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Special Communication

GUIDELINES FOR PROPHYLAXIS OF RABIES IN PAKISTAN

*Dr. Niloufer Sultan Ali**

SUMMARY:
Rabies is highly fatal and ends in an extremely painful and torturous death. All carnivorous animal (dog, cat, fox, jackal, skunk, mongoose, raccoon) and bats are considered potentially rabid. Rodents (rat, mouse, squirrel), rabbit or bird are not rabid. Transmission is usually through the bite of an infected animal. However, the percentage of rabid bites leading to clinical disease ranges from 10% (on the legs) to 80% (on the head). Rabid animals can also transmit the disease by licking abraded skin or mucosa and by scratching. Patients with scratches from rabid animals are about 50 times less likely to develop rabies than those with bites. World Health Organization (WHO) Rabies Survey in 1992 estimated that 90% of human rabies occurred in the developing world. There are no known studies on the incidence of rabies in Pakistan; the problem of dog bite from possibly rabid dogs is rising alarmingly. Therefore the prevention of rabies infection after exposure is of utmost importance. It is preventable if WHO guidelines for post exposure treatment are followed. This guideline includes, immediate local treatment of the wound, passive immunization with rabies immunoglobulin and administration of an efficacious vaccine. Although there is a great urgency to improve post-exposure treatment, it will remain a costly and inefficient method of controlling rabies. It is the canine rabies epidemic which needs to be addressed.

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INTRODUCTION

The incidence of rabies in Karachi only is estimated to be 9 per million populations[1]. According to a newspaper report from Karachi, 55-60 cases of dog bites are reported per day including 10-15 new cases, from the major referral centers including Jinnah Postgraduate Medical Center, Civil Hospital Karachi and Edhi Center[2]. Cases occurring in rural areas and small cities are usually unreported. WHO estimates that each year 30,000-50,000 people die of rabies worldwide[3-5]. An attack from a rabid animal is more likely to be unprovoked than provoked. Although rabies is transmitted by animal bite, it has been known to occur after handling animal carcasses and through aerosal of bat secretions in closed caves. However theoretically transmission of rabies virus can occur through saliva of a rabid patient but human to human transmission has not been recorded other than corneal transplantation. There is no local data available about the mode of transmission of rabies in Pakistan. Routine gown and glove precautions may be taken when handling a patient with rabies.

The importance of prompt local treatment of all bite wounds and scratches that may be contaminated with rabies virus, even if the person

* Dr. Niloufer Sultan Ali
Assistant Professor
Family Medicine,
Department of Community Health Sciences,
Aga Khan University Hospital,
Stadium Road, Karachi, Pakistan.

Correspondence:

Dr. Niloufer Sultan Ali
E-mail: niloufer.ali@aku.edu

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presents after a prolonged period should be emphasized. All dog bites carry a risk of infection, therefore immediate thorough flushing and washing of the wound with soap and water can significantly decrease that risk. If possible, suturing of wounds should be avoided. The incubation period is variable and may range from a few weeks to several years; on average it is 1-3 months. Usually bites on the head, face and neck have a shorter incubation period than that elsewhere. The severity of manifestations depends upon the depth of the wound, abundance of nerve supply and proximity to the brain (e.g. face, upper limbs). Assessment for the risk of tetanus and rabies virus infection, and subsequent selection of prophylactic antibiotics, are essential in the management of dog bites. Once the disease is established, therapy is symptomatic as death is inevitable. There have been only four recorded cases of survival from clinical rabies in the world literature[6]. Therefore the prevention of rabies infection after exposure is of the utmost importance.

PREVENTION

Rabies is preventable if World Health Organization (WHO) guidelines for post exposure treatment are followed. These guidelines stresses on[7]:

- Immediate local treatment of the wound.
- Passive immunization with rabies immunoglobulins (RIG) and
- Administration of an efficacious vaccine.

Pregnancy and infancy are never contraindications to post-exposure rabies vaccination [7]. Persons who present for evaluation and treatment even months after having been bitten should be dealt with in the same manner as if the contact occurred recently[7].

LOCAL TREATMENT OF WOUNDS

Immediate thorough washing and scrubbing of the wound with soap and water and followed by irrigation will reduce the viral or bacterial load by washing of the saliva. Then application of an antiseptic, like tincture of iodine or spirit can prevent rabies in a significant number of cases [8,9]. This is recommended in all cases of animal or human bites and must be done as a priority, even if the person presents after a prolonged period. People should be warned not to apply red chilies, grounded form of tobacco or soil, which may further contaminate the wound. If possible, suturing of wounds should be avoided. However, if suturing is necessary, rabies immunoglobulin should be infiltrated into and around the wound. Necrotic or devitalized tissues should also be removed before closure. Other treatments, such as antibiotics and tetanus immunization and tetanus immunoglobulins should be administered if appropriate.

ANTIBIOTIC TREATMENT

Treatment with prophylactic antibiotics for three to seven days is appropriate for dog bite wounds, unless the risk of infection is low or the wound is superficial[10-12]. If frank cellulitis is evident, a 10-to14-day course of treatment is more appropriate[13]. The common pathogens involved are Streptococcal species, staphylococcus aureus, bacteroides and other anaerobes. Amoxicillin-clavulanate potassium (Augmentin) is the antibiotic of choice for a dog bite. For patients who are allergic to penicillin, doxycycline(Vibramycin) is an acceptable alternative, except for children younger than eight years and pregnant women. Erythromycin can also be used as an alternative. Patients need to be hospitalized if there is systemic signs of infection, like fever or chills, severe or rapidly spreading cellulitis or involvement of a bone, joint, tendon or nerve.[11] Tetanus immunization and tetanus immune globulin should be administered, if appropriate.

RABIES IMMUNOGLOBULIN

Rabies immunoglobulin (RIG) should be given for all category III exposures (single or

multiple transdermal bites or scratches or contamination of mucous membrane with saliva), irrespective of the interval between exposure and beginning of treatment. Two kinds of rabies antibody preparations may be used: Human rabies immunoglobulin (HRIG) and Equine rabies immunoglobulin (ERIG). A skin test must be performed before administration of ERIG. As much as possible of the recommended dose (20 IU/kg of body weight of HRIG or 40 IU/kg of body weight of ERIG) should be infiltrated around the wounds if anatomically feasible[7]. The remainder should be administered intramuscularly into the gluteal region in a single dose and followed by a complete course of vaccine. HRIG has not been known to cause reaction but is very expensive and is often in short supply. Rabies immunoglobulin of equine origin (ERIG) is available and is considerably cheaper than HRIG. It is highly purified and quite safe, however a skin test should always be carried out prior to its use. The patient must be given the option of ERIG/HRIG. The dose of RIG must not be exceeded since it may reduce the anti-genicity of the vaccine.

HRIG —— 1 vial of 2ml has 300 IU, costs Rs.5698/- (Hyperab)

ERIG —— 1 vial of 5 ml has 1000 IU, costs Rs.739/- (Equine Anti-rabies IG)

RABIES VACCINE

Tissue culture rabies vaccines are remarkably safe and free of significant side effects. Imported cell vaccines available in Pakistan are:

Purified Vero Cell Vaccine (PVRV), Verorab, Imovax. 1 vial/0.5ml-Rs.512/-

Human Diploid Cell Vaccine (HDCV). Rabivac.

Purified Duck Embryo Vaccine (PDEV). Lyssavac 1 vial/0.5ml- Rs.750/-

Sheep brain vaccine produced and distributed by NIH, Islamabad is not adequately immunogenic, hence it should no longer be used[14]. Cell culture vaccines are highly immunogenic and are costly when used in the standard 5 dose IM schedule. One dose should be administered on days 0,3,7,14 and 28 into the deltoid muscle, never into the gluteal region because of poorer absorption in a large muscle mass.

WHO in June 2000 endorsed two vaccine regimens, which give an option of using the same vaccine with equal efficacy and lowered cost. It is based on the principle that low dose intradermal (ID) application of the vaccine will produce a rapid and sustained rise in titer[18]. It meets WHO standards of safety, potency and efficacy requirements. This regimen considerably lowers the cost of vaccination against rabies, as the total volume of vaccine required is much less than that required for intramuscular regimens. Separate syringes and needles must be used for each dose. Intradermal injections should be administered only by staff who have been trained in this technique. Vaccine vials should be stored between 4°C and 8°C after reconstitution and the total contents should be used as soon as possible. The method is particularly appropriate when there is less money and in centers dealing with large numbers of patients.

Two intradermal regimens have been approved by WHO:

A) 2-site intradermal method (2-2-2-0-1-1)

This is for use with PVRV, PCECVand PDEV where IM dose is 0.5ml

Regimen: 0.1ml is given ID (intradermal) over each deltoid.

It is written simply as: 2-2-2-0-1-1, indicating the number of sites of the ID injections is to be given on the days 0,3,7, (none on day14) and a single ID dose on days 28 and 90.

B) 8-site intradermal method: (8-0-4-0-1-1)

This is for use with HDCV and PCECV where IM dose is 1ml/dose.

Regimen: Day 0: 0.1ml at 8 sites, both deltoids, lateral thighs, supra-scapular regions and lower quadrant of abdomen.

Day 3: no vaccine

Day 7: 0.1ml at 4 sites, both deltoids and thighs.

Day 14: no dose

Day 28 and 90: 0.1ml at 1 site into the deltoid.

Due to confusing dose schedules and reluctant to use ID technique this regimen is not practiced much, despite the relatively low cost. Institutions where large numbers of cases are seen daily can adopt this system which would considerably save the cost, while offering same efficacy.

Pre-exposure immunization

Pre-exposure immunization should be offered to persons at high risk of exposure, such as laboratory staff working with rabies virus, veterinarians, animal handlers and individuals who are living in or traveling to areas where rabies is endemic. Such immunization should preferably consist of three full intramuscular doses of tissue culture rabies vaccine of potency at least 2.5 IU per dose given on days 0,7 and 28. Periodic booster injections are recommended for persons at continuing risk of exposure to rabies. All persons who work with live virus in a diagnostic, research or vaccine production laboratory should have a serum sample tested for rabies virus- neutralizing antibodies every 6 months and a booster administration when the titre falls below 0.5 IU/ml.[7]

Post- exposure treatment of previously vaccinated persons:

Persons who have previously received full pre or post- exposure treatment with a potent cell- culture vaccine should be given only two booster doses, either intramuscularly or intradermally, on days 0 and 3, but no rabies immunoglobulin.[7]

Table- I: Recommendations for tetanus prophylaxis in wound management[15,16]

	Clean, minor wound		*Large, dirty wound*	
History of Tetanus Toxoid Immunization	*TT*	*TIG*/ATS***	*TT*	*TIG*/ATS***
None, Unknown or incomplete	+ Begin Pre-exposure series	No	+ Begin Pre-exposure series	Yes
Last booster >5 years back	Booster	No	Booster	Yes
Complete, last booster within 5 years	No	No	No	No

* TIG (Tetanus Immunoglobulin) Dose: 250 IU IM once only at time of injury. No serious side effects. Test dose not recommended. May be given with TT at different site. Cost: Rs. 490/per dose of 250 IU.

** ATS(Antitetanus serum) Dose: 3000 IU IM once only at time of injury. Side effect: serum sickness or anaphylaxis. Test dose recommended: 0.1ml of 1:1000 dilution injected intradermally, and the site examined after 30minutes. If no reaction, the serum may be administered. ATS may not be given simultaneously with TT. TT may be given 2 weeks later. Cost: Rs. 10/dose.

TT, TIG, ATS must preferably be given into the deltoid

Table- II: + Pre-exposure series

Timing	*TT*
Day 1	0.5ml
6-12 weeks	0.5ml
6-12 months after 1st dose	0.5ml
Every 10 years	0.5ml

Table- III: Guide for post-exposure treatment for Rabies[7,17]

Category	*Type of contact with suspected or confirmed rabid animal or if unavailable for observation*	*Recommended treatment*
I.	Touching or feeling of animal. Lick on intact skin	None, if reliable history is available
II.	Nibbling of uncovered skin. Minor scratches or abrasions without bleeding. Licks on broken skin	Administer vaccine immediately. Stop treatment if animal remains healthy for 10 days after bite.
III.	Single or multiple transdermal bites or scratches. Contamination of mucous membrane with saliva	Administer RIG and vaccine immediately. (Stop treatment if animal remains healthy throughout observation period of 10 days, or if animal is killed and is found to be negative for rabies).

CONCLUSION

Rabies is a dreaded disease. But having said that, it can be preventable if WHO guidelines are immediately followed. Rabies immunoglobulin either Human Rabies Immunoglobulin (HRIG) or Equine Rabies Immunoglobulin (ERIG) and Rabies vaccine must be advised despite cost, if the disease and death are to be prevented. The newer method of intradermal injection of the vaccine is both effective and economical, particularly in centers dealing with large numbers of patients with fewer resources. Immediate local treatment of the wound is recommended in all cases as a first priority.

There is also a need to stress for immunization of domestic animals with rabies vaccine. Post exposure treatment of rabies alone will remain a costly and inefficient method of controlling rabies. Reduction of rabies reservoirs is required to decrease human deaths due to rabies in Pakistan and other developing countries in which canine rabies is endemic. Pakistan needs to consider some strategies for destruction of stray dogs and develop national programs for the control of rabies in dogs.

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