Title: Adverse Events following the use of tissue Culture Anti-Rabies Vaccines at anti Rabies clinic of J.L.N. Medical College, Ajmer

Author: **Dr. (Mrs.) Renu Bedi1, Dr. Vinod Kumar Saini2, Dr. Aleefah K S3**

1. Dr. (Mrs.) Renu Bedi, MD (Community Medicine), Senior Professor & Head, Department of Community Medicine, Jawaharlal Nehru Medical College, Ajmer, India.
2. Dr. Vinod Kumar Saini, MBBS, 2nd year PG student, Department of Community Medicine, Jawaharlal Nehru Medical College, Ajmer, India
3. Dr. Aleefah K S. MBBS, 1st year PG student, Department of Community Medicine, Jawaharlal Nehru Medical College, Ajmer, India.

Keywords Dog bite, Cell-culture Anti rabies vaccine, Adverse effects.

Abstract

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ORIGINAL RESEARCH ARTICLE

Adverse Events following the use of tissue CultureAnti-Rabies Vaccines at anti Rabies clinic of J.L.N. Medical College, Ajmer

Dr. (Mrs.) Renu Bedi[1], Dr. Vinod Kumar Saini[2], Dr. Aleefah K S[3]

[1]Dr. (Mrs.) Renu Bedi, MD (Community Medicine), Senior Professor & Head, Department of Community Medicine, Jawaharlal Nehru Medical College, Ajmer, India.

[2]Dr. Vinod Kumar Saini, MBBS, 2nd year PG student, Department of Community Medicine, Jawaharlal Nehru Medical College, Ajmer, India.

[3]Dr. Aleefah K S. MBBS, 1st year PG student, Department of Community Medicine, Jawaharlal Nehru Medical College, Ajmer, India.

Abstract

Research Question: Are there any significant adverse events with tissue culture vaccines at Anti Rabies Clinic? Objectives : To assess the short-term adverse events of tissue culture ARV to be studied by longitudinal study. Setting : Anti rabies clinic of the department of community medicine of the tertiary care hospital J.L.N. Medical Ajmer. Participants: 6739 new beneficiary of all ages who attended the anti-rabies clinic to seek post exposure treatment. Time period: Study period was in 1 January to 31 December 2019. Results: 6739 new beneficiary following animal bites who attended the ARC took post exposure vaccination of Tissue culture anti rabies vaccines which is purified inactivated rabies vaccine. Presently two different types of tissue/cell culture vaccine have been supplied by government. These are from Serum Institute of India Pune-purified rabies antigen(Strain-Rabies virus Pitman-Moore Strain 3218-VERO adapted and grow on vero cells, inactivated by using β-propiolactone not less than 2.5 IU per dose of 1 ml/ 0.1ml) and other from human biological institute Tamil Nadu-purified lyophilized rabies antigen derived from rabies virus (L. Pasteur 2061/Vero strain propagated in vero cells) inactivated potency: > or equal to 2.5 IU. All were followed for total 5Doses in IM (ESSEN Regimen)and 4 doses in ID (THAI RED CROSS). Complaint such as fever, pain & in durations at injection site, dizziness, nausea/abdominal discomfort and less common allergic anaphylactic reactions were recorded. The beneficiary with complaint of anaphylaxis due to vaccine were referred for hospitalization of they were followed regularly. All the adverse reactions are summarised as frequencies and percentage. The incidence of minor adverse reactions was 498 (07.3%, 95% CI- 6.68%- 7.92%)for injection site reactions, 296 (4.39%, 95% CI-4.44%-5.42%) for pain at injection site, 478 (07.09%, 95% CI-7.70%-6.47%) for in durations, 13 (0.192%, 95% CI-0.086%-0.296%) for fever, 270 (04.00%, 95% CI- 3.532%-4.467%) for Nausea/Abdominal discomfort, 13 (0.192%, 95% CI- 0.0874%-0.296%) for dizziness. It is imperative that the health personnel involved in rabies control programme at health centre or in campaign should be aware of these adverse events so as to follow and provide the comprehensive management.

Key words: Dog bite, Cell-culture Anti rabies vaccine, Adverse effects

Introduction:

Rabies is one of the most deadly infectious disease that has a high case fatality rate. It has a world wide distribution with few exceptions, such as Japan, Antarctica, and Singapore.[1] Rabies is endemic in dogs in most South-East Asian countries. Most cases occur in Africa and Asia, in which China has the second largest population of human rabies death, only after India. (2)

The rabies virus is transmitted through exposure to saliva from an infected animal bite, such as dogs, bats, skunks, raccoons, and cats. It is rarely transmitted by inhalation of aerosolized rabies virus. (22) Few cases have been reported from infected organ/tissue/ corneal transplant or where broken skin or mucous membranes come into contact with any secretion of the person with rabies, whether humans or mammals. (6)

In India, dogs are responsible for about 95% human rabies, followed by cat 2%, jackals, mongoose and others 1%. Therefore,

***Corresponding Author** : Dr. (Mrs.) Renu Bedi, Senior Professor & Head, Department of Community Medicine, Jawaharlal Nehru Medical College, Ajmer, India. Email: dr.renu.bedi@gmail.com

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the disease is mainly transmitted by the bite of a rabid dog. (6)

Deaths due to hydrophobia occur mainly in those who cannot access timely and effective PEP. Prompt PEP following severe exposures is 100% effective in preventing rabies. (4)

The incubation period is typically 1–3 months, but can vary from a few days to more than 1 year. (5)

Vaccines are administered at Public Health facilities 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 minor, moderate and 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. (6)

The CCV's 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. Mild systemic adverse events following immunization (AEFI). Included headache, malaise, nausea and fever. Symptomatic treatment may be needed. Minor and transient erythema, pain and/or swelling may occur at the site of injection, particularly following intradermal administration. (6) Once AEs occurred, immediate medical treatment and appropriate change of vaccine and vaccination schedule were of significance. It was also important and challengeable to determine the relationship among adverse reactions, vaccines residues and laboratory tests for patients, to choose a proper vaccine shifting from one brand/ type of CCV's to another brand/type and should not be encouraged in routine practice, however, under unavailable circumstance, available brand/type may be used to complete PEP in resumed vaccination, to avoid the reoccurrence of AEs and to ensure adequate immune response. (7) Severe adverse events (AEs) following post-exposure rabies vaccination had been occasionally described in previous studies. Serious AEFI, many of allergic or neurological nature occur rarely. (6)

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 some adverse reactions also. Most commonly occurring at injection site reactions (e.g., erythema, indurations and pain), fever, headache, nausea and rash and some rare adverse events like allergic/ anaphylactic have been considered. (8)

Rabies vaccine can be administered by intradermal route. In Feb. 2006 as per WHO recommendations, results of clinical trial on safety, efficacy and feasibility DCGI approved the use of safe efficacious and economical intradermal (ID) route of inoculation of Rabies vaccines. (6,9, 10)

National Rabies Control Program Strongly advocates use of intradermal route of Rabies vaccine. The use of the ID route leads to considerable saving in the total amount of vaccine needed to complete PrEP or PEP, thereby reducing the cost of active immunization. (6) As the volume of an ID vaccine dose is lesser then that of an IM dose, the intradermal route is especially suitable for treating many patients at the same centre or where attendance of animal bite cases is more. However entire vial content should be utilized within 6 hours after reconstitution of the vaccine. (6) However, intradermal administration is not the preferred route of Rabies vaccine administration for immune-compromised individuals or individuals receiving Chloroquine, Hydroxy chloroquine or long-term corticosteroid or other immuno suppressive therapy. (6)

Adverse event may include mild itching, erythema, rarely body ache and fever that are usually self-limiting. Symptomatic management using analgesics and antihistamines may be needed. (6)

As with all other immunization, vaccinated persons, vaccinated persons should be kept under medical supervision for at least 30 minutes following vaccination. Previous reaction to any component is a contraindication to the use of the same vaccine preparation for PEP or (PrEP) pre-exposure prophylaxis. (6)

In view of this situation, the objective of the present study was to find out 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.

MATERIAL AND METHOD:

This longitudinal study followed up beneficiary in the anti-rabies 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 J.L.N. Medical College, Ajmer. The study was undertaken at anti-rabies clinic under Department of Community Medicine of J.L.N. Medical College Ajmer of Rajasthan State. Around 6739 people receive ARV for animal bite treatment as post exposure prophylaxis

were started vaccine with purified vero cell rabies vaccine. Vaccination was caried out with Essen schedule (IM) of 5 doses 0,3,7,14,& 28 with intramuscular in deltoid and in ID (THAI RED CROSS) 4 doses 0,3,7,28. Beneficiary of who had received the complete vaccine in anti-rabies clinic from 1 January 2019 to 31 December 2019, were included in the study.

Result:

A total of five follow-up visits were planned for the vaccinated beneficiary. The first follow-up was within one hour of vaccination considering the first dose as day 0. The remaining three/four follow up were then made subsequently at 3, 7, 14 and 28 days. The remaining three/four visits were then made at 3, 7,14 or 28 days respectively according to schedule of vaccine administration.

Table 1:Adverse event during the Anti-Rabies vaccine schedule

Adverse Event	Beneficiaries reporting events following anti rabies vaccine under I/M and I/D schedule									Total	
Day of vaccination	0		3		7		14	28			
Route	IM	ID	IM	ID	IM	ID	IM	IM	ID	IM	ID
Local Reaction	102	196	30	70	17	35	40	2	6	191	307
Pain at injection site	80	99	16	32	10	27	30	0	2	136	160
Induration	142	107	66	102	15	26	12	1	7	236	242
Fever	2	5	1	2	0	2	1	-	-	4	9
Nausea/ Abdominal discomfort	70	98	15	33	10	11	18	6	9	119	151
Dizziness	1	6	0	3	0	2	1	-	-	2	11
Allergic/Anaphylaxis	-	-	-	-	-	-	-	-	-		
Total	397	511	128	242	52	103	102 (1.51%)	9	24	688	880
Total	908 (13.47%)		370 (5.49%)		155 (2.30%)		102 (1.51%)	33 (0.48%)		1568 (23.26%)	

Table 2: Distribution of cases animal bite cases according to age group and gender

Age group	Male (%)	Female (%)	Total (%)
0-5 yr	460 (6.82%)	238 (3.53%)	698 (10.35%)
5-15yr	130390 (19.33)	470 (6.97%)	1773 (26.30%)
15-60 yr	2660 (39.47%)	1022 (15.16%)	3682 (54.63%)
>60 yr	366 (5.43%)	220 (3.26%)	586 (8.69%)
Total (%)	4789 (71.06%)	1950 (28.93%)	6739 (100%)

Table 3: Distribution of new cases according to the type of biting animals

Year	Dog (%)	Monkey (%)	Cat (%)	Pig (%)	Others (%)	Total (%)
2018	6132(91%)	208(3.1%)	330(4.9%)	33(0.5%)	36(0.5%)	6739(100.00%)

Table 4: Distribution of new cases according to category of bite

Category of Bite	No. of Cases	Percentage
Category I	357	5.3%
Category II	4717	70%
Category III	1665	24.7%
Total	6739	100.00%

A total of 6739 beneficiaries of animal bite reported in this one-year study. Majority of the new cases were male 4789 (71.06%) and remaining were female 1950 (28.93%). 698 (10.35%) cases were in the age group of 0-5 years, 1773 (26.30) of the beneficiaries were 5-15 year of age and 3682 (54.63%) were in age group 15-60 year and 586 (8.69%) patients were senior citizen (above 60 year of age). Category II bite being the common 4717 (70%) and the most commonly affected. Dog bite was responsible for 6132 (91%), cat bite 330(4.9%), monkey bite 208 (3.1%), pig 33 (0.5%) and others in 36 (0.5%) of the animal bite cases.

6739 beneficiary following animal bites who attended the ARC took post exposure vaccination by the Tissue culture anti rabies vaccines of the human biological institute Tamil nadu (govt. supply). All were followed for total 5 Doses in IM (ESSEN Regimen) and 4 doses in ID(THAI RED CROSS). Complaint such as fever, pain & indurations at injection site, dizziness, nausea/abdominal discomfort and less common allergic anaphylactic reactions were recorded. The beneficiary with sign and symptoms of anaphylaxis due to vaccine were observed in the OPD for 30-40 minutes, they were also monitored in their follow up visits. All the adverse reactions are summarised as frequencies and percentage. The incidence of minor adverse reactions was 498 (07.3%) for injection site reactions, 296(4.39%) pain at injection site, 478(07.09%) indurations, 13 (0.192%) fever, 270(04.00%) Nausea/Abdominal discomfort, 13(.192%) dizziness. The health personnel involved in rabies control campaign should be aware of these adverse events so as to this adverse reaction and monitor the beneficiaries.

Discussion:

Slight side effects like fever, weakness, headache, nausea, local pain and swelling usually occurred in patients following rabies vaccination[16]. Mostly, these symptoms were transient and could be relieved naturally. In Shietal.[17] a multi-centre study documented those adverse reactions were highest after first/second injection (8.9%), progressively lower in third (8.5%), fourth (5.9%), fifth (2.3%) injection and most of them were non-serious. Similarly in our Study adverse reaction were highest in first 13.47%, followed by second 5.49%, third 2.30%, fourth 1.51% and fifth 0.48%.

In present study adverse reaction after first dose was 13.47% and after second dose was 5.49% and progressively lower in third 2.30% and fourth 0.48%. Similar to the Shichun Huang et al[14] China, a multi-center study documented that in Essen route, adverse reactions were the highest reported in first/second injection (8.9%), progressively lower in third (8.5%), fourth (5.9%), injection and most of them were non-serious.

Severe allergic reactions related to vaccines were rarely reported and it was of difficulty and urgency to figure out the specific reason that cause AEs. in a previous study.15 Also in our study no any severe allergic reaction reported.

In the present study 4789 (71.06%) males and 1950 (28.93%) females were exposed to animal bite and the male to female ratio was found to be 3.2:1. This may be due to the fact that men are more likely to go out their home for work as compared to female in this area. Similar finding were reported by Bedi et al.[18] and Patil et al.[17] and Shah et al.[19] where the male and female were 71.69% and 73.94% and 76% respectively.

In our study, new cases were maximum due to Category II bite 4717 (70%) which was similar to study done by Bedi et al.[18] (71.16%) and Agarwal and Reddaiah et al. [19] (80%)

Our study also showed that majority 6132 (91%) were victim of dog bite followed by cats (4.9%), monkeys (3.1%), pigs (0.5%) and others (0.5%). The finding is similar to the other study done by Bedi et al.[18] and Goglas et al.[20] and national guidelines for rabies prophylaxis 2019[11] and Park K. textbook (25th edition)[21] where 90.5% and 89.1%, 95% and 90% were dog bites respectively.

Summary:

The prevalence of and local adverse reaction to (human biological institute Tamil nadu (govt. supply) are similar to adverse reactions of other tissue culture vaccine like Rabipur, Vaccirab, Vero-rab, Abhayrab. No systemic adverse reaction has been found in our study. Systemic anaphylactic reactions are rarely observed with tissue culture vaccine but such reactions require

impending attention by the treating health personnel. Need to discontinue the vaccine after any serious systemic reaction must be carefully considered since the disease carries 100% fatality.

Conclusion: Clinicians should be watchful of adverse effects in prescribing rabies vaccination especially in patients with a history of allergic conditions. A thorough clinical assessment should be made to weigh benefits versus risks of proceeding with rabies vaccination, bearing in mind that the disease is deadly. The majority of AEFI cases were common adverse reactions, while the serious vaccine reactions caused by vaccines were negligible. Increase sensitivity of AEFI surveillance may reduce the incidence of developing serious AEFI cases and should be reported to the vaccine adverse event reporting system (VAERS), even if it is a rare observation. This system is a useful tool for enumerating the safety profile of vaccine and identification of rare serious adverse risk events to tissue culture vaccines.

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