Title: IMPORTANCE OF RABIES IMMUNOGLOBULINS IN POST EXPOSURE PROPHYLAXIS

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Keywords

Abstract

Rabies is an acute viral zoonosis that occurs in many countries including India and poses a potiential threat to more than 3.3 billion people worldwide. The virus is found in domestic animals(urban cycle) and wild animals (sylvatic cycle) and is transmitted to other animals and to humans through their saliva (i.e bites scratches, licks on broken skin and mucous membrane).

Review Article

Importance of Rabies Immunoglobulins in Post Exposure Prophylaxis

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Rabies is an acute viral zoonosis that occurs in many countries including India and poses a potential threat to more than 3.3. billion people worldwide. The virus is found in domestic animals (urban cycle) and wild animals (sylvatic cycle), and is transmitted to other animals and to humans through their saliva (i.e. bites, scratches, licks on broken skin and mucous membrane). In India, the disease is mainly transmitted by dogs, which are responsible for about 95% of animal bite cases and are the source of 99% of human rabies infections. In humans, rabies is almost invariably fatal once clinical symptoms have developed. Fortunately, the disease is preventable to a large extent if exposures to animals are managed properly and on time. Even following high-risk exposure, proper Post-Exposure Prophylaxis (PEP) which includes local wound treatment and administration of Rabies Immunoglobulins and Cell Culture Vaccines is almost invariably effective in preventing rabies. Therefore proper and timely PEP of animal bite cases is of prime importance in a country like India.

Majority of the estimated 55,000 deaths, which occur worldwide due to rabies each year, are from Africa and Asia. In India alone, 20,000 deaths are estimated to occur annually.

The incubation period of rabies is commonly 1–3 months, but may vary from less than 1 week to more than 1 year. The length of the incubation period depends upon various factors like the amount of virus inoculated, the degree of innervation at the site of viral entry, and the proximity of the bite to the central nervous system (CNS).

WHO guidelines for post exposure prophylaxis Rabies Immunoglobulin (RIG) is a life saving drug in all category III exposures. WHO-APCRI Indian Rabies Survey (2004) revealed that the use of RIGs was as low as 2 % in our country. Even now the usage of RIGs in Category III exposures is low in India.

Administration of RIG delivers Rabies Virus Neutralizing Antibodies to the anatomical region where the rabies virus could be inoculated consequent to the animal exposure.

Convincing clinical evidence was gathered following an incident of wolf bite that occurred in Iran in 1954, which proved that the administration of anti-rabies serum (along with vaccine) to patients who were exposed to rabid animals, reduced the risk of rabies. In this incident, different doses of anti-rabies serum and/or vaccine were administered to 29 patients who had severe bite wounds after being exposed to a rabid wolf.

Of the 29 bite victims, 17 who had severe head wounds were treated as follows:

5 patients received two doses of anti-rabies serum plus vaccine - all 5 patients survived

7 patients received one dose of anti-rabies serum plus vaccine - 1 patient died of rabies,

5 patients received only vaccine - 3 patients subsequently died of rabies.

The other patients exposed to the wolf were bitten in the trunk and legs and were administered either vaccine alone, or vaccine and serum. All of these patients survived. This incident proved the life saving effect of RIGs, beyond doubt.

Indications for RIGs

RIGs should be administered in the following situations:

1. All Category III exposures.
2. Even Category II exposures in immune

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WHO guidelines for post exposure prophylaxis

Category	Type of contact with a suspect or confirmed rabid domestic or wild animal, or animal unavailable for testing	Recommended post exposure prophylaxis
I	- Touching or feeding of animals. - Licks on intact skin.	- None, if reliable case history is available.
II	- Nibbling of uncovered skin. - Minor scratches or abrasions without bleeding. - Licks on broken skin	- Local treatment of wounds. - Administer vaccine immediately - Stop vaccination, if animal remains healthy throughout the observation period of 10 days or if the animal is killed humanely and found to be negative for rabies by appropriate lab techniques.
III	- Single or multiple transdermal bites or scratches - Contamination of mucous membrane with saliva (i.e. licks) - Exposure to bats & wild animals	- Local treatment of wounds. - Administer rabies immunoglobulin & anti rabies vaccine immediately. - Stop vaccination, if animal remains healthy throughout the observation period of 10 days or if the animal is killed humanely and found to be negative for rabies by appropriate lab. techniques

deficient or immune compromised individuals (including HIV infected people & AIDS patients).

It is a common belief among medical practitioners that only severe, multiple wounds on head, neck and face require RIG administration. According to WHO, all transdermal bites or scratches i.e., wounds that bleed, (irrespective of site, number and severity) are Category III exposures. This includes exposures even in pregnant women and lactating mothers.

Role of RIGs

Administration of Rabies Vaccine stimulates production of neutralizing antibodies by the patient's immune system. Protective levels of antibodies are seen 7 to 14 days after starting the first dose of vaccine and can be expected in all the vaccines only by day 14 (after administration of three doses on days 0, 3 and 7). Moreover incubation period of the disease will be short when the bites are on the head, neck, face & hands.

Thus the patients are vulnerable to develop rabies during this window period of 7 to 14 days, despite giving proper wound care and starting rabies vaccine at the earliest. Hence, administration of RIGs, after thorough cleansing of wounds, is life saving as their timely and proper administration neutralizes the virus at the entry point and aborts the risk of developing rabies.

Types of Rabies Immunoglobulins

a) Human Rabies Immunoglobulin (HRIG): Human rabies immunoglobulin has a relatively slow clearance (the half-life is about 21 days). Therefore it is the preferred product, particularly in cases of multiple severe exposures and bites on the head, face and hands. It is homologous in origin and virtually free of side effects. It is available as 2ml vials with a potency of 150 IU/ml.

However, HRIG is imported and expensive and therefore cannot be used routinely in all Category III exposures in our country.

The dosage of HRIG is 20 IU per kg body weight, subject to a maximum of 1500 IU.

b) Equine Rabies Immunoglobulin (ERIG): Where HRIG is not available or affordable, equine immunoglobulin or F(ab´) 2 products of equine immunoglobulin should be used, although they have a faster clearance than HRIG. Most of the new equine rabies immunoglobulin preparations are potent, purified, safe and considerably less expensive than HRIG.

These are produced both in the government and private sectors in our country. These are available in adequate quantities and at an affordable price. Therefore they are preferred in most of the cases. These are available as 5 ml vials with a potency of 300 IU/ml. These are produced from hyper immunized horses and therefore are heterologous in origin.

The dosage of ERIG is 40 IU per kg body weight subject to a maximum of 3000 IU.

Administration of immunoglobulins:

As much of the calculated dose of RIG, as is anatomically feasible, should be infiltrated into and around the wounds. After all the wounds have been infiltrated, remaining of the RIGs, if any, should be administered by deep intramuscular injection at an injection site distant from the vaccine injection site.

Multiple needle injections into the wound should be avoided as far as possible.

It is important to infiltrate all wounds with RIGs to neutralize the virus locally. Systemic [intramuscular] administration of RIGs, alone, is of very little value. The common mistake done by doctors and nurses (mostly for convenience) is to inject the full dose of RIGs intramuscularly, most often into gluteal region, which serves very little purpose.

The old recommendation was to give anti rabies serum half into wounds and half intramuscularly. This is no longer recommended and may lead to treatment failure.

Sometimes there may be multiple animal bite wounds, especially in children. In such cases, the calculated dose of the RIG may not be sufficient to infiltrate all the wounds. In these circumstances, the calculated dose of RIGs can be diluted with sterile physiological saline to enable infiltration of all the wounds.

PRECAUTIONS

The RIG vials should always be gently brought to room/body temperature before RIGs are administrated to the patient.

RIGs should never be administered with the same syringe as the one with which the vaccine is administered.

RIGs must never be given intravenously.

The total recommended dose of RIGs (1500 IU for HRIG and 3000 IU for ERIG) must not be exceeded as it may suppress the antibody production induced by the vaccine in the host.

If RIGs were not administered when vaccination was begun, it can be administered up to the seventh day after the administration of the first dose of vaccine. Beyond the seventh day, RIGs are not indicated since an antibody response to anti-rabies vaccine would have occurred and RIGs may suppress the antibody production induced by the vaccine.

Those administering ERIG should keep emergency medications readily available. ERIG should be given by experienced hands and under close medical supervision.

Side effects of RIGs

There may be pain, tenderness and swelling at the injection site and a brief rise in body temperature. Itching at the site of administration may be seen with ERIG.

The incidence of anaphylactic reaction after ERIG administration is 1 in 45,000 cases. Till date, fortunately, none has died of anaphylaxis following ERIG administration.

Serum sickness occurs in 1% to 6% of patients receiving ERIG, usually 7 to 10 days after injection of ERIG. The clinical manifestations of serum sickness are fever, pruritis, urticaria, erythema, arthralgia and lymphadenopathy

CONCLUSION

Rabies Immunoglobulins (RIGs) are life saving in all Category III exposures. These should be administered whenever indicated .

The Equine Rabies Immunoglobulins (ERIGs), currently available in our country, are purified, economical, safe and cost effective. Their benefits clearly outweigh the remote risk of anaphylaxis due to ERIG. HRIGs are to be used if they can be afforded by the patients.

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