Title: ADVERSE EVENTS FOLLOWING THE USE OF TISSUE CULTURE ANTIRABIES VACCINES IN CHILDREN OF GWALIOR

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Keywords Dog bite, cell culture, Antirabies vaccine, Adverse effects

Abstract This Longitudinal study aims to assess the short term adverse events following the use of different tissue culture vaccines in children.

Original Article

Adverse Events following the use of tissue Culture Antirabies Vaccines in Children of Gwalior (M.P.)

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ABSTRACT

Research Question : What are the adverse reactions in children with tissue culture vaccines?

Objectives : This longitudinal study aims to assess the short-term adverse events following the use of different tissue culture vaccines in children

Setting : Anti rabies clinic of G. R. Medical College and J. A. Group of Hospital Gwalior

Participants : 1350 children of 1 to 12 years age group who attended the anti rabies clinic to seek post exposure treatment

Time period : Study was undertaken in 1 July 2011 to 30 June 2012.

Results : Around 1350 children of 1 to 12 years who attended the ARC took post exposure vaccination following bites by animals were prescribed the Tissue culture antirabies vaccines with the brand name Rabipur, Vaxirab, Abhayrab & Verorab. 1310 children of 1 to 12 years were followed for at least 3 times at total 5 doses. Events such as fever, pain & indurations at injection site, dizziness, nausea/abdominal discomfort and less common allergic/anaphylactic reactions were recorded. Surveillance was maintained on the referral ward for hospitalization due to anaphylaxis following vaccination. The incidence of adverse reactions is summarised as frequencies and percentage with 95% confidence interval (CI). The incidence of minor adverse reactions was 7.55% (95% CI 6.21-9.15) for injection site reactions, 5.27 %((95% CI 4.15-6.66) for indurations, 7.33% (95% CI 6.01-8.91) for fever, 5.04 %(95% CI 3.95-6.40) for Nausea/Abdominal discomfort, 3.36% (95% 2.48-4.52) for dizziness and moderate adverse events observed in 4 children 0.30% (95% 0.10-0.83) only. Moderate adverse events following cell-culture vaccine are more with purified duck embryo cell culture vaccine (Vaxirab) in comparison to others. Hence the health personnel involved in rabies control campaign should be aware of these adverse events.

Key Words : Dog bite, Cell-culture Antirabies vaccine, Adverse effects

INTRODUCTION

Vaccines are applied at Public Health Services in order to prevent disease and minimize health costs. Like any other pharmacological medication, vaccines also pose some risks and therefore quality control of the production process and of the product to be released is needed to prevent as much as possible any risks these immunizing substances may pose. A vaccine, like any medicine, is capable of causing serious problems, such as severe allergic reactions. The risk of a vaccine causing serious harm, or death, is extremely small. Serious problems from rabies vaccine are very rare[1].

In the case of control of human rabies in developing countries such as India, Several brands of rabies vaccine are available and reactions may vary between brands. Presently, a number of different types of 2nd generation tissue/cell culture vaccines are employed both for prophylaxis and treatment. They are purified chick embryo cell-culture vaccine (Rabipur), Purified Vero cell rabies vaccine (Verorab & Abhayrab) and Purified duck embryo vaccine (Vaxirab). In spite of improved tolerability and immunogenicity that were finally achieved with cell-culture vaccines there are adverse reactions also. Most commonly occurring are injection site reactions (e.g., erthyma, indurations and pain), fever, headache, nausea and rash and some rare adverse events like allergic/ anaphylactic had been considered[2].

Although vaccines produced in cell culture are available on the market, In any case, adverse effects

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Table 1
Adverse events during the Anti rabies vaccine schedule

Adverse Events	Children reporting events following Anti rabies vaccine under 'Essen'(IM) Schedule					Total (n=1310)	Percent of Children (95% CI)
	Day						
	0	3	7	14	28		
Local Reaction	51	22	09	11	06	99	7.55(6.21-9.15)
- Pain at injection site	35	21	06	04	03	69	5.27(4.15-6.66)
- Indurations	48	27	09	07	05	96	7.33(6.01-8.91)
Fever							
Nausea/Abdominal	29	24	07	04	02	66	5.04(3.95-6.40)
discomfort	19	14	06	02	03	44	3.36(2.48-4.52)
Dizziness	2	0	1	1	0	04	0.30(0.10-0.83)
Allergic/Anaphylaxis							

of the vaccine are known to occur and are a constant source of concern for the producing laboratories.

In view of this situation, the objective of the present study was to evaluate the quality control of the vaccines distributed by the Health Department. It was not our objective to evaluate the vaccines in terms of efficacy and potency in the protection against rabies, but rather in terms of the non-specific protein components they contain which may affect their immunogenic competence and which are probably responsible for the triggering of adverse effects after immunization in children because they are the most common victims of adverse reactions following tissue culture vaccines[3].

MATERIAL AND METHOD

This longitudinal study followed up children in the antirabies clinic over a period of four weeks for adverse events following the ARV. The study design was reviewed and approved by the ethical committee on research studies of G. R. Medical College, Gwalior. The study was undertaken in the antirabies clinic of JA Group of hospitals and G. R. Medical College, Gwalior of Madhya Pradesh State. Around 3260 people receive ARV for animal bite treatment as post exposure prophylaxis in which 1350 children of age 1 to 12 years were started vaccine with one of four cell-culture vaccine. Vaccination was carried out with Essen schedule (IM) of 5 doses 0,3,7,14 & 28 with intramuscular in deltoid[4]. Children of 1 to 12 years, who had received the complete 5 doses of vaccine in antirabies clinic from 1 July 2011 to 31 June 2012, were included in the study and 40 children were lost during follow up due to various reasons. So, study sample was of 1310 children.

This study was conducted to observe the immunogenicity and safety of the vaccine under clinical conditions in children 1 to 12 years of age. All the 1350 children attended our centre for taking post-exposure vaccination following bites by suspected rabid animals or contact with hydrophobia patients.

The vaccine reactions that were compared, were PCEC – Rabipur, Chiron Behring Vaccines Pvt. Ltd., PDEV – Vaxirab, Cadilla Healthcare Limited, PVRV – Verorab, Aventis Pasteur (Sanofi Pasteur) India Pvt. Ltd. and PVRV – Abhayrab, Human Biologicals Institute.

A total of five follow-up were made for the vaccinated children. The first follow-up was under 1 hour after the 0 dose. The remaining four follow-up were then made subsequently at after 30 minutes of 3, 7, 14 and 28 days. At least 3 follow up were made to the children. The first was on day 0 under one hour of vaccination considering the first dose as day0. The remaining two visits were then made in between 3, 7, 14 or 28th day as possible.

Presence of mild symptoms such as injection site reactions, fever, and nausea was recorded. Moderate symptoms suggestive of allergic/anaphylaxis was enquired. The incidence

Table 2
Adverse events following different cell culture vaccines

Adverse Events	Vaccine Type and Brand (Total n=1310)			Total (n=1310)
	PCEV (Rabipur) (n= 635)	PDEV (Vaxirab) (n= 545)	PVCV (Abhayrab/ Verorab) (n= 130)	
Local Reaction				
-Pain at injection site	38(5.98)	50(9.17)	11(8.46)	99
-Indurations	24(3.77)	37(6.78)	08(6.15)	69
Fever	39(6.14)	47(8.62)	10(7.69)	96
Nausea/Abdominal	23(3.62)	35(6.42)	08(6.15)	66
discomfort				44
Dizziness	17(2.67)	22(4.03)	05(3.84)	04
Allergic/Anaphylaxis	0(0.0)	4(0.73)	0(0.0)	

of adverse events is summarised as frequencies and percentages with 95% confidence interval (CI).

OBSERVATION

The number of 1 to 12 years old children followed up in the study following the cell-culture vaccination was 1310. The mean (SD) age was 7.55 (2.72) years, and included 889 boys (67.86%) and 421 girls (32.14%). The mean (SD) duration of follow-up of the vaccinated children was 4.60 (0.77) days. The children followed-up in all the five visits were 1012 (77.25%). The children followed-up at least three visits were 228 (17.40%) and 40 (2.96%) were lost to follow-up.

The frequency of adverse events observed is presented in Table 1. Pain at the injection site was the commonest event reported followed by fever lasting for 3 days. Events related to allergic/ anaphylaxis was reported only with the PDEV (Vaxirab) (Table 2).

CONCLUSION

Children are the most common victims of dog bites around 70% and requiring medical attention involve children suffer more with adverse reaction following post exposure anti rabies treatment[5].

The Cell Culture Vaccines are widely accepted as the least reactogenic rabies vaccines available today. However, few studies have now shown that adverse effects can be either general in nature or allergic in origin. The general adverse reactions include sore arm, headache, malaise, nausea, fever and localised oedema at the site of injection. Symptomatic treatment may be needed[6].

This study shows that minor adverse events are common following immunisation with the cell-culture anti rabies vaccines in 1 to 12 years children. The incidence of pain at the injection site in 99 (7.55%), fever reported was 96 (7.33%), in durations at the injection site in 69(5.27%), nausea/abdominal discomfort and dizziness were found respectively in 66 (5.04%) and 44(3.36%) of the vaccinated children. (Table1) while moderate systemic hypersensitivity reaction such as anaphylaxis occurred in 4 (0.3%) children and all were found by the duck embryo cell culture-'Vaxirab' (PDEV).

In a post marketing surveillance study found 4% mild to moderate clinical reaction with cell culture vaccine include pain and tenderness and indurations at the site of injection and fever while two children developed hypersensitivity reactions[7]. Amlan Goswami[2] had reported that modern CCVs are considered to be safe and well tolerated, although reported reactions rates to primary immunization have varied with the different types. Following IM immunization with the CCVs, mild and self limiting local reactions such as pain at the site of injection, redness and swelling occur in 21-74%. Mild systemic reactions such as fever, dizziness and gastrointestinal symptoms occur in 5-40%, and systemic hypersensitivity following booster injection in 6% of vaccine, but are less common following primary immunization. With chick embryo and Vero cell base vaccines the rate of local and mild reactions are similar to other type of vaccines, but no systemic reactions have been reported. Shyam C also observed very few adverse effects like Local: pain, erythema, swelling, or indurations (in 15 to 24 per cent of recipients), Itching, Headache, malaise, myalgia, or dizziness (10 to 25 percent), Gastrointestinal symptoms (in less than 10 percent); and allergic reactions during primary vaccination (in 0.1per cent)[8].

In present study moderate systemic hypersensitivity reaction such as anaphylaxis occurred in 4 (0.3%) children and all were found by the purified duck embryo vaccine 'Vaxirab' (PDEV) (Table 2). Similarly Garner et al[8] had observed in studies with vaccines produced from duck embryos, 5% of the vaccinated population presented sensitivity and allergy to the vaccine this is a high and significant rate for a population of 59,000 persons vaccinated per year predicts hypersensitivity reactions with DEV like our study.

Rupprecht CE (2004)[10] had also found that cell culture rabies vaccine used today had a some side effects, they are generally mild: sore arm(15-25%), headache (5-8%) or nausea and vomiting (2-5%). The severe side effects has also been reported to follow vaccination in about one of every 10,000 doses of vaccine given.

The different rate of adverse events observed in different cell-culture study and in the present study

could be due to the different age groups studied and to the estimation of the events in the present study which is based on symptoms.

It must be noted that the sample chosen for the present study was to identify the mild and moderate adverse events and not intended to identify the rare serious hypersensitivity reactions.

SUMMARY

The prevalence of local and mild systemic adverse reactions to PCEC, PDEV and PVCV based vaccines such as 'Rabipur', 'Vaxirab" and 'Abhayrab / Verorab' were more or less similar but systemic hypersensitivity had been reported only with PDEV-'Vaxirab' Although serious systemic, anaphylactic, or neuroparalytic reactions are rare during and after the administration of rabies vaccines but such reactions pose a serious dilemma for the patient and the attending physician. A patient's risk of acquiring rabies must be carefully considered before deciding to discontinue vaccination. Advice and assistance on the management of serious adverse reactions for persons receiving rabies vaccines may be sought from the state or local health department.

All clinically significant adverse events occurring following administration of rabies biologics should be reported to the Vaccine Adverse Event Reporting System (VAERS), even if causal relation to vaccination is not certain. Although VAERS is subject to limitations common to passive surveillance systems, including underreporting and reporting bias, it is a valuable tool for characterizing the safety profile of vaccines and identifying risk factors for rare serious adverse reactions to vaccines[11].

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