Review Article

Intradermal rabies immunization for pre- and post-exposure prophylaxis

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ABSTRACT

Human diploid cell rabies vaccine and similar tissue culture-produced vaccines are too expensive for widespread use in India, but alternative regimes can reduce the cost of post-exposure treatment by 60%. Multiple-site intradermal injections of tissue culture vaccine have proved effective, economical and safe. As these vaccines are becoming more freely available, the intradermal method can now be used to accelerate the replacement of nervous tissue vaccines.

INTRODUCTION

The untreated mortality following rabid dog bites in India has been found to be between 35% and 57%, and the risk of infection rises to 88% after severe facial bites. Semple rabies vaccine has been used in India for more than 85 years and has saved many lives, but treatment failures are not uncommon. Studies in Delhi and Thailand show that 10% of the patients with rabies encephalitis had received a full course of Semple vaccine. Life-threatening neurological reactions still occur. Using active surveillance, the incidence in Bangkok has been estimated at 1:220 recipients. The incidence in India, estimated by passive surveillance, is about 1:5000 recipients. The long overdue change to modern tissue culture vaccines has been hindered by their higher cost but the use of an economical low-dose regime can and should make safer vaccines available to many more people.

CURRENT POST-EXPOSURE PROPHYLAXIS IN INDIA

Rabies vaccines of nervous tissue origin

Semple vaccine remains the most widely used vaccine for rabies prophylaxis. Estimates of the number of people receiving the vaccine annually vary from 500,000 to 3,000,000. Semple vaccine is manufactured at 12 centres all over India and is provided free by the Government. The post-exposure course comprises 10 or 14 daily injections of 5 ml of the β-propiolactone or phenol-inactivated sheep brain homogenate, at a cost of about Rs 100 ($3.25). Booster doses, when given, add to the price. Compliance with this painful regime is poor, especially among children. Among 18,682 people who began post-exposure treatment in Kasauli in 1981, 66% did not complete the course. Some of the defaulters developed rabies encephalitis. At the Infectious Diseases Hospital in Delhi, 17% of the 47 rabies patients received only between 2 and 12 injections and 10% completed the 14-dose course. In Kasauli, 31% of the 80 rabies patients had incomplete Semple vaccine treatment.

Tissue culture rabies vaccines

Modern, safer tissue culture vaccines have been imported into India for several years, but few can afford them. For example, they are given to only 2–5% of post-exposure patients in a government hospital in Pondicherry (Rajavelu, personal communication).

The vaccine produced in human diploid cell culture has been in use for 16 years, its efficacy is well established and it is now the international reference vaccine. The 5 doses of a conventional post-exposure course of human diploid cell vaccine (HDCV) [Imovax rabies, Merieux]; 1 ml intramuscularly (i.m.) on days 0, 3, 7, 14 and 30, costs Rs 2500 ($81) in India, which is prohibitively expensive.

Purified chick embryo cell (PCEC) vaccine (Rabipur, Behring) is freely available at Rs 1075 ($35) for 5 doses. It has been studied in Delhi, and is now produced at Ankeleshwar in Gujarat.

Purified vero cell rabies vaccine (PVRV; Verorab, Merieux) costs Rs 1125 ($36.25) for a course of 5 doses. It is currently imported but indigenous production is in progress and it will soon be available from the Pasteur Institute, Coonoor.

Purified duck embryo vaccine (PDEV; Lyssavac-N, Berna) is said to be free of all neural antigens. The dose is 1 ml and is given according to the i.m. regime advised for tissue culture vaccine.

Rabies immune globulin

Passive immunization with rabies immune globulin (RIG) may immediately neutralize the virus in a wound and stimulate a T-lymphocyte mediated immune response prior...
to the appearance of vaccine-induced immunity. RIG of human and equine origin are of comparable efficacy. The dose of human RIG is 20 IU per kg, but that of equine RIG is 40 IU per kg because of its shorter half-life in man.

All victims of rabid animal bites should ideally be given passive as well as active immunization, but RIG treatment is especially important following severe bites. In practice, RIG is available only at a few centres in India, and in Thailand less than 5% of post-exposure patients can obtain and afford it. The cost of human RIG for a 60 kg person in India is Rs 1720 ($56). Equine RIG is less expensive but the supplies are limited. Between 1% and 6% of the recipients of equine RIG develop serum sickness, but this has not been detected following human RIG.

**INTRADERMAL HDCV FOR POST-EXPOSURE PROPHYLAXIS**

Accumulated evidence shows that the speed and height of antibody response to rabies vaccine is increased by doubling the amount of antigen used or by giving the vaccine by injection at several sites on the same day. The cost of treatment is reduced if the dose of HDCV is divided between multiple intradermal (i.d.) sites.

Further studies of HDCV compared the antibody response of volunteers to multiple i.d. injections with those of the i.m. and subcutaneous (s.c.) routes, and also with a Semple vaccine regime. Thus, an economical post-exposure regime using 8-site i.d. HDCV was derived, with a wide margin of safety. Four visits to the clinic are required. The vaccine is administered as follows:

- **Day 0**: 0.1 ml at 8 sites (right and left deltoid, suprascapular, thigh and lower abdominal areas) using up the whole 1 ml ampoule
- **Day 7**: 0.1 ml i.d. at 4 sites (deltoids and thighs)
- **Days 28 and 91**: 0.1 ml i.d. at 1 site (deltoid)

The distribution of sites is designed to stimulate as many different groups of lymph nodes as possible, and so accelerate humoral and also possibly T-lymphocyte mediated immunity. A clean needle and syringe must be used for every patient to prevent viral cross-infection and i.d. injections should be given with care, as for BCG.

The regime was compared with Semple vaccine in a post-exposure trial in 155 people bitten by proven rabid animals. Seventy-eight patients were given 8-site HDCV and only those with severe bites were also given equine RIG. After 2 years, no deaths from rabies had occurred. Neutralizing antibody induction was fast; 88% of the 42 recipients of 8-site HDCV alone (without RIG) were positive by day 7, making it the treatment of choice when RIG is not available for severe bites. All 72 of the 8-site HDCV recipients tested had antibody detectable for at least one year, in contrast to the recipients of Semple vaccine, of whom 48% had no detectable antibody a year later.

A pilot study had shown that if only 4 i.d. injections were given on day 0, the initial antibody response was still very good, but this cannot be guaranteed for 10% of the population who have a lower antibody response which is relatively delayed. Serological testing is not necessary following this or any other recommended post-exposure vaccine regime. The management of patients with chronic disease or patients taking other medications is the same as for Semple or other vaccine treatment.

Less than 2 ampoules of HDCV are needed for this 8-site i.d. regime, a 60% reduction of the standard i.m. method, if 2 or more new patients are treated per day, or if a group of 4 are vaccinated together. An ampoule of vaccine can be shared between more than 1 patient if a strict aseptic technique is used to remove the vaccine into a clean needle and syringe for each patient. Ampoules of vaccine are at great risk of microbial contamination once the bung has been punctured, resulting in loss of potency. Trakunchang (personal communication) found no loss of potency of reconstituted HDCV after 2 weeks at 4 to 6 °C but Phanuphak (unpublished data) found an average loss of 14% potency after storing PVRV at 4 to 10 °C for a week. It would be reasonable to keep an open ampoule at 4 °C for 1 or 2 days.

A 1 ml ampoule of vaccine is used on day 0 for each patient, avoiding wastage, contamination or errors with the dose. The rapid immune response induced by this intense antigenic stimulus is especially important in over 90% of the cases when no RIG is available. The treatment is given only on 4 days, instead of between 10 and 16 days for Semple vaccine, saving the patients the cost of travel and the time off work.

**POST-EXPOSURE INTRADERMAL USE OF OTHER TISSUE CULTURE VACCINES**

**PCEC vaccine**

The antibody response to the 8-site i.d. regime using PCEC vaccine has been found to be similar to that of the conventional 5-dose i.m. schedule, and significantly greater than that of the suckling mouse brain vaccine.

In India, either PCEC vaccine or HDCV was given by a different 8-site i.d. regime to patients bitten by dogs. Fifty-seven of the 200 people had had proven exposure to rabies, and 40 patients with severe bites were treated with equine hyperimmune serum. The neutralizing antibody levels seem comparable for the two vaccines, but the results were not analysed statistically.

The use of PCEC vaccine with the 8-site regime described above could cost Rs 408 ($13) if ampoules were shared between patients under strict aseptic conditions (see above). Further studies are warranted. The advantages over nervous tissue vaccines are: an accelerated antibody response which is higher and lasts longer; freedom from the risk of post-vaccinal encephalitis, and 4 instead of about 14 visits to the clinic. If the only alternative is a nervous tissue vaccine, it seems advisable to use this i.d. PCEC method.

**PVRV**

The i.m. dose of PVRV is only 0.5 ml. This concentrated vaccine has been given as a 2-site i.d. regime (0.1 ml at 2 sites on days 0, 3, 7 and 0.1 ml at one site on days 30 and 90), requiring 5 clinic visits. A hundred Thai subjects with proven exposure to rabid animals received this regime with RIG and no one developed rabies during a year's observation. The method is now used in Bangkok. This regime has a relatively narrow margin of safety since less than half of a standard i.m. dose is given on day 0 and errors of injection might occur. If, as for any course of treatment, some patients are unable to attend the next appointment, the amount of antigen given may be low.
PRE-EXPOSURE USE OF INTRADERMAL TISSUE CULTURE VACCINE

Pre-exposure rabies vaccination with i.d. HDCV is now widely recommended.29-31 Three injections of 0.1 ml of vaccine are given on days 0, 7 and 28. A dose of 0.1 ml of HDCV is packaged especially for this purpose in the USA. Malaria chemoprophylaxis with chloroquine inhibits the antibody response to i.d. HDCV,32 so the full 1.0 ml i.m. dose must be given to anyone taking this or any other potentially immunosuppressive drug. If continued protection is needed, booster doses can be given or the neutralizing antibody level checked every 6 months to 2 years depending upon the risk of exposure to rabies.29,30

The Government of India currently provides i.m. pre-exposure HDCV for some staff at high risk in animal houses and laboratories.

The economical i.d. pre-exposure regime using PCEC vaccine gave satisfactory serological results compared to those of i.m. PCEC vaccine and HDCV.33-35

TREATMENT AFTER RE-EXPOSURE TO RABIES

Repeated exposure is common in rabies enzootic countries such as India, where the dog is the dominant vector species. Immediate thorough wound treatment is still mandatory. A full course of Semple vaccine is repeated in India if more than 6 months have elapsed since a previous course. A shortened course of 2 doses of a tissue culture vaccine i.m. on days 0 and 3 can be used if pre- or post-exposure treatment with a recognized tissue culture vaccine has been received previously, and no RIG is needed. This regime may also be used if a satisfactory neutralizing antibody level (>0.5 IU/ml) is recorded following any rabies vaccine therapy.29,30

SIDE-EFFECTS OF HDCV

Minor local reactions occur in about 15% of the patients, and mild systemic reactions in 7%,36 but estimates vary greatly.30 These rates are similar for i.d. and i.m. regimes, except that transient local itching is more frequent following i.d. injections, occurring in up to 35% of the patients.24 The 8-site i.d. HDCV treatment is reported to cause significantly fewer local side-effects than Semple vaccine.24 Neurological illness following HDCV is exceptionally rare, and a causal relationship is difficult to establish.30 Late booster injections are reported to have caused a mild hypersensitivity (immune complex-like) reaction in 6% of recipients in the USA. This allergic response to vaccine components has never been life-threatening and is treated symptomatically.30,37

ROLE OF INTRADERMAL REGIMES IN INDIA

Rabies is an entirely preventable disease. If optimum wound cleaning, tissue culture vaccine and RIG are given promptly in the correct manner, survival is virtually 100%. The European manufacturers seem to have no intention of licensing their vaccines for use with economical post-exposure regimes, despite the World Health Organization’s (WHO) recommendations to use the i.d. route.29 It is the responsibility of physicians to make the best use of the resources at their disposal and to provide the safest treatment.

The 8-site post-exposure regime is preferable to Semple vaccination, and has been acknowledged by the WHO to be reliable.30 The efficacy, measured by antibody production, is clearly superior,24 and protection against death from rabies has been tested in patients exposed to proven rabid animals.24 The risk of neurological complications to Semple vaccine is eliminated.

The i.d. technique is familiar to many who routinely give neonatal BCG injections. There is a wide margin of error using the 8-site regime since, as mentioned above, a good antibody response is still obtained if only 4 i.d. injections are given on day 0.29 The i.d. method is not only ideal for busy centres, but there can also be considerable saving if only 2 patients are treated simultaneously. The great fear of rabies overcomes any patients’ concern about the multiple injections, and the regime is much preferred to Semple vaccination. It is ethically justifiable and defensible to use the method today, with HDCV, in any patient requiring post-exposure treatment.

The i.d. method for pre-exposure vaccination is widely accepted and if the post-exposure regime were similarly recognized, some patients would be saved a horrifying death from rabies or iatrogenic morbidity and mortality resulting from nervous tissue vaccines. Exciting new products are being developed for active and passive rabies prophylaxis for the future.29,39,40 Meanwhile, in view of the accelerated antibody response, proven clinical efficacy and considerable reduction in cost, there should be no hesitation in adopting the i.d. method extensively in developing countries to enable the benefit of tissue culture vaccine to reach more people and hasten the replacement of nervous tissue vaccines.

REFERENCES

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Obituaries

Many doctors in India practise medicine in difficult areas under trying circumstances and resist the attractions of better prospects in western countries and in the Middle East. They die without their contributions to our country being acknowledged.

The National Medical Journal of India wishes to recognize the efforts of these doctors in a new section ‘Obituaries’. We invite short accounts of the life and work of a recently deceased colleague by a friend, student or relative. The account in about 500 to 1000 words should describe his education and training and highlight the achievements as well as the disappointments. A photograph should accompany this article.

—Editor