 2 and 3 (13), the vaccine used was PVRV which the volume of full dose is 0.5 ml. It is questionable, either the HDCV or PCEC or PDRV which is 1 ml dose, should be given as 0.1 ml ID at each site or need to be double. The results of giving PCEC 0.1 ml at each injection site by 2-2-2-0-1-1 schedules are satisfactory, both with and without HRIG on the first day (Table 6) (14,15). However, the study in children, showed preferable results to IM than ID when HDCV and PVRV were investigated (16). Recent report showed that the 0.1 ml PDEV was not as good as 0.2 ml at each site (17).

These results should be interpreted carefully, since neutralizing antibody levels were demonstrated and much higher than the antibody elicited by nervous tissue vaccine. The antigenic value of vaccines are much

Table 6. NT Ab (IU/ml) after PCEC ID by days after immunization (14).

Day	Antibody level	Group 1 PCEC N = 81	Group 2 PCEC + HRIG N = 52
7	<0.04	16%	0
	0.04-0.499	84%	100%
14	>0.5	100%	100%
	range	3.47-26.74	3.43-36.84
365	0.31-0.499	13%	31%
	>0.5	87%	69%
	range	0.37-19.10	0.31-3.30

influenced. If the vaccine has high potency i.e. antigenic value higher than 5 IU/dose, the antibody response is better (17).

The purpose of using small doses intradermally is initially by shortage of vaccine supply in group vaccination and economic for the direct and indirect cost. Since the early reports of multisites ID (8-0-4-0-1-1) evoked better immune response i.e. early antibody detection and cell-mediated immunity, it might be helpful when RIG is not available.

The feasibility of the ID regimen in the small rural hospital is also questionable. Some doctors prefer the conventional IM when the exposure is severe. The ID regimen in group vaccination in mild and moderate exposure is generally accepted.

In the countries where the ID regimen is adopted, it is important to cooperate with the manufacturer to assure that the antigenic value of vaccine is higher than minimal WHO requirement, at least 5 IU/dose.

It is important to conduct clinical trial study for the reduced regimens in different countries since the genetic and environmental factors might play some role. The clinical trial should be performed step by step, from preexposure immunization first, then move to postexposure treatment. The research study should be approved by the national authorities for the scientific merit and ethical standpoint.

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