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Pre-exposure prophylaxis against rabies in children

Safety of purified chick embryo cell rabies vaccine (Vaxirab N) when administered by intradermal route

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Animal bites in humans are a public health problem. Children are the most frequently exposed, representing 50% of human exposures in canine rabies infected areas. Pre-exposure vaccination using cell culture vaccines is a safe and effective method of preventing rabies among children in these highly endemic regions. The development of immunological memory after pre exposure vaccination has established long lasting immunity against rabies in humans. The present study assessed the safety of Purified Chick Embryo cell Rabies Vaccine (Vaxirab N) administered as a three-dose intradermal pre-exposure regimen on days 0, 7, and 21 in healthy volunteered children of 5–10 y age group from an urban poor locality in Bangalore, India. One hundred fifty three apparently healthy children of both sexes between 5 and 10 y of age were enrolled in the study and 123 (80.4%) completed all three doses. A total of 405 doses of intradermal vaccine was administered, among which 25 adverse reactions were reported from 17 children. The adverse reactions were pain at the injection site 15 (3.7%), redness 2 (0.5%), itching at the site of injection 1 (0.2%), fatigue 1 (0.2%), fever 3 (0.7%), myalgia 2 (0.5%) and allergy 1 (0.2%). All reactions subsided without any complication. In conclusion, pre exposure vaccination against rabies is a useful tool for protecting children living in highly endemic regions and Vaxirab N has proved to be safe and well tolerated by intradermal route among children.

Introduction

Rabies is a viral zoonosis that occurs in >100 countries in the World. It is transmitted to humans and other animals through close contact with saliva from infected animals i.e., bite, scratches, licks on broken skin and mucous membranes. Although a number of carnivorous animals serve as natural reservoirs, dogs are the main source of human infections and poses a potential threat to >3.3 billion people Worldwide.[1]

In India, animal bites in humans are a public health problem and an estimated 17.4 million animal bites occur annually.[2] In urban areas, the disease is mainly transmitted by dogs, being responsible for 96% of animal bite cases.[3] Children are the most frequently exposed age group, representing 50% of human exposures in canine rabies infected areas.[4] Children playing outdoors are particularly vulnerable to dog bites, since unvaccinated community dogs are commonly observed on the streets and on or around public places and school playgrounds. They are more likely to be bitten by dogs, and are also more likely to be severely exposed through multiple bites in high-risk sites on the body. Severe exposures make it more difficult to prevent rabies unless access to good medical care is immediately available. Therefore, pre exposure prophylaxis (PrEP) in these children would prevent a number of unnecessary deaths due to rabies.

Pre-exposure rabies vaccination using cell culture vaccines is a safe and effective method of preventing rabies in children. The development of immunological memory after pre exposure vaccination with cell culture vaccines has established long lasting immunity against rabies in humans. Individuals who had received their primary series 5–21 y previously showed good anamnestic responses after booster vaccination.[5] Long-term immunity is also achieved with intradermal immunization and may persist even when antibodies are no longer detectable. The ability to develop an anamnestic response to a booster vaccination is related neither to the route of administration of the initial series (intramuscular or intradermal) nor to whether the patient has completed a pre-exposure or post-exposure series.[6]

Pre exposure prophylaxis in children living in areas of high risk of exposure to rabies would reduce the number of vaccine booster doses required to only two on days 0 and 3. It eliminates the need to administer rabies immunoglobulin (RIG) which is costly and may not be available at all time/place after an exposure

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Table 1. Socio demographic characteristics of children

Socio demographic characteristics		Values
Mean age (± SD) in years		7.29 ± 2.7
Sex	Male	93 (60.8%)
	Female	60 (39.2%)
Education	Primary school	153 (100%)
Socio economic status	Low income	140 (91.4%)

Table 2. Compliance to vaccination among study subjects

Dose	Number	Percentage
1	153	100.0
2	129	84.3
3	123	80.4

has occurred any time later and therefore, WHO recommends vaccines produced in cell culture to be used for pre exposure vaccination of humans.[4]

This study assessed the safety of Purified Chick Embryo cell Rabies Vaccine (Vaxirab N) which is a licensed anti rabies vaccine by National authorities for use by both intramuscular and intradermal route and available in the market. The study vaccine has already been evaluated for safety and immunogenicity in other clinical trials conducted in India as pre and post exposure prophylaxis both by intramuscular and intradermal route and is found to be safe and immunogenic. The study vaccine is administered as a three-dose intradermal pre-exposure regimen on days 0, 7, and 21 in healthy volunteered children of 5–10 y age group from an urban poor locality in Bangalore, India.

Results

Socio-demographic profile. One hundred and 50 three children were included in the study. Among them 93 (60.8%) were boys and 60 (39.2%) girls. Their mean age was 7.29 y (range 5–10 y). All the children were going to primary school. Majority of the children i.e., 110 (71.8%) belonged to class IV socio economic status and were economically poor (**Table 1**).

Compliance for full course of vaccination. Among 153 children who received 1st dose of pre exposure vaccination, 129 (84.3%) took the 2nd dose and 123 (80.4%) completed all three doses according to the recommended PrEP schedule (**Table 2**). The reason for dropout was children went out of station since there were holidays to the school during the subsequent visits.

Safety. All 153 children were included in the safety analyses, having received at least one dose of vaccine. A total of 405 doses of intradermal PCECV (Vaxirab N) was administered, among which 25 adverse reactions were reported from 17 children. Among them, 18 were local and 7 systemic reactions (**Table 3**). All the reactions were mild and subsided without any complications.

The most common solicited adverse reaction to the injections was pain at the injection site 15 (3.7%). Other reactions included redness 2 (0.5%), itching at the site of injection 1 (0.2%) and fatigue 1 (0.2%) which subsided without any medication. Children having fever 3 (0.7%), myalgia 2 (0.5%) and allergy 1 (0.2%) took basic medications such as anti-inflammatory and antihistamines and were relieved of their symptoms within one day. None of the study subjects dropped out due to adverse reactions.

Discussion

Rabies can be effectively prevented by means of pre-exposure or post-exposure prophylaxis, but still continues to pose a significant public health problem in many countries. Pre-exposure prophylaxis against rabies is a valuable tool recommended for anyone who will be at continual, frequent or increased risk of exposure to the rabies virus, either as a result of their residence or occupation and specially in children who are the most frequently exposed age group, representing 50% of human exposures in canine rabies infected areas.[4]

WHO recommends that children living in highly endemic regions be considered for PrEP, since they are at particular risk because of their playful nature and unable to protect themselves when they are attacked by dogs. Children playing outdoors are particularly vulnerable to dog bites since unvaccinated community dogs are commonly observed on the streets and on or around public and school playgrounds. Furthermore, children may not report animal bites to their parents or may delay reporting of bites. Since young children constitute the majority of the victims of rabies and are most likely to suffer unreported or unknown exposures, implementation of PrEP in children would prevent a number of unnecessary deaths in this vulnerable population.

Re-exposures are also common in childhood and it is up to 15% in rabies endemic areas,[7] but if a child has received PrEP any time in the past, there is no need for RIG which is costly and may not always be always available; instead only two booster doses of anti-rabies vaccine on days 0 and 3 is recommended.[8]

The cost of cell culture vaccines (CCVs) for intramuscular administration limits their widespread use in many areas where canine rabies is prevalent. Intradermal administration of CCVs offers an equally safe and immunogenic alternative reducing the volume used and the direct cost of vaccine by 60–80% compared with standard intramuscular vaccination.[1] The use of intradermal route leads to considerable savings in terms of the total amount of vaccine needed for a full pre-exposure vaccination thereby, reducing the cost of active immunization.

Pre exposure vaccination has also been shown to be safe and effective in children and even with 5 y follow up and showed that co-administration of rabies PrEP with DPT and inactivated poliomyelitis vaccine at 2 and 4 mo and 1 y, elicited satisfactory antibody titers to all antigens with no interference with other antigens used.[9]

Similarly, previous studies among children have demonstrated that pre-exposure prophylaxis using Purified Chick Embryo Cell Vaccine (PCECV) is safe and well tolerated by school going children who will be at continual, frequent or increased risk of exposure to the animal bites.[10,11]

The present study was done in an urban poor locality among school going children who are at frequent and continual risk of exposure to dog bite because of their playful nature, and protecting these poor children against rabies was the novel intention of our study.

The study vaccine has been evaluated for safety and immunogenicity following pre-exposure vaccination by intramuscular route and post-exposure administration both by intramuscular route and intradermal route and is found to be safe and immunogenic with the rabies neutralizing antibody (RVNA) assessed by rapid florescent focus inhibition test (RFFIT) at WHO Collaborating Center for Reference and Research on Rabies, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India. The RVNA titers obtained by subjects from day 14 onwards was much greater than the required level of 0.5 IU/mL and adequate titers were present on day 180.[12,13] The present study also showed that Purified Chick Embryo Cell Vaccine (Vaxirab N) when administered as pre-exposure prophylaxis by intradermal route in children aged between 5 and 10 y is safe and well tolerated with minimal adverse reactions such as pain at the site of injection, redness and itching at the site of injection which subsided without any medication. Systemic reactions like fever and myalgia were relieved within a day with basic medication. None of the study subjects dropped out due to adverse reactions.

In conclusion, pre exposure vaccination against rabies is a useful tool for children living in highly endemic regions. PrEP using cell culture vaccines (PCECV) has proved to be safe and well tolerated by intradermal route; this may be considered for all children in these regions as it is intended to protect against rabies and saves the lives of the vulnerable population. WHO encourages the implementation of carefully designed studies on the feasibility, cost-effectiveness and long-term impact of incorporating CCVs into the immunization programs of infants and children where canine rabies is a public health problem.[14] Pre exposure prophylaxis also reduces the number of vaccine booster doses required and eliminate the need to administer rabies immunoglobulin after a re-exposure any time later, which is not so uncommon in children especially in rabies endemic areas.

Materials and Methods

This study was conducted in accordance with ICH - GCP norms. The study was conducted from September 2012 to October 2012 as a part of World Rabies Day, 2012 activity. The study subjects included children of an urban poor locality which comes under the community practice area of the Department of Community Medicine, Kempegowda Institute of Medical Sciences (KIMS), Bangalore, India. Prior to the vaccination, all the children and their parents were given health education regarding prevention of rabies and importance of pre-exposure vaccination through door to door health education and distribution of handouts, school health education and public announcements. All children who came with their parents voluntarily to the vaccination site were included in the study. The pre-exposure vaccination was done at the community urban health center of KIMS, Bangalore.

Table 3. Adverse reactions following vaccination

Adverse reactions	Day 0	Day 7	Day 21	Total
Local				
Pain	2	12	1	15
Redness	1	1	-	2
Itching	-	1	-	1
Systemic				
Fever	-	3	-	3
Myalgia	1	-	1	2
Allergy	-	1	-	1
Fatigue	1	-	-	1
Total	**5**	**18**	**2**	**25**

Subjects. One hundred and 53 apparently healthy children who had not received any anti rabies vaccination in the past or not allergic to egg protein or to any of the study drug components, of both sexes between 5 and 10 y of age were enrolled in the study.

Methods. The socio demographic profiles of all the study children were recorded. All the subjects were vaccinated free of charge with three intradermal pre-exposure vaccination on days 0, 7, and 21. A single dose of 0.1 ml injection was administered on all the three days intra dermally over the deltoid muscle by the trained doctors. The vaccine administered was purified chick embryo cell rabies vaccine (Vaxirab N) manufactured by Zydus Health Care Ltd., Ahmedabad, India having a potency of > 2.5 IU per single intramuscular dose and procured from the marketed batch having the batch number CK101 and expiry date Oct 2013.

A physician was designated to assess the tolerability/reactogenicity/safety parameters among all the vaccinated children. Subjects were observed for 30 min after vaccine administration for any adverse drug reactions. During that time, a short public video on prevention of rabies, produced by Rabies in Asia (RIA) foundation was shown in the waiting room for both the children and their parents. After 30 min, the data regarding safety was recorded by asking both the children and their guardians regarding any reactions and then transcribed to the case record form. Local and systemic reactions were recorded which included pain at the injection site, redness, swelling, fatigue, headache, fever, myalgia, systemic allergic reactions and any other adverse drug reactions. The adverse drug reactions were also collected throughout the study period, when they came for subsequent vaccination and two weeks after the last dose.

A rabies pre-exposure prophylaxis certificate was completed indicating the type of vaccine, route of administration and vaccine regimen used and given to all the vaccinees who had completed three doses of pre-exposure vaccination.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. World Health Organization. Rabies vaccines: WHO position paper, Weekly Epidemiological Record, No. 32, 2010, 85:309-20.
2. Sudarshan MK, Madhusudana SN, Mahendra BJ, Rao NS, Ashwath Narayana DH, Abdul Rahman S, et al. Assessing the burden of human rabies in India: results of a national multi-center epidemiological survey. Int J Infect Dis 2007; 11:29-35; PMID:16678463; http://dx.doi.org/10.1016/j.ijid.2005.10.007
3. National Institute of Communicable Diseases, Ministry of Health & Family welfare. National guidelines for rabies prophylaxis and intra-dermal administration of cell culture rabies vaccines. New Delhi, India. 2007.
4. World Health Organization. WHO expert consultation on rabies. TRS 931. WHO Geneva 2005.
5. Suwansrinon K, Wilde H, Benjavongkulchai M, Banjongkasaena U, Lertjarutorn S, Boonchang S, et al. Survival of neutralizing antibody in previously rabies vaccinated subjects: a prospective study showing long lasting immunity. Vaccine 2006; 24:3878-80; PMID:16530893; http://dx.doi.org/10.1016/j.vaccine.2006.02.027
6. Gherardin AW, Scrimgeour DJ, Lau SC, Phillips MA, Kass RB. Early rabies antibody response to intramuscular booster in previously intradermally immunized travelers using human diploid cell rabies vaccine. J Travel Med 2001; 8:122-6; PMID:11468113; http://dx.doi.org/10.2310/7060.2001.24445
7. Sudarshan MK, Ravish HS, Ashwath Narayana DH. Time interval for booster vaccination following re-exposure to rabies in previously vaccinated subjects. Asian Biomedicine 2011; 5:589-93
8. World Health Organization. Human and dog rabies prevention and control, Report of the WHO/Bill & Melinda Gates foundation consultation, Annecy, France, 2009.
9. Lang J, Duong GH, Nguyen VG, Le TT, Nguyen CV, Kesmedjian V, et al. Randomised feasibility trial of pre-exposure rabies vaccination with DTP-IPV in infants. Lancet 1997; 349:1663-5; PMID:9186385; http://dx.doi.org/10.1016/S0140-6736(96)10085-4
10. Shanbag P, Shah N, Kulkarni M, Juvekar M, Madhusudana SN, Vakil HB, et al. Protecting Indian schoolchildren against rabies: pre-exposure vaccination with purified chick embryo cell vaccine (PCECV) or purified verocell rabies vaccine (PVRV). Hum Vaccin 2008; 4:365-9; PMID:18398307; http://dx.doi.org/10.4161/hv.4.5.5987
11. Kamoltham T, Thinyounyong W, Phongchamnaphai P, Phraisuwan P, Khawplod P, Banzhoff A, et al. Pre-exposure rabies vaccination of children in Thailand using Purified Chick Embryo Cell Rabies Vaccine intra dermally is immunogenic and safe. J Pedod 2007; 151:173-7; http://dx.doi.org/10.1016/j.jpeds.2007.02.044
12. A clinical evaluation of safety and immunogenicity of purified chick embryo cell rabies vaccine (Vaxirab N) administered intradermally as pre exposure prophylaxis in healthy volunteers. 2010, India.
13. A clinical evaluation of safety and immunogenicity of purified chick embryo cell rabies vaccine (Vaxirab N) administered intramuscularly as post exposure prophylaxis in animal bite cases. 2011, India.
14. Current strategies for human rabies pre and post-exposure prophylaxis 2010, Available at: www.who.int/rabies/human/WHO_strategy_prepost_exposure/en/html accessed on: 12.01.2013.