Title: OUTCOME OF SKIN SENSITIVITY TESTING FOR PREDICTING REACTIONS OF RABIES EQUINE IMMUNOGLOBULIN IN A TERTIARY SETUP

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Keywords ERIG, Skin Sensitivity Test

Abstract Rabies immunoglobulin provides immediate protection and is life saving to patients with severe exposure to rabies. Equine rabies immunoglobulin (ERIG) is subjected to high degrees of purification in spite of the stringent procedure of manufacture it is still found to produce reactions. Manufactures of ERIG still recommend a skin sensitivity test before administration of the hetrologous serum.

Original Article

Outcome of Skin Sensitivity Testing for Predicting Reactions to Rabies Equine Immunoglobulin in a Tertiary Setup

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ABSTRACT

Background : Rabies immunoglobulin provides immediate protection and is life saving to patients with severe exposure to rabies. Equine rabies immunoglobulin (ERIG) is subjected to high degrees of purification; in spite of the stringent procedure of manufacture it is still found to produce reactions. Manufacturers of ERIG still recommend a skin sensitivity test before administration of the heterologous serum. WHO recommends that there are no specific grounds for performing the skin sensitivity test (SST) before its administration, as the SST does not predict reactions. This study tries to unveil the use of SST in predicting adverse events to ERIG.

Methods : The study was carried out at the anti rabies clinic of Veer Surendra Sai Medical College, Burla, Odisha. The period of the study was 12 months (May 2011- April 2012). The skin sensitivity was validated by evaluating its sensitivity, specificity, positive predictive value and negative predictive value.

Results : A total of 1123 category III patients attended the anti rabies clinic during the study period. Out of which 77% (865) of the patients had no reaction and rest 23% (258) had reaction. Out of the 258 who showed reaction 3% (8) had severe reaction whereas adverse reactions were found in 2% (17) of the patients who had a negative SST.

Conclusion : As the study reveals that the use of SST before the administration of ERIG may not be required, as recommended by the WHO.

Key Words: ERIG, Skin Sensitivity Test.

INTRODUCTION

Rabies continues to be a major public health problem killing an estimated 20,000 people in India annually. This virtually cent percent fatal disease is nearly hundred percent preventable by timely and appropriate post exposure prophylaxis[1]. Based on vaccine and immunoglobulin utilisation approximately 3 million people receive post exposure treatment in the country. The importance of immunoglobulin administration has been well documented, immunoglobulin's are available in two forms the depending upon the source i) equine rabies immunoglobulin (ERIG) ii) human rabies immunoglobulin (HRIG)[1]. The human rabies immunoglobulin being the ideal form is imported, expensive and scarce. Whereas the ERIG is indigenously produced, less expensive and more widely available. Equine rabies immunoglobulin (ERIG) is subjected to high degrees of purification; in spite of the stringent procedure of manufacture it is still found to produce reactions[4-6].

A recent WHO recommendation states that there are no scientific grounds for performing a skin test before administering ERIG, because testing does not predict reactions and it should be given irrespective of the result of the test[7]. It also suggests that the treating physician should be prepared to manage anaphylaxis which, although rare, could occur during any stage of administration. Because of this confusion regarding the predictive value of SST, we studied the utility of SST in predicting adverse reactions to ERIG.

METHODS

The data was analysed from the records of the anti rabies clinic of the Veer Surendra Sai medical college, Burla, Odisha. The period of study was 12 months (May 2011-april 2012). A total of 1123 cat

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Table I
Relation of adverse events to the results of skin sensitivity test

Diagnostic test	Adverse reaction		Total
	Present	Absent	
Positive	8	250	258
Negative	17	848	865
Total	25	1098	1123

III patients had received purified ERIG. The brand used was only Equirab (Bharat Serums &Vaccines Limited, Mumbai) as it was supplied by the government of Odisha free of cost.

For the SST, 0.1 ml of sterile normal saline was injected intradermally using an insulin syringe (26G needle) into the flexor aspect of the right forearm. This raised a 5 – 6 mm orange skin-like induration (control injection). Similarly, 0.1 ml of ERIG was taken in another insulin syringe and mixed with 0.9 ml of sterile normal saline in the same syringe; 0.1 ml of this 1:10 dilution of ERIG was injected intradermally into the flexor aspect of the left forearm, which raised another 5 – 6 mm size orange skin-like induration (ERIG test dose). A constant watch was kept on the pulse, blood pressure and respiratory rate of the patient for the next 20 minutes. The test was read as follows:-

1. 6-10mm diameter of weal and erythema - negative
2. >10mm diameter of weal and erythema - positive

A test was considered negative when there was no reaction in any of the forearms. A list was made of the result of SST and the type of adverse event. 'Immediate reactions' were those that occurred within 30 minutes after administration of the full dose of ERIG, and included itching, giddiness, vomiting and drowsiness. 'Delayed reactions' were defined as those that occurred within 28 days of ERIG administration. We calculated the sensitivity, specificity, positive and negative predictive value and false-positive and false-negative values of the SST.

RESULTS

Of the 1123 patients who received ERIGs, 865 (77%) of patients had a negative SST and 258 (23%) had a positive reaction. 258 patients were reported to have a weal and erythema of size greater than 10mm out of these 8 (3%) patients reported to have adverse reaction and rest didn't have any adverse reaction. The adverse reactions ranged from head reeling, vomiting, chest congestion, severe itching, fever, local erythema etc. Adverse reactions were more frequent (2 %) in those who had a negative SST. The SST had a sensitivity of 32%, specificity of 77%, positive predictive value of 3.1%, and negative predictive value of 98.03%.

TABLE II
Results of skin sensitivity test and adverse events in each patient who received equine rabies immunoglobulins

Patients Immediate	Skin sensitivity	Adverse reactions
1	Positive	Rashes, fever, chills, pain abdomens
2	Positive	Giddiness
3	Negative	Vomiting, fever
4	Negative	Pain , rashes, itching
5	Negative	Fever, rashes, vomiting Delayed
6	Negative	Rashes, itching
7	Negative	Itching, body ache
8	Negative	Swelling
9	Negative	Pain
10	Negative	Fever
11	Positive	Headache
12	Negative	Swelling
13	Negative	Redness
14	Positive	vomiting
15	Positive	Itching, body ache
16	Negative	Cough
17	Negative	Rashes, fever, chills, pain abdomen
18	Positive	vomiting
19	Negative	Pain, itching
20	Negative	Pain, itching
21	Positive	Itching, body ache
22	Negative	fever
23	Negative	pain
24	Negative	fever
25	Positive	Rashes, itching

DISCUSSION

Equine immunoglobulin appears to be reasonably safe. We encountered an adverse event rate of 3% among the persons who were found positive to SST. Most of the adverse events were mild to moderate in nature and subsided without

any medication. However, as ERIGs are of heterologous origin, they do carry a small risk of anaphylactic reaction (1/45 000 cases) [7-9].

The procedure for SST is cumbersome and time-consuming, especially in a busy healthcare facility. This may compel the hesitant and reluctant healthcare practitioner to give only the vaccine and skip the ERIG. This would leave the patient rabies prone as the vaccine alone cannot guarantee adequate protection in those with severe (WHO category III) exposures to rabies.

The immediate reactions that occur with the use of heterologous sera may be mediated by IgE and can be detected by SST (anaphylactic reactions), or are triggered by complement activation, non-immunological activation of mast cells or of modulators of arachidonic acid, and do not depend on previous exposure to antigens (anaphylactoid reactions). These are not detected by SST.

Generally, users of ERIGs in Brazil, India, Thailand, the Philippines and Sri Lanka have found them to be quite safe. SST has been abolished in Brazil and WHO too does not advocate SST any more[2]. In this background of adequate evidence and appropriate recommendations, it is time that we also stop using SST for ERIGs. The producers of ERIGs, after approval of the regulatory authority, i.e. Drugs Controller General of India (DCGI) should modify the product insert by deleting the portion on SST. Consequently, ERIGs should be promoted as an 'institutional product' and given by trained persons in all first referral unit (FRU) hospitals, i.e. community health centres / taluka/ tehsil hospitals and higher-level institutions in the government sector, as has been done with anti-snake venom serum. Healthcare personnel working in these facilities should be prepared to manage anaphylaxis which, although rare, could occur during any stage of administration of ERIG. Similarly, in the private sector, nursing homes, private hospitals, etc. which have similar facilities may provide ERIGs. This would promote the use of ERIGs and go a long way in reducing the burden of mortality due to human rabies in India[2].

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