Post-exposure Prophylaxis for Rabies

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Rabies (rage or madness in Latin) has been the subject of fear ever since the disease was recognised. Worldwide the number of deaths annually, due to rabies, is estimated to be between 35,000 to 50,000 approximately. The highest incidence of rabies is in India with approximately 30,000 cases of rabies reported annually. The causative agent of rabies is a Lyssavirus type 1. It is a bullet shaped virus and is found in the wild as well as some domestic animals. Rabies is essentially a zoonotic disease with man being the dead-end host. Rabies is transmitted to man most commonly as a result of bites or scratches by a rabid animal but there are some other uncommon modes of transmission of rabies as listed in Table I. Since rabies is 100% fatal (only six cases reported so far where survival occurred after developing clinical rabies), prevention of rabies is the best and only option for cure. Post-exposure rabies vaccination forms the most integral part of prevention of rabies. This article discusses the various available vaccines for rabies prophylaxis and their schedules.

Table I: Modes of transmission of Rabies.

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<th>Animal to man</th>
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<td>1. Bites of rabid animals.</td>
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<td>2. Scratches by rabid animals.</td>
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<td>3. Licks on abraded skin or mucous membranes.</td>
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<th>Aerosols</th>
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<td>1. In caves harbouring rabies infested bats.</td>
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<td>2. In laboratories handling rabies infected neural tissue*.</td>
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<th>Oral**</th>
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<td>1. Drinking unboiled raw milk of rabies infected cow or goat.</td>
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<td>2. Eating meat of rabid animal can theoretically lead to rabies.</td>
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<th>Man to man</th>
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<td>1. Corneal transplant from an infected person.</td>
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2. Solid organ transplant (liver, kidney) from an infected person.
3. Bite from a rabid human; theoretical risk but no confirmed cases reported as yet.
4. Kissing an infected person; theoretical risk but no confirmed case reported as yet.

* Contact with body fluids other than saliva and neural tissue (i.e., blood, urine or faeces) is not considered an exposure.
** Rabies virus is inactivated by desiccation, UV radiation and heating or cooking at > 60°. Thus, dry material from a rabid animal can be considered non-infectious.

Antirabies vaccines are of 2 types-Neural and Non-neural vaccines (Figure 1).

Neural vaccines

Although WHO has directed its member nations not to use the neural tissue vaccines, still many developing nations use neural vaccines because of their low cost.

1. Semple Vaccine was developed by Semple at Central Research Institute, Kasauli, and it has been the most widely used vaccine for over half-a-decade. It is a 5% suspension of sheep brain infected with fixed virus and inactivated with phenol at 37°C.

2. Beta propionilactone vaccine (BPL) is a modification of the Semple vaccine in which BPL is used as an inactivating agent instead of phenol. It is believed to be more antigenic, so a smaller dose is required.

3. Suckling mouse brain vaccine was developed with the aim to reduce the encephalitogenic properties of the rabies vaccine. The infant mice (< 9 days old) are used for vaccine production. The amount of myelin in infant brain is scanty and this results in a lower incidence of neuroparalytic side effects.

Neural tissue vaccines (NTV) have many disadvantages:
1) poor immunogenecity as they contain mostly nucleocapsid antigen with only small quantities of glycoprotein G which is the sole protective agent; 2) they may contain infectious agent which may not be inactivated during vaccine production and storage; 3) the neuroparalytic adverse effects. NTV contain myelin, which is responsible for the neuroparalytic side effects of these vaccines (Table II). The incidence of neural complications with vaccines prepared from brains of adult animals is between 1:200 and 1:2,000 and from that of infant mice is 1:3,000 to 1:24,000. These complications usually occur after the sixth or seventh injection of the vaccine. The onset of symptoms is usually within 30 days (88% within 20 days). The condition may result in serious residual paralysis and even death. There is no definite treatment of these neuroparalytic complications, but high dose corticosteroids, plasma exchange and immunoglobulins have been used with variable results.

Because of the above reasons, WHO has recommended phasing out of NTVs by the year 2006. The Government of India has discontinued the use of NTV from December, 2004.

Table II: Neuroparalytic complications of neural vaccines.

1. Meningoencephalitis
2. Meningoencephelomyelitis
3. Mononeuritis multiplex
4. Dorso-lumbar transverse myelitis
5. Ascending paralysis of Landry's type

Non-neural vaccines

Non-neural vaccines were developed with the aim of reducing the neuroparalytic complications associated with the nervous tissue vaccines. They are of 2 types: avian embryo vaccines and primary cell culture vaccines.

Avian embryo vaccines: the prototype avian embryo vaccine is the duck embryo vaccine that was first made available in 1957. It was widely used before the first generation cell culture vaccines became available. This vaccine contains no detectable myelin protein but contains traces of avian antigens. The chief disadvantages of use of duck embryo vaccine are poor immunogenecity and presence of avian antigens that could lead to anaphylactic reaction.

Primary cell culture vaccines: modern cell culture vaccines were first developed in 1964 but were beset with tolerability problems.

1. Human diploid cell vaccine (MIRV-HDC in India): the vaccine is prepared from Pitman Moore strain of rabies virus grown on MRC-5 human diploid cell culture line, concentrated by ultrafiltration and inactivated by BPL. It is supplied in two forms:
   a) Intramuscular administration: a single dose vial containing lyophilised vaccine that is reconstituted in the vial with the accompanying diluent to a volume of 1 ml.
   b) Intradermal administration: a single dose syringe containing lyophilised vaccine that is reconstituted in the syringe to a final volume of
0.1 ml before administration\textsuperscript{14}.

The WHO regards the HDCV as the gold standard among all rabies vaccines. In one of studies in Iran, none of the 45 persons who received HDCV developed rabies following severe bites by rabid dogs or wolves\textsuperscript{15}.

2. Purified chick embryo cell vaccine (PCECV - Rabipur\textsuperscript{TM}): PCECV is prepared from fixed rabies virus strain FLURY LEP grown in primary cultures of chicken fibroblasts\textsuperscript{9}. The vaccine was first marketed in 1984 and is now available in more than 70 countries and more than 30 million doses of PCECV have been administered worldwide. It is available as a single dose vial containing lyophilised vaccine that is reconstituted with diluent to a final volume of 1 ml. Various studies have shown that PCECV is at least as effective as the HDCV\textsuperscript{16-18}. It is cheaper than HDCV.

3. Purified Vero Cell Rabies Vaccine (PVCV – Abhayrab\textsuperscript{TM}, Verorab\textsuperscript{TM}): PVCV contains Wistar strain of virus, with the vero cell line as the substrate, which is a continuous cell line\textsuperscript{9}. The vaccine induces a good immune response after primary as well as secondary immunisation, the results being comparable to those of HDCV\textsuperscript{19}. But the continuous cell lines like vero cell line are abnormal, as their genetic makeup has been altered to allow continuous replication. Therefore they may contain potentially oncogenic substances and vaccines produced in such cell lines must be monitored for residual DNA that is present in each dose. According to European Pharmacopoeia, the content of residual DNA per human dose should be less than 100 pg. The FDA, USA has not yet approved the is vaccine for use in USA.

4. Rabies Vaccine Adsorbed (RVA): is prepared from Kissling strain of challenge virus standard (CVS) rabies virus adapted to foetal rhesus lung diploid cell culture\textsuperscript{20}. The vaccine virus is inactivated by BPL and concentrated by adsorption to aluminum phosphate. It is a liquid rather than lyophilised vaccine and is approved only for Intramuscular use as a 1 ml dose\textsuperscript{9}.

5. Primary Hamster Kidney Cell Vaccine (PHKCV): this vaccine is used in China and Russia locally. The virus is propagated in primary kidney cells of Syrian hamsters\textsuperscript{6}.

\textbf{Potency of anti rabies vaccines}

WHO recommends that the rabies vaccine for human use must have a potency of at least 2.5 IU/dose using the NIH test\textsuperscript{21} for NTVs the minimum potency is 0.3 antigenic value. All WHO recommended modern cell vaccines are safe and effective. To be effective in preventing rabies, specimens collected 2 - 4 weeks after post-exposure prophylaxis should completely neutralise challenge virus at a 1:5 serum dilution by the RFFIT\textsuperscript{4}.

Adverse effects of cell culture vaccines: the modern cell culture vaccines are generally considered safe and have very few adverse effects. Table III enlist the common adverse effects associated with modern cell culture vaccines\textsuperscript{5}.

\textbf{Table III: Adverse effects of cell culture vaccines.}

\begin{itemize}
    \item 1. Local: pain, erythema, swelling, or induration (in 15 to 74 per cent of recipients)
    \item 2. Itching
    \item 3. Local lymphadenopathy
    \item 4. Headache, malaise, myalgia, or dizziness (10 to 25 per cent)
    \item 5. Gastrointestinal symptoms (in less than 10 percent);
    \item 6. Allergic reactions during primary vaccination (in 0.1 per cent [less than 10 per cent of whom have anaphylactic reactions]).*
    \item 7. Type III hypersensitivity reactions (in 6 to 10 per cent after booster doses of human diploid cell vaccine and in fewer during primary vaccination).
\end{itemize}

*Allergic reactions are fewer with 2nd generation cell culture vaccines.

\textbf{Dosage and schedule of cell culture vaccines}

Rabies post-exposure prophylaxis (PEP) is an emergency and as a rule should not be delayed or deferred. There are no contraindications if modern cell culture vaccines are used.

Indications for Antirabies vaccination: post-exposure prophylaxis –

a. In endemic countries like India where terrestrial rabies is rampant, post-exposure prophylaxis should be given to all patients with animal bites except if the dog at
the time of exposure is more than a year old and has a vaccination certificate indicating that it has received at least 2 doses of a potent vaccine, the first not earlier than 3 months of age and another within 6 - 12 months later. In this case the dog may be observed for 10 days and if the dog shows any sign of illness during the observation period, the patient should receive full post exposure prophylaxis11.

b. In other areas where rabies is not terrestrial, indications for post-exposure prophylaxis are8:

1. Bite by a wild animal
2. Unprovoked bites
3. If the biting animal cannot be traced
4. Laboratory tests of the brain of the animal are positive for rabies

PEP for rabies is not indicated if the biting animal is a small rodent or rabbit22. Larger rodents like the woodchuck are more frequently reported to be rabid4. Figure 2 shows a suggested algorithm for post-exposure prophylaxis of rabies4.

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**Fig. 2: Algorithm for post-exposure prophylaxis (PEP) of rabies.**
Indications for Antirabies vaccination: pre-exposure prophylaxis – pre-exposure vaccination is recommended for persons at risk: laboratory workers, diagnosticians, veterinarians and their staff, animal control officers, rabies researchers, and some travellers to endemic areas where rabies is prevalent. WHO recommends that toddlers and children in highly endemic areas may also be considered for rabies pre-exposure vaccination.

Categorisation of bites (WHO)

Category I: touching or feeding of animals or licks on intact skin. In such a case if the history is reliable no treatment is required as there is no exposure to the rabies virus.

Category II: minor scratches or abrasions without bleeding, or licks on broken skin and nibbling of skin. This requires a full course of antirabies vaccine.

Category III: single or multiple transdermal bites or contamination of mucous membrane with saliva. In this case both immunoglobulin and vaccine should be used.

Schedule for pre-exposure vaccination

Pre-exposure vaccination simplifies the management of subsequent exposure as fewer doses of vaccine are required and rabies immunoglobulin is not required. Three doses of vaccine are given on day 0, 7, and 28 by intramuscular route. Alternatively, 0.1 ml of HDCV may be injected intradermally also. Note here is the interference of chloroquine with the immune response of anti-rabies vaccines. So HDCV should not be given intradermally if the person is receiving chloroquine. The need for booster vaccination may be monitored by serologic testing performed every six months to 2 years and booster dose is given when titres fall below 0.5 IU/ml.

Schedule for post-exposure vaccination

Traditionally, modern cell culture vaccines are given intramuscularly. The vaccines should not be administered in the gluteus muscle to avoid injury to the sciatic nerve and to lessen the delivery of vaccine to the adipose tissue. Two regimens are used:

a. Classic 5 dose intramuscular regimen (Essen regimen) in which one dose of vaccine, i.e., 1 ml of HDCV, PCECV or 0.5 ml of PVEV is administered on day 0, 3, 7, 14, and 28.

b. Alternate 2 - 1 - 1 regimen in which 2 doses of vaccine are given on both deltoids on day 0 and then one dose each on day 7 and 21.

Since the cell culture vaccines are very expensive, developing countries like India cannot afford the universal use of cell culture vaccines as recommended by the WHO. In India alone, approximately 2.5 million animal bites occur annually. If Rabipur (PCECV) is used then the annual cost would be approximately Rs. 8.7 billion. The WHO therefore recommends the use of cell culture vaccines by intradermal route. Intradermal vaccination reduces the volume of vaccine required and the cost of vaccination by 60 - 80%. The efficacy and immunogenecity of the intradermal regimen has been established by various studies in Thailand, Sri Lanka and India. However, certain precautions are required that include proper staff training, use of appropriate 1 ml syringe and short hypodermic needles. Two regimens are used, the 8 site Oxford regimen and the 2 site Thai Red Cross regimen (Table IV).

Efficacy of post-exposure rabies prophylaxis

The modern cell culture vaccines are highly effective. Various studies done with the cellular vaccines have shown that the seroconversion rate (i.e., an antibody titre of > 0.5 IU/ml) after 14 days is 100%. On the other hand, the amount of glycoprotein antigen in NTVs is much less. So patients receiving NTVs may seroconvert late or may not seroconvert at all. In a study comparing NTV with PCECV, 14% of patients receiving NTV did not seroconvert, and the average antibody titres in NTV group (3.2 IU/ml) was much less than the PCECV group (13.4 IU/ml).

The cellular vaccines have been in use for over 40 years now. In USA there have been no reported failures after post-exposure prophylaxis with the cellular vaccines. But in South-east Asia and India there have been failures even with the use of cellular vaccines. Most of these failures have occurred when there have been deviations from the
recommended schedule and guidelines. Of importance here is the proper management of the wound and use of ARG especially in severe category III bites34.

Prior to administration, a skin test should be done. A test dose of 0.1 ml of 1 in 10 diluted ERIG is injected intradermally into the left forearm. An equivalent intradermal injection of physiological saline is used as control. An induration of > 10 mm is taken as positive38. The problem however is that a positive skin sensitivity test does not accurately predict anaphylaxis or serum sickness like reactions39. The immediate reactions that occur after use of heterologous sera are either IgE mediated (anaphylactic) or complement mediated (anaphylactoid). The skin test detects the anaphylactic reactions but not the anaphylactoid reactions40. WHO in 1995 had recommended that skin test may not be done prior to ERIG administration39. In Brazil a study was done in which none of the 1,054 patients who were given ERIG were subjected to skin sensitivity test. They were however given ERIG under the cover of antihistamines (anti H1+ anti H2) and corticosteroids. All the patients were observed for 60 - 180 minutes. None of the patients showed any adverse effects41. In 1997 WHO recommended that if the skin test is positive, preferably HRIG should be used. However, if HRIG is not available then desensitisation for horse serum may be considered. Alternatively, ERIG may be given under cover of antihistamines and intramuscular adrenaline/
epinephrine. If however, ERIG cannot be given, then after proper wound toilet the patient should preferably be given 2 doses of a cellular vaccine on day 0 in both deltoids.

Dose of ERIG is 40 IU/Kg of body weight. As much as possible ERIG should be infiltrated around and into the wound(s), even if the lesion has begun to heal. If the calculated dose of ERIG is insufficient, then sterile saline can be used to dilute it 2 - 3 times to permit thorough infiltration. Any remaining ERIG is injected intramuscularly at a site distant from the site of vaccine administration.

With the use of purified ERIG, the incidence of adverse effects has been low (0.8 - 6%)43-45. The incidence of early manifestations is calculated to be less than 1:35,000 treatments38. The adverse effects are of 2 types:

Immediate or anaphylactoid reactions: include hypotension, dyspnoea, syncope, and urticaria. Anaphylaxis is rare (< 1%) with modern purified and pepsin-digested equine rabies immunoglobulins36. This type of reaction is treated with adrenaline, oxygen, hydrocortisone, and antihistaminics.

Delayed or serum sickness like reactions may occur after 6 days. The incidence is < 3%46. This is a type III hypersensitivity reaction and symptoms include fever, pruritis, rash, adenopathy, and arthralgias. These are treated with Nonsteroidal anti-inflammatory agents and antihistamines.

2. Human rabies immunoglobulin (HRIG): HRIG has replaced ERIG in most developed countries. In developing countries the use is limited because of prohibitively high costs of HRIG. The dose is 20 IU/Kg body weight and use is similar to ERIG. It is free from anaphylactic and serum sickness like adverse effects29.

Future vaccines: DNA vaccines have shown efficacy in preclinical animal models in preventing or even treating a variety of diseases caused by infectious organisms. One of the main perceived advantages of DNA vaccines is the low cost. However, in general, immune responses elicited by DNA vaccines are less potent. Although DNA vaccines have shown good efficacy in preventing rabies in animals, their efficacy in phase I human trials has largely been disappointing46.

To conclude, although post-exposure vaccination forms an integral part of rabies control, control of rabies can only be achieved by health education and vaccination of dogs and cats. However availability of cheap and effective human rabies vaccine is of prime importance for preventing mortality from rabies in a country like India.

References
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