Original article

Clinical evaluation of Safety of Equine Rabies Immunoglobulin

Ashwath Narayana D.H[1], Ravish H.S [2], Ramesh Holla[3]

Abstract

The safety of Equine rabies immunoglobulin was assessed in 859 subjects who had severe (WHO category III) exposure to rabies. Majority were adults (59 %), males (70 %), 94 % of the subjects were bitten by dog of which 69 % are stray dogs & 98 % bitten by suspect rabid animal. All the animal bite victims were advised ERIG & incidence of skin sensitivity test (SST) was positive in 113 (13.2 %) subjects. The SST was positive more in adults (69 %) than children (31 %). 746 (87 %) subjects who were negative for SST received full dose of ERIG without premedication. Among those who were SST positive, Full dose of ERIG was administered to 106 (93.8 %) after premedication as per KIMS premedication protocol; 06 (5.3 %) opted for HRIG & 01 (0.9 %) refused ERIG administration. Among those who received full dose of ERIG, Equirab was administered in 577 (68 %) subjects, Abhayrig in 275 (32 %). In 661 (78 %) of subjects exclusive local infiltration of wounds by ERIG was done. The mean volume of ERIG used for full dose was 3.9 mL in children, 8.1 mL in adults & 6.3 mL in both. 5 (0.6 %) subjects had delayed local & 07 (0.8 %) subjects had delayed systemic ADR after full dose of administration of ERIG. However, 01 (0.1%) had giddiness and vomiting as an immediate systemic adverse event to full dose ERIG administration in whom SST was negative.

Keywords: Rabies, equine rabies immunoglobulin, skin sensitivity test, premedication.

Introduction

Rabies is a fatal viral encephalitis but preventable by early initiation of proper post exposure prophylaxis. An estimated 20,000 human rabies deaths & 17.4 million animal bite cases occur in the country[1]. Human rabies deaths can be prevented by timely and proper use of modern rabies vaccines and immunoglobulin soon after the animal bite. The Rabies Immunoglobulins (RIGs) are life saving in severe (WHO category III) rabies exposures[2]. There are two types of rabies immunoglobulin viz. human rabies immunoglobulin (HRIG) and equine rabies immunoglobulin (ERIG). HRIG are imported, expensive and ERIG which are indigenously produced are less expensive, affordable and more widely used in the country. The availability and use of ERIG is limited to metro and bigger cities. One of the main reasons for low usage of ERIG is fear of anaphylaxis among professionals. The presently available ERIG are purified following heat treatment, pepsin digestion and enzyme refinement with very low protein content (<3%). In spite of high purity of ERIG, 1-11% hypersensitivity reactions are known to occur after preliminary skin sensitivity test (SST) [3-6]. WHO recommends, administration of HRIG or pretreatment with adrenaline/epinephrine (intramuscularly) and with antihistamine in those with positive skin test before the full dose administration of ERIG. The technique of skin sensitivity testing (SST), grading of SST & premedication in hypersensitive patients is now available in the country[7].

In this background, this study was undertaken to study the safety of equine rabies immunoglobulin administration & to reassure the professionals to use ERIG even in hypersensitive patients after giving premedication.

Subjects and methods

The study was conducted in the anti-rabies clinic of Kempegowda Institute of Medical Sciences (KIMS) hospital, Bangalore during July 2009 to June 2010. A total of 859 subjects with severe rabies exposures / rabid animal bites (WHO Category III) were enrolled. The detailed history & clinical examination of animal bite cases included an enquiry of receiving equine immunoglobulin / sera in the past viz. anti-diphtheria serum (ADS), anti-tetanus serum (ATS), anti-snake venom serum (ASVS), anti-gas gangrene serum (AGS) or even anti-rabies serum (ARS) and report of any hypersensitivity / allergy were recorded in the case record form. All the subjects were provided the WHO standard rabies post exposure prophylaxis (PEP) of wound care, modern rabies vaccine and RIG.

[1] Professor, [2] Associate Professor, [3] Post-Graduate trainee cum Tutor, Kempegowda Institute of Medical Sciences, Bangalore - 560070
Corresponding author: Dr D. H Ashwath Narayana; **Email:** dhashwathnarayana@gmail.com

The brands of ERIG used were Equirab (manufactured & marketed by Bharat Serums and Vaccines Ltd, Mumbai), Abhayrig (manufactured by Vinpharma, Hyderabad & marketed by HBI, Hyderabad). The brand of HRIG used was Kamrab (manufactured by Kamada Laboratories, Israel & marketed by Synergy diagnostics/ Medlife, Thane, India).

The signed informed consent was taken from all subjects before administration of ERIG. A prior skin sensitivity test was done with ERIG to test for hypersensitivity before administration of full dose.

Procedure of skin sensitivity test (SST)

Using an insulin syringe with 31 gauge needle, 0.1mL of normal saline was injected intradermally (ID) in the right forearm (control). Then 0.1mL of 1:10 dilution (in sterile normal saline) of ERIG was given ID in the left forearm (as test dose). This was done by using an insulin syringe, wherein 4 units of ERIG was drawn in and then normal saline was drawn up to 40 units, thus giving a 1 in 10 dilution of ERIG in normal saline. Both the injections produced a wheal of 3-5 mm in size in the two forearms. The patients were observed for 20 minutes for any increase in the local wheal with or without erythema in the ERIG ID test site and no change in the control (saline) ID site and for any systemic complaints of significant tachycardia (increase in pulse rate of more than 20% from baseline value), significant hypotension (fall in blood pressure of more than 30% from baseline value), fainting, vomiting, breathlessness, chest pain, itching, wheeze or stridor, angioedema or collapse. If one or more of these were present then the test was considered as "positive". If none of these were present than the test was considered as "negative".

Premedication drugs

Severity of skin sensitivity test was assessed based on the wheal developed at the site of ERIG skin testing and comparing with the control. The premedication drugs were used in those who are hypersensitive to SST as recommended by KIMS premedication protocol (Table 1 & 2).

Full dose administration of RIG

As per the WHO guidelines, ERIG @ 40 IU/kg body weight or HRIG @ 20 IU /kg body weight was administrated into and around the animal bite wounds as much as possible, at all the anatomically feasible sites, and the remaining if any was administered intramuscularly at a site away from the site of vaccine administration. If RIG was insufficient, it was diluted with sterile normal saline to a volume sufficient to infiltrate all wounds and administered. Subsequently, the subjects were monitored for a minimum of 1 hour for blood pressure, pulse and oxygen saturation. In the event of any adverse reaction the patients were to be managed as per the standard protocol and with the help of the critical care unit personnel.

Table-1:
Assessment of severity of skin sensitivity test & premedication drugs used

Severity of Skin Sensitivity Test (SST)	Skin Sensitivity Test (SST)	Drugs given
No reaction	The wheal of ERIG = wheal of normal saline.	None
Mild reaction	The wheal of ERIG is double the original size	Inj.Pheniramine + Inj. Ranitidine
Moderate reaction	The wheal of ERIG is double the original size with pseudopodia	Inj.Pheniramine + Inj. Ranitidine + Inj.Hydrocortisone
Severe Reaction	The wheal of ERIG is of any size but with systemic symptoms and signs*	Inj. Adrenaline* + Inj. Hydrocortisone + Inj.Pheniramine + Inj. Ranitidine

*To be used only to counteract anaphylaxis

Table-2:
Details of the premedication drugs, dosage & route of administration

Sl. No.	Drug	Brand	Dose	Route of Administration
1.	Injection Pheniramine maleate (Anti-histamine)	Avil	0.8mg/kg body Weight	Intravenous
2.	Injection Ranitidine Hydrochloride (H_2 blocker)	Ranitac	2mg/kg body weight	Intravenous
3.	Injection Hydrocortison Hemisuccinate (short acting steroid)	Efcorlin	2mg/kg body weight	Intravenous

Assessment of reactogenicity

The occurrence of adverse reaction was recorded only if the subject spontaneously manifested or complained of a problem to a question on general well being i.e., unaided recall. If there was no reaction to skin sensitivity test, ERIG was administered but without any premedication. However, in all SST

positive cases, the appropriate premedication drugs were administered intravenously. Subsequently after about 30 minutes of premedication, the administration of full dose of ERIG was done. Following the full dose administration of ERIG all the subjects were observed for about one hour for immediate adverse events (both local & systemic). All the subjects were given self addressed reply post cards with the instruction to write down any adverse events (delayed ADR) that will occur within 14 days.

Results

Profile of subjects: 859 subjects who had severe (WHO category III) exposure to rabies were included in the study. Majority of the subjects were adults 504 (58.7 %) with 343 (39.9 %) were in the age group of 15 - 44 Yrs & 602 (70.08 %) subjects were males (Table-3). The median age of males was 19 years (Range: 1 to 95 years) & of females, median age was 22 (Range: 1-85 years).

Details of exposure: Majority of the subjects, 809 (94.2%) were bitten by dog & mostly (69 %) by stray & ownerless. Majority of the biting animals (98.7 %) were suspect rabid & 11 (1.3%) were confirmed rabid animal (Table-4).

ERIG administration:

Skin sensitivity test (SST): All the 859 subjects who had category III animal bites, were advised ERIG & SST was done. The incidence of SST was positive in 113 (13.2 %) subjects. The SST was positive more in adults (69 %) than children (31%). SST was mild in 35 (33%) and moderate in 71 (67%) (Table-1).

Full dose administration of RIG: 746 (86.8%) of subjects who were negative for SST were administered full dose of ERIG as per WHO guidelines without premedication. Among 113 (13.2%) subjects who were SST positive, Full dose of ERIG was administered to 106 (93.8 %) after giving premedication as per KIMS premedication protocol, 06 (5.3%) opted for HRIG & 01 (0.9%) did not give consent for ERIG administration after premedication. 35 (33%) of the subjects who had mild reaction were administered Inj. Pheniramine Maleate & Ranitidine; 71 (67%) had moderate reaction were administered Inj. Pheniramine Maleate, Inj. Ranitidine & Inj. Hydrocortisone hemisuccinate.

Table-3:
Profile of study subjects

Age group	Sex		Total
	Male	Female	
0-4	72	37	109 (12.7)
5-14	182	64	246 (28.6)
15-44	246	97	343 (39.9)
45-64	75	54	129 (15.1)
65+	27	05	32 (03.7)
Total	**602 (70.08)**	**257 (29.92)**	**859 (100.0)**

Table-4:
Distribution of Patients according to details of biting animal (N=859)

Type of biting animal/ Exposure	
• **Dog**	**809 (94.2)**
Pet	251 (31.0)
Stray	558 (69.0)
• Cat	17 (02.0)
Pe	11 (64.7)
Stray	06 (35.3)
• Monkey	18 (2.1)
• Wild animals (Zebra)	01 (0.1)
• Exposure to Hydrophobia cases	06 (0.7)
• Consumption of raw milk of suspect rabid cow	08 (0.9)
Classification of biting animal (98.7)	
• Confirmed rabid	11 (1.3)
• Suspect rabid	848

Note: Figures in parenthesis indicate percentages.

Brands of ERIG administered: 852 (88%) who received full dose of ERIG, Equirab was administered in 577 (67.7%) subjects and Abhayrig in 275 (32.3%).

Site of full dose administration of ERIG: In 661 (77.6 %) of subjects exclusive local infiltration of wounds by ERIG was done as per WHO guidelines. In 187 (21.9%) of the subjects the ERIG was administered locally into the wounds & left over was administered systemically (IM) away from the site of vaccine administration. Only in 04 (0.5%) of the subjects, the ERIG was administered systemically (IM) when there were no obvious bite marks; in those exposed to hydrophobia cases & subjects who have consumed raw milk of rabid cow.

Volume of ERIG administered: The mean volume of ERIG required to administer full dose was 3.9 mL in children, 8.1 mL in adults & 6.3 mL combined

Adverse drug events: 5 (0.6%) subjects had delayed local reactions viz. swelling, pain, redness and itching. 07 (0.8%) subjects had serum sickness like reaction after full dose of administration of ERIG. The signs & symptoms of serum sickness like reaction recorded were itching, rashes, fever, headache & body ache. All the adverse events were mild to moderate & were treated with antihistamines, analgesics & H2 blockers. However, 01 (0.1%) subject had giddiness with vomiting as an immediate systemic adverse event to full dose ERIG administration in whom negative for SST.

Discussion

Rabies is endemic in India & continues to be a public health problem. There is improvement in availability & utilization of post exposure rabies prophylaxis in government hospitals during the last 5 years. However, there is more emphasis only on administration of rabies vaccines & not providing life saving RIG to treat Category III animal bite cases. The nonuse of RIG in severe rabies exposures may result in rabies death. Since, HRIG are scarce and expensive, there is a need to use ERIG which is less expensive and more widely available in the country. However, ERIG has an undeservingly poor reputation and the medical professionals hesitate to use it fearing anaphylaxis. But the currently available ERIG are highly purified products and safe. Hence, there is a need to use them to save more lives from human rabies mortality in this country.

In our study, SST was positive in 13.2% of the cases. 0.8% of the subjects had delayed systemic ADR viz. serum sickness like reaction after full dose administration of ERIG which were treated by antihistamines & analgesics. However, 1 (0.1%) who was SST negative developed immediate systemic reaction which subsided with treatment. 11 (1.3 %) subjects who were exposed to confirmed rabid animals and received ERIG are alive even after one year.

In conclusion, the study revealed that ERIG is safe, efficacious and full dose of ERIG can be administered even in cases with positive SST after premedication with H1, H2 blockers & short acting steroid Hydrocortisone hemisuccinate. The findings of this study should instill confidence and encourage doctors to use ERIG in severe exposures to reduce human rabies mortality in the country.

References

1. Association for Prevention and Control of Rabies in India. Assessing burden of rabies in India: WHO-APCRI National Multi-centric Rabies Survey, A report. KIMS, Bangalore, 2004 (www.apcri.org)
2. World Health Organization. Expert Consultation on Rabies, Technical report series 931, Geneva, Switzerland, 2005.
3. H. Wilde, P. Chomchey, S. Pralongsri and P. Punyarata bandhu. Safety of equine rabies immunoglobulins. Lancet. 1987.2(8)1275
4. H. Wilde and S. Chutivongse. Equine rabies immunoglobulins: a product with an underserved poor reputation. Am. J. Trop. Med and Hyg. 1990; 42 (2): 175-178.
5. B. J. Mahendra, T. V. Sanjay, D. H. Ashwath Narayana, M. K. Sudarshan. Rabies immunoglobulins in post-exposure prophylaxis: Study of 236 Subjects. Journal of APCRI. 2003; 5 (1-2). 26-33.
6. M K Sudarshan, B J Mahendra, D H Ashwath Narayana, TV Sanjay, M S Ananda Giri, G M Venkatesh: Evaluation of safety & efficacy of new indigenous equine rabies immunoglobulin. Journal of APCRI. 2006; 8 (1). 13-16.
7. M K Sudarshan, N S Kodandaram, G M Venkatesh, B J Mahendra, D H Ashwath Narayana, B G Parasuramaiu: Evaluation of new premedication protocol for administration of new equine rabies immunoglobulin in patients with hypersensitivity. IJPH. Vol 51 (2) April June 2007, 91-96.