Post Exposure Passive Immunization with Purified Equine Rabies Immunoglobulins – Is Skin Sensitivity Test Needed?

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Abstract

Background: Passive post exposure prophylaxis for rabies is life saving. Equine rabies immunoglobulins (ERIG) are readily available and much cheaper compared to human rabies immunoglobulins (HRIG). Not only several studies conducted across the globe to assess the impact of Skin sensitivity test (SST) but also WHO recommend that, ERIG needs to be administered mandatorily irrespective of SST result. An effort was made in the present study to have hands on experience regarding the usefulness of SST before administering purified ERIG.

Materials and Methods: The present study involves 2528 patients who presented with animal bite wounds in the emergency ward of an infectious diseases hospital for anti rabies post exposure prophylaxis, from 1st August to 31st October 2014. Skin sensitivity test with 0.1ml of 1 in 10 dilutions of ERIG (as per the recommendations of product insert of the company i.e., Bharat serums and vaccines limited, Mumbai / VINS bio products, Andhra Pradesh) was performed for all patients.

Results: Sixty out of 2528 patients (2.37%-p value 0.02) showed positive skin test.
Twenty seven out of 60 (45%) did not show positive reaction to repeat SST and received full dose without any adverse effects.
Seventeen, who could not afford HRIG, received ERIG along with pheniramine maleate and hydrocortisone as premedication with no adverse effects.
Six patients were administered HRIG, while 10 patients refused for any treatment.
5 patients who showed no reaction to SST developed adverse effects on full dose administration in the form of seizures, giddiness, vomiting, rash and itching.

Conclusion: Since Skin sensitivity test does not represent systemic hypersensitivity, ERIG can be administered for those patients who cannot afford HRIG, with extreme caution & preparedness to deal with any untoward reactions.

Index Terms: Post exposure prophylaxis, Equine rabies immunoglobulin, Human rabies immunoglobulin, Skin sensitivity test.

I. Introduction

Lack of political commitment and low socio economic conditions have led to regular reporting of rabid dog bites across India which is now one among the rabies endemic countries. Apart from wound management, one of the most important aspects of prevention of rabies is passive prophylaxis in the form of immunoglobulins, to destroy the virus as early as possible. Most of the victims belong to low socio economic group who cannot afford Human rabies immunoglobulins. Equine rabies immunoglobulins, which are cheap and easily available in the market, carry a small risk of anaphylactic reactions which is why Skin sensitivity test is routinely performed to ensure safety of its administration. While this was true of the earlier crude ERIG, the present preparation marketed by reputed companies are products of indigenous technologies and proven to be much safer with minimum risk of sensitivity (0.8%). Moreover, WHO recommends against the tedious and time consuming SST which may delay the preventive management of a fatal condition, Rabies.

II. Materials and Methods

The study involving 2528 patients presenting to outpatient department of an infectious diseases hospital with animal bite wounds was conducted from 1st August to 31st October 2014. All patients of category III animal bite wounds were included in the study. Detailed history of past illnesses and co morbid conditions like diabetes, epilepsy, hypertension, asthma were noted. Known hypersensitivity to drugs /serum products received in the past was also noted.

The wounds were thoroughly washed with soap water as an immediate therapeutic measure. Meanwhile the dose of equine rabies immunoglobulin at 40 IU per Kg to be administered for each patient would be calculated. Two different brands of ERIG with same composition and strength i.e., Equirab, marketed by Bharat serums and vaccines limited, Mumbai and Vinrig of VINS bio products, Andhrapradesh were used subjected to availability. For SST, 1 ml of ERIG, mixed with 9 ml of sterile normal saline, 0.1 ml of this 1 in 10 dilutions taken in an insulin syringe and injected intra dermally into the flexor aspect of left forearm, raising a wheal 5 to 6 mm size. The patient was kept under observation with frequent recording of pulse, blood pressure and respiratory rate for the next 30 minutes. The test

was considered positive if there was erythrema and/or induration of more than 10 mm at the test site or any other systemic reaction in the form of itching, vomiting, giddiness, and rash. The test was considered negative when there was no change at the test site.

All patients who tested positive for the skin test were given a second test dose to rule out any errors relating to method of administration or interpretation of the test. When the second test showed no reaction, it was considered truly negative and ERIG was given without any premedication.

If repeat SST was positive, patients were advised HRIG and for those who could not afford, ERIG was given after premedication with intramuscular pheniramine maleate and hydrocortisone.

III. Results

Out of 2528 patients, 688 (27.2%) were in 0-12 yrs age group, 1177(46.5%) were in 12-40yrs age group, 506 (20%) were in 41-60yrs age group and 157 (6.2%) were in >60 yrs age group. (Table 1)

One thousand eight hundred and eighteen (71.9%) were males and 710 (28%) were females. (Table 1)

Two thousand four hundred and twenty two (95.8%) were dog bites, and while remaining were cat (37), monkey(58), wild rat(5), pig(5), bat(1) (Table 2).

All patients belonged to category III wounds.

Two thousand three hundred and five (91%) patients reported washing the wounds with soap, water and antiseptics at home. (Table 3).

SST was negative in 2468 (97.6%) patients and received complete dose of ERIG, maximum in filtered locally into the wounds and rest intramuscularly into the gluteal muscle. 5 patients who had negative SST showed certain adverse effects during administration of full dose of ERIG.

- Seizures in a known case of epilepsy
- One patient had vomiting
- One patient had rash and itching all over the body
- Two patients complained of giddiness

All 5 patients recovered with symptomatic management.

Sixty patients (2.37%) had wheal and flair reaction to the skin test initially out of whom 27 (45%) did not show positive reaction on repetition of the test. All 27 patients were given full dose of ERIG without any adverse effects

Though the remaining 33 patients were advised HRIG, only 6 patients could afford it.

Ten patients did not give consent to any form of treatment while 17 patients who could not afford HRIG were given injection pheniramine maleate and hydrocortisone and then the full dose of ERIG; no adverse reactions were noticed in these cases (Figure 1).

IV. Discussion

Rabies is an important zoonotic infection which if not prevented results in 100% mortality. Post exposure prophylaxis in the form of Immunoglobulin is life saving especially in category III wounds. The present study was taken up at an institute approached by all animal bite victims for wound management and anti rabies vaccine from all over the state. Most of them happen to be from poor socio economic background and cannot afford HRIG. Moreover, by the time they reach the hospital, valuable time gets lost in transit and the wound management needs to be done immediately.

In regards to skin sensitivity test (SST), the report of WHO consultation on intra dermal application of human rabies vaccine (1995) [1] clearly states that SST should no longer be used for ERIG, since it neither predicts anaphylaxis nor serum sickness; ERIG can be given directly with preparedness to meet any untoward effects, should they occur. In those patients in whom SST is done and is positive, even then the attending physician has to proceed with ERIG, in case HRIG cannot be purchased, with special precautions like pretreatment with anti histamine, steroids and adrenalin and patient kept under observation for at least 1 hour after full dose administration.[2] Several studies conducted at various centers across the country confirm WHO observation that reactogenicity following purified ERIG administration is minimal, since the equine serum, rich in immunoglobulins gets subjected to heat treatment, pepsin digestion and enzyme refinement with very low protein content[3]. Moreover ERIG is indigenously manufactured in the country unlike HRIG, which is imported from Italy. ERIG is suitable for low socio economic group of patients who constitute the majority of animal bite victims at the present study centre.

Men, in the age group 12 to 40 yrs being active and most ambulant were most commonly affected.

Dogs, as in any other study, were found to be the most offending animal in the present study. The other animals involved were monkey, cat, wild rat, pig, and bat.

The status of animals was mostly unknown, an observation that made it imperative to initiate post exposure prophylaxis as early as possible with readily available ERIG, SST was still performed for all patients and ERIG was administered in appropriate dosage for those with no reaction.

Local reaction with heterologus serum like ERIG, which is immediate and IgE mediated, does not detect systemic reactions, triggered by complement and /or mast cell activation. Hence, the attending medical staff was always ready with adrenaline loaded syringes, antihistamines and steroids to deal with emergency situations. This happened in 5 (0.19%) patients with negative SST. One patient, a known case of epilepsy, developed seizures during ERIG administration; the other 4 suffered from giddiness, vomiting, rash and itching and recovered with symptomatic treatment.

SST was repeated for all 60 patients who showed positive reaction because of a lurking premonition on the part of attending medical team that made them to decide to repeat the test since they wanted to rule out technical and interpretation errors.

Twenty seven patients did not show positive reaction to repeat SST and received full dose of ERIG without any adverse effects, not even in the minimalistic form sooner or later.

Thirty three, who showed positive reaction after repeat SST, would have any way received only ERIG owing to financial constraints since all belonged to low socio economic group except 6 patients who opted for HRIG.

Ten patients who showed positive reaction to repeat SST, in the three month period, randomly, for reasons unknown, in spite

of perseverance of the medical team, did not consent to any form of treatment and left against medical advice.

Seventeen patients who were willing to receive ERIG along with premedication were administered full dose without any adverse effects. Premedication helps in preventing or attenuating possible immediate reactions, especially steroids which act as anti-inflammatory agents, inhibiting the late manifestations of anaphylaxis, reducing continued release of inflammatory mediators, complement activation while having no immunosuppressive effect in the dosage that is administered[4].

V. Conclusions

The present study observed statistically insignificant percentage of (2.37%-p value <0.05) local reactions to SST with minimal systemic adverse effects. The study favors the WHO recommendation that SST is not mandatory for passive anti rabies prophylaxis with equine rabies immunoglobulins. Whenever possible HRIG is to be preferred for affordable patients: however ERIG can be administered without SST for those patients who cannot afford HRIG, with extreme caution and preparedness to deal with any untoward reactions.

Table: 1 showing Age and Gender distribution.

	0-12 yrs	13-40 yrs	41-60 yrs	>60 yrs	Total
Male	497	869	342	110	1818
Female	191	308	164	47	710
Total	688	1177	506	157	2528

Table: 2 showing details of animals involved in bites.

Animals	Total
Dog	2422
Cat	37
Monkey	58
Wild Rat	5
Pig	5
Bat	1
Total	2528

Table: 3 details of first aid measures.

Washed with soap / Antiseptic	2305
Washed with water only	17
Used home remedies	16
Not washed	190
Total	2528

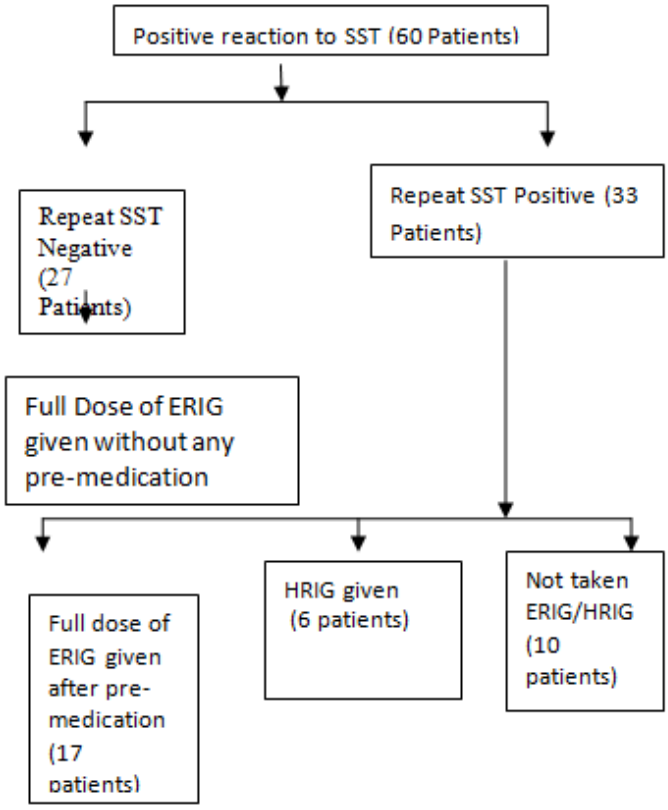

Figure 1 : Diagrammatic representation of the Study

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