Title: SAFETY OF EQUINE RABIES IMMNUNOGLOBULIN IN CHILDREN

Author: **Ravish HS1, Rupsa Banerjee2, Narayana Ashwath DH3. Rachana AR4**

1. Associate Professor.
2. Post Graduate Student.
3. Professor & Head.
4. Post Graduate Student

Department of Community Medicine, Kempegowda Institure of Medical Science, Bangalore

Keywords Anti rabies vaccine, children, equine rabies immunoglobulin, post exposure prophylaxis, safety abstract

Abstract In India, animal bites are a major public problem an estimated 17.4 million animal bites occur annually. Children are the most frequently exposed age group, representing 50% of human exposure in canine rabies infected areas and most of them are category III exposures requiring immunoglobulin. Human rabies immunoglobulin is virtually unavailable in most rabies endemic countries or it is far too expensive to be used in public sector..

Original Article

Safety of Equine Rabies Immunoglobulin in Children

Ravish H.S[1], Rupsa Banerjee[2], D.H. Ashwath Narayana[3], Rachana A.R[4]

ABSTRACT

In India, animal bites are a major public health problem and an estimated 17.4 million animal bites occur annually. Children are the most frequently exposed age group, representing 50% of human exposures in canine rabies infected areas and most of them are category III exposures requiring rabies immunoglobulin. Human rabies immunoglobulin is virtually unavailable in most rabies endemic countries or it is far too expensive to be used in the public sector. Equine rabies immunoglobulin that are manufactured presently are affordable and highly purified and the occurrence of adverse events has been significantly reduced. WHO – APCRI survey reports, the usage of rabies immunoglobulin to be as low as 2% in India and one of the most common reasons for not using equine rabies immunoglobulin by medical profession is the fear of anaphylaxis. Therefore, the present study was conducted at the anti rabies clinic, Department of Community Medicine, KIMS, Bangalore to assess the safety of equine rabies immunoglobulin in children. The study subjects included children ≤ 15 years who came to the hospital with category III bites for post exposure prophylaxis during the study period of January 2012 to April 2014. The safety data was collected and analyzed. Only15(1.6%)children reported immediate local adverse reactions such as pain at the site of injection, redness and itching at the site of injection which subsided without any medication. In conclusion, ERIG is safe and well tolerated by children. Therefore, this study will instill confidence among the practicing physician to infiltrate ERIG into all the wounds, in all category III bites as it is intended to protect against rabies and save the lives of these vulnerable population.

Key Words: anti rabies vaccine, children, equine rabies immunoglobulin, post exposure prophylaxis, safety Abstract.

INTRODUCTION

Rabies is a viral zoonotic disease that occurs in over 100 countries throughout 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 major public health problem and an estimated 17.4 million animal bites occur annually which accounts to an incidence of 1.7 %.[2,3] Timely and correct post exposure prophylaxis (PEP) for these animal bite victims is necessary to prevent rabies. Proper wound management and simultaneous administration of rabies immunoglobulin (RIG) combined with prompt administration of anti rabies vaccine (ARV) is almost invariably effective in preventing rabies, even after high-risk exposure[4].

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. Most of the reported bites are category III exposures requiring early administration of RIG. Rabies immunoglobulins are ready made anti rabies antibodies providing passive immunity and immediate protection. Even the best of modern vaccines take 7-14 days to elicit the protective antibody titre and thus RIGs cover this vulnerable short duration in Category III exposures[5].

Rabies immunoglobulin is a life saving drug in all category III exposures, but, the WHO-APCRI Indian rabies survey revealed that, the usage of RIGs was as low as 2% in India and one of the most common reasons for not using RIGs by medical profession is the fear of anaphylaxis, more so among children[3]. Therefore, the present study was conducted to study the safety of ERIG, especially in children who are the vulnerable group.

MATERIALS AND METHODS

The present study was conducted at the anti rabies clinic, Department of Community Medicine, Kempegowda Institute of Medical Sciences, Bangalore. The study subjects included children≤ 15 years who came to the hospital with category III bites for post exposure prophylaxis during the study period of January 2012 to April 2014.

The socio-demographic characteristics & details of exposure were collected from all the study subjects using pre-structured proforma. A signed informed consent was taken from the parents and/or guardians of all subjects before administration of ERIG. A prior

[1]Associate Professor, [2]4Postgraduate Students, [3]Professor & Head
Department of Community Medicine, Kempegowda Institute of Medical Sciences, Bangalore.

skin sensitivity test was done in the subjects who were administered ERIG to test for hypersensitivity. Complete PEP was given to all the animal bite victims as recommended by World Health Organization.

In all category III exposures, ERIG was administered locally into the wounds and all the subjects were observed for half an hour for possible immediate local/ systemic adverse drug reactions (ADRs). At the end of half an hour, reactogenicity was recorded, only if the subject spontaneously complained of a problem to a question on general well being i.e., unaided recall. Data regarding safety was recorded and then transcribed to the case record form. Local reactions included pain at the injection site, redness, swelling, itching and any other adverse drug reactions. The delayed adverse drug reactions, if they report any time after administration of ERIG was also documented.

STATISTICALANALYSIS

The data was analyzed statistically by computing percentages, mean and standard deviation.

RESULTS

3033 animal bite cases reported to the hospital for PEP during the study period. Among them, 1245 (41.05%) were children< 15years of age. All the animal bitten children were categorized according to WHO classification and amongst them, 1036(83.2%) had category III exposures. Among category III exposures, 98(9.4%) of them took HRIG and 938(90.6%) received ERIG.

Socio - demographic profile : 938 children who received ERIG were included in the study. Among them 669(71.3%) were boys and 269(28.7%) girls. Their mean age was 7.42 +3.78 years (range 0–15 years). All the children were going to school.

The biting animal was dog in majority (98.8%) of the study subjects. Most of the dog bites were unprovoked (64.5%) and on the limbs (67.9%) (Table 1).

ERIG: Two brands of ERIG were used during the study period. 93% of the study subjects received Equirab (manufactured & marketed by Bharat Serums and Vaccines Ltd, Mumbai) and 7% of the subjects Abhayrig (manufactured by Vinpharma, Hyderabad & marketed by HBI, Hyderabad). ERIG was given as per WHO guidelines, in all Category III subjects in a dose of 40 IU/kg body weight.

Safety: All the study subjects who received ERIG were included in the safety analyses. Prior to the administration of ERIG, skin sensitivity test (SST) was done to all the study subjects. Amongst them, 82 (8.7 %) had positive skin sensitivity test (SST) (Table 2). All the SST positive cases were also given ERIG, after giving pre medication.

Table 1
Characteristics of the study population:

Characteristics	Study Subjects (n=938)
Age range (mean+S.D)	0–15 years (7.42±3.78)
Sex: Male	669 (71.3%)
Female	269 (28.7%)
Biting animal: Dog	926 (98.8%)
Cat	4 (0.4%)
Monkey	8 (0.8%)
Provocation: Unprovoked	605 (64.5%)
Provoked	333 (35.5%)
Site of bite: Lower limb	382 (40.7%)
Upper limb	255 (27.2%)
Trunk	71 (7.6%)
Head & Neck	230 (24.5%)
Immediate wound wash: Yes	851 (90.7%)
No	87 (9.3%)

Table 2
Results of Skin Sensitivity Test

	Equirab	Abhayrig
Administered	873	65
Positive SST	72	10
Percentage	8.24%	15.3%

15(1.6%) children reported immediate local adverse reactions. The most common solicited adverse reaction to the injections was pain at the injection site 10 (1.06 %). Other reactions included redness 2 (0.2%), itching at the site of injection 2 (0.2%) and induration1(0.1%) which subsided without any medication. None of the subjects during the study period reported any delayed adverse events (Table 3).

Discussion:

India is highly endemic for rabies and has the largest number of animal bites in the world. Most of them being category III bites, which requires early administration of RIG. RIG's are ready-made antibodies, which provide passive immunity and help in tiding the patient over the initial phase of the infection[6]. There are two types of RIG used globally: Human rabies immunoglobulin (HRIG) and Equine rabies immunoglobulin (ERIG). HRIG is virtually unavailable in most rabies endemic countries or it is far too expensive to be used in the public sector. ERIG

Table 3
Adverse drug reactions to Equine rabies immunoglobulin (n =938)

Local Adverse drug reactions	Equirab	Abhayrig	Total
Pain	4	6	10 (1.06%)
Redness	0	2	2 (0.22%)
Itching	1	1	2 (0.22%)
Induration	0	1	1 (0.1%)
Total	5	10	15 (1.6%)

that are manufactured presently are affordable and highly purified and the occurrence of adverse events has been significantly reduced. ERIGs are now manufactured by several institutes in India, China, Thailand, and South America. They have been tested and approved by their individual government regulators, are relatively in expensive and should be used[7].

The current recommendation of WHO for RIGs used globally is 20 IU/kg body weight for HRIG and 40IU/kg body weight for ERIG. Regardless of whatever the RIG which is used, as much of this biological product as is anatomically feasible should be infiltrated into and around the wound sites[4]. Any remaining RIG should be administered by deep intramuscular injection at a site that is distant from the vaccination site in order to prevent the RIG from neutralizing the rabies vaccine that was injected. Published data indicates that ERIG can even be safely injected into already infected animal bite wounds following proper wound cleansing and the administration of appropriate antibiotics[8].

ERIGs are cheaper and affordable, especially in developing countries and most ERIGs that are manufactured presently are highly purified and the occurrence of adverse events has been significantly reduced. Unlike the original unpurified rabies antisera which resulted in adverse reactions in as many as 40% of recipients, the adverse reaction rate of patients receiving highly purified ERIGs has been reduced to < 1-2%. Early local injection site reactions consisting of erythema and itching are not uncommon with ERIGs and serum sickness can occur one week after administration of ERIG in 1-3% of recipients[7]. Therefore, ERIG should only be used by medical staff, trained and equipped to manage even when there are adverse reactions. As per current DCGI guidelines, ERIG has to be infiltrated after testing for hypersensitivity reaction by giving SST. ERIG can still be administered locally, if SST is positive, after giving pre medication[9].

The present study also confirmed that ERIG is safe and well tolerated in children 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 and none of the study subjects had any anaphylaxis. Similarly, many studies done previously also confirms the safety of ERIG in adult population[10,11].

CONCLUSION

ERIG is safe and well tolerated by children. Therefore, this study will instill confidence among the practicing physician to infiltrate ERIG into all the wounds in all category III bites as it is intended to protect against rabies and save the lives of these vulnerable population.

REFERENCES

1. World Health Organization. Rabies vaccines: WHO position paper, Weekly Epidemiological Record, No. 32, 2010, 85: 309-20.
2. Sudarshan M K, Madhusudana S N, Mahendra B J, Rao N S, AshwathNarayana D H, Abdul R 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.
3. Sudarshan M K, Mahendra B J, Madhusudana S N, AshwathNarayana D H, Abdul R S, Rao N S, et al. An epidemiological study of animal bites in India: results of a WHO sponsored national multi-centric rabies survey. The Journal of Communicable Diseases 2006; 38 (1): 32-9.
4. World Health Organization. WHO expert consultation on rabies. Technical report series 982. WHO Geneva, 2013.
5. World Health Organization. WHO expert consultation on rabies. Technical report series 931. WHO Geneva, 2005.
6. National guidelines for rabies prophylaxis and intradermal administration of cell culture rabies vaccines, National Institute of Communicable Diseases, Ministry of Health & Family welfare, New Delhi, India. 2012.
7. Sudarshan MK, AshwathNarayana DH, Giriyanna G. A critical appraisal of usage of rabies immunoglobulin in an anti-rabies clinic in India. APCRI Journal. 2012; 13:11-2.
8. Wilde H, Chomchey P, Punyaratbandhu P, Phanupak P, Chutivongse S. Purified equine rabies immune globulin: a safe and affordable alternative to human rabies immune globulin. Bull World Health Organ. 1989; 67:731-6.
9. Sudarshan MK, Kodandaram NS, Venkatesh GM, Mahendra BJ, AshwathNarayana DH Evaluation of a new premedication protocol for administration of equine rabies immunoglobulin in patients with hypersensitivity.Indian J Public Health. 2007;51(2): 91
10. Sudarshan M K, Mahendra B J, AshwathNarayana D H, Sanjay T V, Anandagiri M S, Venkatesh G M. Evaluation of safety and efficacy of new indigenous equine rabies immunoglobulin. Journal of APCRI, 2006;8(1):13-16.
11. AshwathNarayana D H, Ravish H S, Ramesh Holla. Clinical evaluation of safety of equine rabies immunoglobulin.Journal of APCRI, 2011;12(2):12-15.