Short Report

Boosting effect of purified chick embryo cell rabies vaccine using the intradermal route in persons previously immunized by the intramuscular route or vice versa


ABSTRACT

Background. At present, in the event of re-exposure to rabies, 2 booster doses are recommended for people who have been previously vaccinated with cell culture rabies vaccines by the conventional intramuscular route. As the intradermal route of vaccination is likely to be introduced in the future, we investigated the immune response to a cell culture rabies vaccine after crossing over from the intramuscular to the intradermal route and vice versa.

Methods. Twenty healthy adult volunteers who had received a primary course of rabies vaccination with purified chick embryo cell (PCEC) rabies vaccine by either the intramuscular (n=10) or intradermal (n=10) route received booster vaccination with the same vaccine by the alternative route. The regimen used was 0.1 ml of vaccine by the intradermal route at two sites (deltoid area) for the intramuscular group, or 1 ml of vaccine by the intramuscular route (deltoid muscle) to the intradermal group on days 0 and 3.

Results. There was a 15-fold rise in the rabies virus neutralizing antibody response both by the intradermal and intramuscular routes of booster vaccination (p<0.0001). Thus, the change of route of purified chick embryo cell booster vaccination did not alter the anamnestic immune response to the vaccine. No side-effects were observed after vaccination with either of the routes.

Conclusion. Purified chick embryo cell vaccine was found to be safe and immunologically efficacious following booster vaccination after crossing-over from the intradermal to the intramuscular route and vice versa.

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INTRODUCTION

Human rabies continues to be a public health problem in India, as an estimated 20,000 patients with rabies die and 17 million animal bites are reported to occur every year. Following a Supreme Court judgment the production of sheep brain (Semple) vaccine was stopped in December 2004 and cell culture vaccines (CCVs) now constitute the mainstay of antirabies vaccination in India. Meanwhile, the Indian Council of Medical Research (ICMR) has concluded a feasibility study of intradermal rabies vaccination (IDRV), which is considered a cost-effective alternative to CCVs given intra-muscularly and a replacement for the reactogenic Semple vaccine. With this background, we evaluated a new 5-injection, 2-site intradermal schedule using purified chick embryo cell (PCEC) rabies vaccine in healthy adult volunteers and compared it with the conventional intramuscular regimen. The regimen of administration consisted of 0.1 ml of PCEC vaccine given intradermally at 2 sites (deltoid area) on days 0, 3, 7, 14 and 28 (synchronous with the days of vaccination in the presently used intramuscular regimen). This new regimen was found to be safe and immunologically efficacious for a period of 1 year. Presuming that IDRV will shortly be approved by the Government of India, this regimen will allow cross-over from the intramuscular to the intradermal route if it becomes unavoidable in certain circumstances. As an extension of the previous study, we did a follow up study to evaluate the booster effect of PCEC vaccine and assess the feasibility of crossing over from the intradermal to the intramuscular route and vice versa.

MATERIALS AND METHODS

Twenty consenting vaccinees from the previous study were enrolled for this follow up study after approval of the Kempegowda Institute of Medical Sciences (KIMS) institutional ethics committee. The vaccinees mean (SD) age was 23 (0.8) years, mean (SD) weight 60.85 (7.8) kg and mean (SD) height 166.25 (8.2) cm. Of these, 10 had previously received PCEC vaccine (Rabipur, potency 9.43 IU per ml) by the intramuscular route (Essen regimen) and another 10 had received the same PCEC vaccine by our new intradermal regimen. The Essen regimen involved administration of 1 ml of PCEC vaccine intramuscularly into the deltoid muscle on days 0, 3, 7, 14 and 28. The intradermal regimen consisted of administration of 0.1 ml of PCEC vaccine at two sites, one in each deltoid area, on days 0, 3, 7, 14 and 28, synchronous with the dates of the Essen regimen. These subjects now received PCEC vaccine (Rabipur, potency 8.5 IU per ml) by a different route; those who had received the primary vaccination by the intramuscular route now received it by the intradermal route and vice versa. The regimen of booster vaccination was as advocated by WHO, viz. 1 ml of PCEC vaccine by the intramuscular route or 0.1 ml (at two sites) of PCEC vaccine by the intradermal route on days 0 and 3. These subjects were followed up for a fortnight. Two blood samples were drawn from each subject, one on day 0 (for baseline titre) and the second on day 14 to measure the effect of this 2-dose booster series.

Estimation of rabies virus neutralizing antibodies (RVNA)

This was done by performing the rapid fluorescent focus inhibition test (RFFIT) as recommended by WHO, with some
modifications. The cell line used was baby hamster kidney (BHK) 21 (C13) and the virus used was challenge virus strain (CVS) adapted to grow in the same cells. The reciprocal of the highest dilution of serum showing 50% inhibition of the fluorescent foci was considered as the RVNA titre and was expressed in IU/ml. This was compared with an in-house reference preparation of rabies immune globulin (RIG) previously calibrated against a second international preparation of RIG having a potency of 30 IU/ml, obtained from the National Institute of Biologicals, UK. RVNA titres >0.5 IU/ml on day 14 are considered adequate for protection against rabies.

Statistical analyses

The statistical evaluation of RVNA response was measured by calculating the geometric mean titres, 95% confidence intervals, t-test and p value for significance.

RESULTS

The subjects were 20 healthy adult volunteers (14 men). The mean (SD) time lag between the primary and booster vaccinations for both the groups was 760 (41) days. The RVNA titres of these subjects are shown in Table I. All the 20 vaccinees had RVNA titres >0.5 IU/ml on day 14. There was about a 15-fold rise in the RVNA titres following PCEC booster vaccination both in the intradermal and intramuscular groups, which was found to be statistically significant (p<0.0001; Table I). None of the subjects experienced any adverse effects following PCEC booster vaccination by either route.

DISCUSSION

Currently, CCVs are administered in India by the intramuscular route and a patient requires 5 doses of vaccine as per the latest WHO guidelines. The availability of these vaccines in government hospitals is poor due to their high cost and insufficient production. Following the ban on the Semple vaccine there has been a steep rise in the demand for CCVs and the production capacity by various manufacturers, both government and private, is yet to meet this demand. If the IDRV is approved by the Government of India, it would offer some relief as vaccine usage and demand may drop by about one-fifth. However, the intramuscular usage of CCVs would continue in the private sector though IDRV may find a place in the government sector.

We foresee the need for a change or cross-over in the route of administration of the vaccine from the intradermal to the intramuscular route or vice versa when vaccinees for reasons of cost, non-availability, etc. shift between the government and private healthcare sectors. WHO does not recommend a change in route of administration of CCVs but due to prevailing local factors and personal difficulties people may resort to such practices. In this context, our study shows that a change in route of PCEC booster vaccination, irrespective of the route, produces a good RVNA response in the vaccinees.

Anamnestic response to antigen is a physiological phenomenon observed with many bacterial and viral vaccines. This physiological response can be conveniently used in the context of post-exposure rabies immunization, particularly in developing countries, where the availability and cost of vaccine is an important issue and re-exposure to animal bites is not uncommon. Several earlier studies have shown that there is a good anamnestic response to CCVs administered by both the intramuscular and intradermal routes. This effect was observed with pre-exposure and post-exposure vaccination with the presently available CCVs. A recent study from Thailand involving 118 rabies vaccine recipients, who had received pre- or post-exposure regimens with tissue culture rabies vaccines by intradermal or intramuscular schedules 5–21 years previously, showed an accelerated antibody response following 2 booster injections of 0.1 ml given intradermally. Indeed, a study has also shown that a very good anamnestic response could be obtained after administration of a single dose of CCV to people previously immunized even with nerve tissue vaccines. However, this study demonstrates that crossing over of the route when administering a booster dose will not affect the anamnestic immune response and subjects who have had an intramuscular course of vaccination can be given booster doses by the intradermal route and vice versa.

We are in the process of further assessing the rapidity of immune response following booster doses as this becomes important in endemic countries such as India where repeated exposures to animal bites is common and treatment strategies in such cases need to be properly evaluated, particularly in the light of the WHO recommendation that re-exposure cases need not be administered rabies immunoglobulin.

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REFERENCES


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