

Brief communication (Original)

Rabies postexposure vaccination in Thailand: is it performed according to international guidelines?

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Background: Animal bites are one of the leading causes of visits to an emergency room (ER) in Thailand. Rabies is an almost invariably fatal disease.

Objectives: We evaluated the appropriateness of rabies vaccination in clinical practice following the World Health Organization (WHO) guidelines.

Methods: All patients who visited the ER at Ramathibodi Hospital of Mahidol University because of mammal bites and received rabies vaccination by the WHO rabies postexposure regimen were enrolled. Data were retrieved from medical records. Wound categories were classified by WHO guidelines both in real practice and by the investigators on subsequent investigation.

Results: The agreement between clinical practice and the WHO guidelines was calculated and reported as kappa statistics. There were 372 eligible patients. The mean age was 36 years and 172 patients were male. The agreement between clinical practice and the WHO guidelines was a disturbing 26.9% with a kappa statistic of -0.02 , $P = 0.56$.

Conclusion: Even in a referral and teaching hospital, rabies postexposure vaccination in Thailand was not appropriate according to WHO guidelines.

Keywords: Postexposure, pragmatic study, rabies, vaccination, WHO guideline

Rabies, caused by a lyssavirus, is a central nervous system infection and has the highest mortality rate among infectious diseases. The World Health Organization (WHO) reported that at least 55,000 people die from rabies annually worldwide, mostly in developing countries and from dog bites [1, 2].

Dog and animal bites are still a common problem in Thailand and in other canine endemic developing countries. Dog bites accounted for 5.3% of injuries in a major emergency room in Thailand [3], while animal bites were 0.3%–1% in other countries [4–10]. WHO has published guidelines for postexposure rabies vaccination [11]. The roles of vaccination by both passive and active immunization depend on wound categories and animal factors. Data on appropriateness of vaccination according to WHO

guidelines in Thailand are still limited. Knowing them may improve treatment quality and save lives and costs.

Methods

All patients who visited the Emergency Department of Ramathibodi Hospital with mammalian bites and received rabies vaccinations, supposedly according to posted WHO rabies postexposure management guidelines, were enrolled. The study period was between January 1 and December 31, 2006. Data were retrieved from medical records. Study variables included baseline characteristics of patients, visit times, details of animals, characters of wounds, rabies and tetanus vaccination details, antibiotic treatment, complications of animal bites, and vaccination treatment and outcomes. Wound categories were classified by WHO guidelines on admission and after review of records by investigators. The study protocol was approved by the committee on human rights related to research involving human subjects of the Faculty of Medicine, Ramathibodi Hospital of Mahidol University.

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Operational definitions

1. Wound categories were classified as class 1, 2, and 3 according to WHO guidelines.

2. Rabies postexposure vaccination regimen used was the standard WHO intramuscular (IM)

schedule.

3. Rabies immunoglobulin (RIG) is indicated for WHO wound category 3.

4. “Under treatment” is defined as when rabies postexposure prophylaxis was administered at a lower than actual WHO wound category. For example as treatment at category 1 in a patients with category 2 wound.

5. Appropriate treatment is when given according to the actual WHO wound category.

6. “Over treatment” is defined when rabies postexposure prophylaxis was given at a higher WHO wound category; such as in a patient with a wound category 2 when it is only category 1.

7. Inappropriate treatment includes under or over treatment.

Statistical analyses

Baseline data were presented as mean (+SD) or percentage. The correlation of treatment and wound category according to WHO guidelines was executed

by kappa statistics and the exact symmetry test. Factors associated with inappropriate treatment were also calculated by logistic regression analysis. All analyses were computed by Stata version 9 (Stata Corp, College Station, Texas, USA).

Results

During the study period, there were 372 patients who met the study criteria. All patients received Verorab (purified Vero cell rabies vaccine; PVRV) 0.5 ml IM at days 0, 3, 7, 14, and 28. Of these, 172 were male (46.2%). The median age of all patients was 36 years (range 1–86 years). 186 patients visited the Emergency Department between 7 AM and 4 PM (50%); whereas 158 patients visited the hospital between 4 PM and midnight (42.5%) and 28 patients (7.5%) visited the hospital during midnight to 7 AM. The median duration of “bite to hospital” was 4 hours (range 1–720 hours). The majority of patients were bitten by dogs (272 patients (73.1%) shown in **Table 1**. Only almost half of the patients (47%) cleaned the wound using water and soap prior to the hospital visit (**Table 2**). 41 patients (11%) did not receive antibiotic treatment (**Table 3**). Tetanus toxoid and tetanus antitoxin were given in 304 patients (81.7%) and 14 patients (3.8%), respectively.

Table 1. Types of animal bite

Type	Number	Percentage
Dog	272	73.1
Cat	67	18
Rat	17	4.6
Monkey	5	1.3
Man	8	2.2
Bat	1	0.3
Squirrel	2	0.3

Table 2. First aid prior to hospital visit

Methods	Number	Percentage
No data	88	23.7
Cleaned with soap	175	47
Cleaned with water	22	5.9
Cleaned with alcohol or povidone-iodine	34	9.1
Cleaned at private clinic	35	9.4
Did nothing	18	4.8

Table 3. Antibiotic prescription details in patients who received rabies vaccination according to WHO rabies guidelines

Antibiotics treatment	Numbers	Percentage
No antibiotics	41	11.0
Augmentin	131	35.2
Amoxicillin	160	43.0
Penicillin V	6	1.6
Cloxacillin	20	5.4
Macrolide	6	1.6
Clindamycin	4	1.1
Doxycycline	1	0.3
Bactrim	1	0.3
Cephalosporins	1	0.3

Wounds were classified as category 1, 2, or 3 according to WHO guidelines in 3, 14, and 355 patients respectively (**Table 4**). “Under treatment” was found in 267 patients or 71.5% (wound category 2 treated as 1 in 3 patients; wound category 3 treated as 1 in 20 patients, and wound category 3 treated as 2 in 244 patients). The rate of “over treatment” was 1.6% (wound category 1 treated as 2 in 3 patients and wound category 2 treated as 3 in 3 patients). The appropriate and inappropriate treatment rates were 26.9% and 73.1% respectively. The concordance of wound category and treatment in categories 1, 2, and 3 were 0, 8, and 91 patients respectively. The unweighted kappa measure of agreement: was -0.002 ($P = 0.559$). The only factor associated with inappropriate treatment was duration of animal bite to hospital visit (odds ratio of 1.018, $P = 0.025$) as shown in **Table 5**.

There were 174 patients (46.7%) who received all five doses of rabies vaccination. Ten patients (2.6%) developed wound infection (mostly cellulitis). None of the patients had an antibiotic or other adverse reaction.

Discussion

This was a retrospective one year study of the application of WHO guidelines for rabies postexposure prophylaxis in real life at a teaching and referral hospital in a canine rabies endemic region. The agreement between guidelines and actual practices was sadly low (26.9% agreement) with a kappa of just -0.002 . Most agreement occurred in wound category 3 (91/372 patients). Overall inappropriate treatment was 73.1%; mostly “under treatment” (71.5%). Most patients with wound category 3 were treated as wound category 2; yet the most agreement between practice and guidelines was also in wound category 3. Importantly, this group was undertreated as wound category 2 in 244 patients who actually had category 3 wounds. Failure of rabies postexposure prophylaxis was 1:80,000 and 1:30,000 in less developed and developing countries respectively. Factors associated with postexposure management failures include delayed treatment, inadequate wound cleansing, immune-compromised host, severe wounds at face, head and hands, wrong vaccination site,

Table 4. Agreement of WHO wound categories and treatment provided to all patients who received rabies vaccination according to WHO rabies guidelines

	WHO cat 1	WHO cat 2	WHO cat 3	Total
Treat cat 1	0	3	20	23
Treat cat 2	3	8	244	255
Treat cat 3	0	3	91	94
Total	3	14	355	372

Exact test for table symmetry, asymptotic symmetry test chi-square, marginal homogeneity test chi-square: $P < 0.001$

Table 5. Factors associated with inappropriate treatment in patients who received rabies vaccination according to WHO rabies guidelines

Factors	Odds ratio	95% CI	P
Age (per year increase)	1.005	0.993 to 1.016	0.43
Sex (female vs. male)	1.013	0.639 to 1.606	0.96
Timing of visit			
7 AM to 4 PM	1	0.440 to 1.146	0.16
4 PM to midnight	0.710	0.371 to 2.332	0.88
midnight to 7 AM	0.930		
Type of animal bite			
Dog	1		
Cat	0.999	0.546 to 1.825	0.996
Rat	0.673	0.240 to 1.884	0.45
Others	2.568	0.570 to 11.57	0.22
Duration of animal bite to hospital visit (hour)	1.018	1.002 to 1.035	0.03
Cleaning prior to emergency room (n = 284)			
Cleaning with soap	1	0.808 to 2.312	0.25
Others	1.366		
Wound morphology			
Lacerated wound	1	0.527 to 1.438	0.59
Others	0.871		

such as injecting vaccine into buttocks, or no—or intramuscular—rather than intra-wound administration of human or equine rabies immunoglobulin [6]. Our study confirmed that delayed treatment was significantly associated with inappropriate treatment (odds ratio of 1.018; 95% confidence interval of 1.002 to 1.035). Unlike the Thai Red Cross animal bite clinic in Bangkok and at similar institutions in other Asian countries, where many rabies exposure cases are seen daily and the intradermal regimen is used, we could not apply it in the emergency room of our hospital. The Thai Red Cross WHO approved intradermal regimen has been shown to be more cost-effective [12], but it is not suitable for use in the emergency departments of most general hospitals in Asia. There are few patients per day, and one partly used ampoule of vaccine cannot be stored for longer than eight hours according to current WHO and manufacturer guidelines. This, even though at least 4 studies have shown that modern rabies vaccines will retain immunogenicity and sterility if stored as long as one month in a refrigerator [13–16]. Therefore, all of our patients had to receive the more costly intramuscular regimen of 5 full doses.

According to the WHO guidelines, 355 patients were in category 3 and should receive both rabies vaccine and rabies immunoglobulin injected into

and around their wounds (Table 4). There were 267 patients who received inappropriate treatment under WHO guidelines; mostly as undertreatment. Three patients were in WHO category 2, yet received inappropriate immunoglobulin therapy. Whereas, 264 patients in category 3, did not receive immunoglobulin therapy, and were thus under treated (68.7%). Fortunately, there was no report of a rabies death in our patients. We did review our data with the Department of Disease Control, Ministry of Public Health, Thailand.

Antibiotic treatment of animal bites is recommended, particularly in patients with severe wounds and those who were bitten more than 12 hours before presentation, had wounds at the head or hand bites, or had comorbid conditions such as diabetes, postsplenectomy, or were immunocompromised. The recommended antibiotics are amoxicillin or doxycycline, which are particularly effective against *Pasteurella spp.* [17]. There were 160 patients (43.0%) who received amoxicillin. Only 10 patients (2.6%) developed wound infections.

In conclusion, WHO rabies postexposure management guidelines were not followed at a major teaching and referral hospital in a rabies endemic country. The agreement rate in clinical practice with WHO guidelines was only 26.9% in this retrospective

study. We believe that this is not unique and reflects the general situation throughout this region. More intensive physician training at all levels in management of potential rabies exposures is urgently needed.

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References

1. Freuling CM, Kloss D, Schroder R, Kliemt A, Muller T. The WHO Rabies Bulletin Europe: a key source of information on rabies and a pivotal tool for surveillance and epidemiology. *Rev Sci Tech.* 2012; 31:799-807.
2. Vigilato MA, Cosivi O, Knobl T, Clavijo A, Silva HM. [Rabies update for Latin America and the Caribbean.](#) *Emerg Infect Dis.* 2013; 19:678-9.
3. Bhanganada K, Wilde H, Sakolsataydorn P, Oonsombat P. [Dog-bite injuries at a Bangkok teaching hospital.](#) *Acta Tropica.* 1993; 55:249-55.
4. Aghahowa SE, Ogbevoen RN. Incidence of dog bite and anti-rabies vaccine utilization in the, University of Benin Teaching Hospital, Benin city, Nigeria: A 12-year assessment. *Vaccine.* 2010; 28:4847-50.
5. Weiss HB, Friedman DI, Coben JH. Incidence of dog bite injuries treated in emergency departments. *JAMA.* 1998; 279:51-3.
6. Thompson PG. The public health impact of dog attacks in a major Australian city. *Med J Aust.* 1997; 167: 129-32.
7. Ahmed H, Chafe UM, Magaji AA, Abdul-Qadir A. Rabies and dog bite in children: a decade of experience in Sokoto, Nigeria. *Sokoto J Vet Sci.* 2000; 1:2-10.
8. Yin CP, Zhou H, Wu H, Tao XY, Rayner S, Wang SM, et al. Analysis on factors related to rabies epidemic in China from 2007-2011. *Virol Sin.* 2012; 27:132-43.
9. Abubakar SA, Bakari AG. Incidence of dog bite injuries and clinical rabies in a tertiary health care institution: A 10-year retrospective study. *Ann Afr Med.* 2012; 11:108-11.
10. Hampson K, Dobson A, Kaare M, Dushoff J, Magoto M, Sindoya E, et al. Rabies exposures, postexposure prophylaxis and deaths in a region of endemic canine rabies. *PLoS Negl Trop Dis.* 2008; 2:e339.
11. Hermann J, Fry A, Reising M, Patterson P, Siev D, Gatewood D. Rabies vaccine standards: comparison of the 5th and 6th WHO international reference standards to the USDA veterinary reference standard. *Vaccine.* 2012; 30:6892-6.
12. Jaiaroensup W, Lang J, Thipkong P, Wimalaratne O, Samranwataya P, Saikasem A, et al. Safety and efficacy of purified Vero cell rabies vaccine given intramuscularly and intradermally. (Results of a prospective randomized trial). *Vaccine.* 1998; 16: 1559-62.
13. Khawplod P, Tantawichien T, Wilde H, Limusanno S, Tantawichien T, Saikasem A, et al. [Use of rabies vaccine after reconstitution and storage.](#) *Clin Infect Dis.* 2002; 34:404-6.
14. Khawplod P, Wilde H, Tantawichien T, Limusanno S, Tantawichien T, Mitmoonpitak C, et al. Potency, sterility and immunogenicity of rabies tissue culture vaccine after reconstituted refrigerated storage for one week. *Vaccine.* 2002; 20:2240-2
15. Kamoltham T, Khawplod P, Wilde H. Rabies intradermal post-exposure vaccination of humans using reconstituted and stored vaccine. *Vaccine.* 2002; 20: 3272-6.
16. Lodmell DL, Ewalt LC. Rabies cell culture vaccines reconstituted and stored at 4°C for 1 year prior to use protects mice against rabies virus. *Vaccine.* 2004; 22: 3237-9.
17. Goldstein EJC. Management of human and animal bite wounds. *J Am Acad Dermatol.* 1989; 21:1275-9.