

Brief communication (Original)

Use of rabies immune globulin in seven urban emergency rooms in Pakistan

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Background: Human rabies is a fatal infectious disease that is entirely preventable if correct and timely postexposure prophylaxis is given. Unfortunately, rabies immune globulin (RIG) administration, a life-saving biological, is often avoided by Emergency Room health care providers (HCPs).

Objective: To understand the practices of HCPs for administration of RIG in severe dog-bite exposures, which are common causes of emergency room visits in Pakistan.

Methods: A cross-sectional study was conducted among 103 HCPs working in seven hospitals in three cities of Pakistan.

Results: Of 103 HCPs who responded to the questionnaires, 97.1% had administered rabies vaccine and 31.1% had administered ERIG in the past three years of their practice; three quarters said they would prefer to use HRIG if available; 35% said they would not inject wounds at all, 24.3% would only vaccinate a patient with severe dog bites, but not administer RIG. More than 55% were concerned about the cost of human and equine RIG.

Conclusion: Although there is awareness about use of RIG, this life saving biological is grossly underused because of poor availability in Emergency Rooms (ERs) even though stocked by local dealers. Animal bite centers must make RIG available for severe exposures.

Keywords: Animal bites, medical officers' practices, rabies immune globulin, rabies prophylaxis

Rabies is primarily a zoonotic infection caused by a virus that is transmitted through the saliva of a rabid animal, most commonly dogs. It is transmitted to humans by a bite or lick on broken skin or mucous membrane. Death from rabies occurs if prophylaxis is delayed, inadequate, or incomplete. Rabies causes an estimated 55,000 global deaths annually, most of which are in Asia [1].

With an estimated human: dog ratio of 7.4 in urban areas and 14.3 in rural areas of Asia, around 2.5 billion people are at risk of rabies [2]. After a potential rabies threat, it is vital that the patient be given proper postexposure prophylaxis (PEP). This includes thorough wound washing to remove saliva and dirt; administration of a complete course of potent anti-rabies vaccine (ARV) which stimulates the body's immune system to produce antibodies actively, and local infiltration of rabies immune globulin (RIG) into the wound that neutralizes rabies virus at site before native antibodies from vaccination appear. However, in many developing countries RIG is either under used

or not used at all even in high risk exposures. This study was done to understand the reasons why health care providers in emergency rooms fail to administer RIG where indicated.

Materials and methods

To investigate attitudes of physicians regarding administration of RIG to rabies-exposed patients, a questionnaire was prepared consisting of 27 questions with options. There were 103 responses from seven institutions in three cities of Pakistan- Islamabad, Lahore, and Karachi. The questionnaires were completed by health care providers based either in ERs or in private clinics where dog bite victims present frequently for management. The Statistical Package for Social Sciences (ver. 16, SPSS, Chicago, IL, USA) was used to analyze the data. Frequencies and percentages were presented for HCP practice location, the number of severe dog bites seen by a facility per year, the treatment usually administered by the HCP for treating severe dog bites, and the concerns of those HCPs why they are not giving RIG. Type of facility was categorized as ER, government sector non-ER, private sector non-ER, whereas the number of severe dog bites seen annually was

categorized as no animal bite cases, 100 or less, and more than 100 cases of animal bites. For these categorical variables, chi-square test was used to assess statistical significance between with their concerns. A $p < 0.05$ was considered significant.

Results

Of 103 health care providers who responded to the questionnaires, 51.5% were in an Emergency Room (ER) setting and nearly half had seen more than 100 severe dog bites in a year. Almost all the HCPs interviewed had administered rabies vaccine (97.1%), 31.1% had administered ERIG; and 63.1% had administered tetanus toxoid in the past three years of their practice. Almost three-quarters indicated that they would use HRIG if it were made available to them. Among these HCPs, 35% said they would never inject wounds, 24.3% would only vaccinate a patient with severe dog bite, but not administer rabies immunoglobulin (RIG). More than 55% were concerned about the cost of ERIG (**Table 1**). The

primary concerns of the 70 HCPs who stated they did not give ERIG for severe dog bites were anaphylactic reaction (57.1%), cost (52.9%), and local adverse reactions (45%), almost 36% had concerns about local wound infection being made worse by injections followed by 29% who indicated unfamiliarity of injecting wounds (**Table 2**). A larger proportion of HCPs from facilities that had never seen severe dog bites were more concerned about their unfamiliarity with injecting wounds (62.5%), in comparison to those seeing a hundred or less (18%) and those facilities seeing more than 100 severe dog bite cases per year (31%) ($p < 0.05$) as shown in **Table 3**. Statistically significant differences were seen in the proportion of HCPs who were concerned over anaphylactic reaction from ERIG based on their facility setting. Nearly 93% of the HCPs from private non-ER settings, and 72% from ER settings were concerned over anaphylactic reaction in comparison to 31% HCPs from a government non-ER setting ($p < 0.001$) (**Table 4**).

Table 1. Facility and HCP description

	n (%)
Practice Location	
Govt. setting-Non ER	32 (31.1)
Private-non ER	15 (14.6)
ER setting	53 (51.5)
Other	3 (2.9)
HCP Age	
20–29	42 (40.8)
30–39	31 (30.1)
40–49	16 (15.5)
50+	4 (3.9)
unknown	10 (9.7)
Severe dog bites seen per year	
None	8 (7.8)
1–100 cases	51 (49.5)
100+	42 (40.8)
Don't Know	4 (1.9)
Treatment administered by HCP for severe dog bite	
Tetanus Toxoid	65 (63.1)
Rabies Vaccine	100 (97.1)
Equine RIG	32 (31.1)
% of HCPs who would administer HRIG, if available	74 (71.8)
% HCPs who would not inject wounds at all	36 (35.0)
% HCPs who would only vaccinate pt with severe dog bite but not administer ERIG	25 (24.3)
% HCPs concerned about cost of ERIG	57 (55.3)

Table 2. Concerns of those HCPs not giving ERIG for severe dog bites (n = 70)

Concerns	n (%)
High cost of ERIG	
Not concerned	32 (45.7)
Concerned	37 (52.9)
Don't know	1 (1.4)
Local adverse reactions	
Not concerned	38 (54.3%)
Concerned	32 (45%)
Anaphylaxis	
Not concerned	30 (42.9%)
Concerned	40 (57.1%)
Local wound infection made worse by injections	
Not concerned	43 (61.4%)
Concerned	25 (35.7%)
Don't know	2 (2.8%)
Causing additional pain to pt by injecting wounds	
Not concerned	52 (74.3%)
Concerned	18 (25.7%)
Unfamiliarity of injecting wounds	
Not concerned	49 (70.0%)
Concerned	20 (28.6%)
Don't know	1 (1.4%)

Table 3. Concerns regarding administering ERIG, based on facility dog-bite burden (n = 101)

Concerns	No animal bite (n = 8)	1–100 animal bites (n = 51)	>100 animal bites (n = 42)	Total (n = 101)	p
Local adverse reactions					
Not concerned	3 (37.5%)	22 (43.1%)	22 (52.4%)	47 (46.5%)	NS
Concerned	5 (62.5%)	29 (56.9%)	20 (47.6%)	54 (53.5%)	
Anaphylaxis					
Not concerned	3 (37.5%)	16 (31.4%)	18 (42.9%)	37 (36.6%)	NS
Concerned	5 (62.5%)	35 (68.6%)	24 (57.1%)	63 (63.4%)	
Local wound infection made worse by injections					
Not concerned	5 (62.5%)	29 (59.2%)	27 (64.3%)	61 (61.6%)	NS
Concerned	3 (37.5%)	20 (40.8%)	15 (35.7%)	38 (38.4%)	
Causing additional pain to pt by injecting wounds					
Not concerned	6 (75.0%)	39 (76.5%)	31 (73.8%)	76 (75.2%)	NS
concerned	2 (25.0%)	12 (23.5%)	11 (26.2%)	25 (24.8%)	
Unfamiliarity of injecting wounds					
Not concerned	3 (37.5%)	41 (82.0%)	29 (69.0%)	73 (73.0%)	0.02
Concerned	5 (62.5%)	9 (18.0%)	13 (31.0%)	27 (27.0%)	

Table 4. Concerns regarding administering ERIG, based on facility type (n = 103)

Concerns	Govt. Setting (non-ER) (n = 32)	Private Setting (non-ER) (n = 15)	ER Setting (n = 53)	Other (n = 3)	Total (n = 103)	<i>p</i>
Local adverse reactions						
Not concerned	20 (62.5%)	4 (26.7%)	22 (41.5%)	2 (66.7%)	48 (46.6%)	0.08
Concerned	12 (37.5%)	11 (73.3%)	31 (58.5%)	1 (33.3%)	55 (53.4%)	
Anaphylaxis						
Not concerned	22 (68.8%)	1 (6.7%)	14 (26.4%)	1 (33.3%)	37 (36.6%)	<0.001
Concerned	10 (31.2%)	14 (93.3%)	38 (71.7%)	2 (66.7%)	63 (63.4%)	
DK	-	-	1 (1.9%)	-	1 (1.0%)	
Local wound infection made worse by injections						
Not concerned	23 (71.9%)	7 (46.7%)	29 (54.7%)	2 (66.7%)	61 (61.0%)	NS
Concerned	8 (25.0%)	7 (46.7%)	23 (43.4%)	1 (33.3%)	39 (38.4%)	
DK	1 (3.1%)	1 (6.7%)	1 (1.9%)	-	3 (2.9%)	
Causing additional pain to pt by injecting wounds						
Not concerned	23 (71.9%)	10 (66.7%)	41 (77.4%)	3 (100%)	77 (74.6%)	NS
Concerned	8 (25.0%)	5 (33.3%)	12 (22.6%)	-	25 (25.3%)	
DK	1 (3.1%)	-	-	-	1 (1.0%)	
Unfamiliarity of injecting wounds						
Not concerned	22 (68.8%)	10 (66.7%)	39 (73.6%)	2 (66.7%)	73 (70.9%)	NS
Concerned	8 (25.0%)	5 (33.3%)	13 (24.5%)	1 (33.3%)	27 (26.2%)	
DK	2 (6.2%)	-	1 (1.9%)	-	3 (2.9%)	

Discussion

Rabies affects mainly the poor and under-privileged population of developing countries where stray dogs roam the streets [3]. Unimmunized pet dogs are also often responsible for transmitting rabies to humans, especially to children who are unable to escape or defend themselves from attacks. Once the virus enters the body and symptoms begin, the disease is almost always fatal. However, timely and correct postexposure prophylaxis can prevent the disease.

Thorough wound washing can reduce the chances of rabies by 30–40%. Wound severity must be categorized according to depth, and further management instituted. A superficial scratch may be treated with vaccine alone given according to schedule, while deep or multiple wounds indicate a larger risk and must be treated with passive rabies immune globulin in addition to vaccination. The quantity of RIG must be calculated according to the patient's weight and infiltrated into the wounds to kill the virus and provide immediate protection until antibodies against the virus are mounted through use of the vaccine.

In a previous study, conducted in eight Asian countries including Pakistan [4], and in which the author participated; only 22% of Category III bite

victims received RIG. Several other studies done in Pakistan have revealed serious gaps in understanding of wound severity classification and correct use of vaccine and RIG [4, 6, 7].

Three classes of RIG are presently available: human (HRIG), equine (ERIG), and highly purified F (ab)2' ERIG products. HRIG is produced from donors under strict manufacturing conditions and is devoid of adverse effects [8]. However, its production is limited and its cost is exorbitant and hence unaffordable in developing countries. ERIG is produced from horse serum and in the past was responsible for up to 40% adverse effects and even anaphylaxis. Current ERIG products are highly purified and almost devoid of adverse effects. WHO no longer recommends skin tests, but exercises caution in their use [8]. F (ab)2' products of ERIG are cleared more rapidly than ordinary ERIG and have virtually no side effects. However, experience has caused many end users nevertheless to be apprehensive of using the product. Many potentially rabid bites are still inadequately treated, resulting in many rabies deaths.

Production of the conventional polyclonal RIGs is labor intensive and requires a modern horse farm for success. This results in global shortages, though poor distribution is also a serious problem. A positive

breakthrough in recent years is the innovation of a human monoclonal antibody (mAb), which is likely to replace RIG [9, 10]. mAb would be produced in larger quantities and would in due course, overcome RIG scarcity and expense. Phase 4 trials are currently underway. Whether these problems will be more affordable than HRIG in the poorer countries remains to be seen.

This study clearly shows that, although many HCPs in the study appreciate the importance of using RIG, they have not acquired sufficient upgraded information on RIG quality improvement. ERIG and purified F (ab)₂' ERIG are safe and effective and carry very low adverse reaction rates similar to those of most injected antibiotics, including penicillins. National Regulatory Authorities should facilitate import and distribution of ERIG, and all Rabies Prevention Centers should be supplied ERIG at affordable cost. Moreover, nurses and doctors should receive training on correct use of vaccine and RIG infiltration.

The authors have no conflict of interest to report.

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