Title: OUTCOME OF SKIN SENSITIVITY TEST FOR ASSESSING ADVERSE REACTIONS TO EQUINE RABIES IMMUNOGLOBULIN IN A TERTIARY SETUP OF SOUTH ODISHA

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Keywords Skin sensitivity testing (SST), ERIG, Validation

Abstract Rabies immunoglobulin is life saving in patients exposed to Rabies virus. Despite the high degree of purification of equine rabies immunoglobulin, the manufacturer still recommends a skin sensitivity test before administration of this heterologous serum. A recent WHO recommendation states that there is no scientific ground for performing a skin test before administrating ERIG because testing does not predict reaction so it should be given irrespective of the test results. So we assessed the value of skin sensitivity testing in predicting adverse reactions toERIG.

Background : Rabies immunoglobulin is life saving in patients exposed to Rabies virus. Despite the high degree of purification of equine rabies immunoglobulin, the manufacturer still recommends a skin sensitivity test before administration of this heterologous serum. A recent WHO recommendation states that there is no scientific ground for performing a skin test before administrating ERIG because testing does not predict reaction so it should be given irrespective of the test results. So we assessed the value of skin sensitivity testing in predicting adverse reactions to ERIG.

Materials &Methods : The study was carried out in the Anti Rabies clinic of MKCG,MCH, Berhampur, Odisha. Thestudy was conducted for a duration of 4 months (February 2017 May 2017). The skin sensitivity test was validated by assessing its sensitivity, specificity, positive predictive value and negative predictive value.

Results : A total of 648 Category III patients attended the Anti Rabies clinic during the study period and they were administered Rabies immunoglobulin. Out of which 24.38% (158) patients had positive skin sensitivity testing and remaining 75.61% (490) had negative skin sensitivity testing. The sensitivity,specificity, positive predictive valueand negative predictive value of skin sensitivity test to predict an adverse reactions was 26.78%,77.14%, 10.13% and 91.63% respectively.

Conclusion : The study reveals that the skin sensitivity test before administrating ERIG may not be required , as recommended by WHO.

Original Article

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ABSTRACT:

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INTRODUCTION:

Rabies is a viral zoonosis and human infection usually occurs following a transdermal bite or scratch by an infected animal.[1] Rabies causes about 26,000 to 55,000 deaths worldwide per year, more than 95% of which occurs in Asia & Africa[2].Rabies is a 100% fatal disease which can be prevented by timely and appropriate anti rabies prophylaxis[3]. Every year more than 15 million people worldwide receive post exposure vaccination to prevent the disease[4].

Apart from wound management, one of the most important aspects of prevention of Rabies is passive prophylaxis in the form of immunoglobulin prevents the entry of the virus into the peripheral nervous system as early as possible. Two types of immunoglobulin are available that are Human rabies immunoglobulin (HRIG) & Equine rabies immunoglobulin (ERIG).Most of the victims belong to low socio-economic status who could not afford Human rabies immunoglobulin.Equine rabies immunoglobulin is cheap and indigenously available in the market.With the use of purified ERIG the incidence of adverse reactions has been low (0.8%-6%) still it is found to produce reactions , and most of those that occurred were minor, and relationated to local reactions and serum sickness[5,6,7].

A recent WHO recommendation states that there are no scientific grounds for performing a skin sensitivity test prior to administration of Equine Rabies. Immunoglobulin(ERIG) as the test does not predict anaphylaxis or serum sickness reaction. So it should be given irrespective of the test result. WHO recommends that the treating physician should be prepared to manage anaphylaxis which, however rare could occur at any stage of ERIG administration[8]. Because of the uncertainty associated with the validity of SST in predicting anaphylaxis, this study was conducted to assess the utility of skin sensitivity testing before administration of ERIG.

METHODOLOGY:

A cross-sectional study was conducted in the Anti rabies clinic of MKCG medical college and hospital, Berhampur, Odisha from February 2017 to May 2017. Purposive sampling technique was adapted. All category III animal bite cases attending the ARC of MKCG Medical College and Hospital were included in the study. The sample size for the study was 638.

All the category III animal bite cases received purified ERIG and skin sensitivity test was done prior to the administration of Equine rabies immunoglobulin.

Procedure of skin sensitivity test followed was :

- 0.1 ml ERIG diluted 1:10 in physiological saline

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was injected intra-dermally into the flexor surface of the forearm to raise a bleb of about 3-4 mm diameter

- ❖ An equal amount of normal saline as a negative control was injected on the flexor surface of the other forearm
- ❖ After 15 minutes induration of > 10mm surrounded by flare is taken was positive skin test, provided the reaction on the saline test was negative.
- ✶ An increase or abrupt fall in blood pressure, syncope, hurried breathing, palpitations and any other systemic manifestations was taken as positive test

The results of the SST was noted. The cases were observed for immediate reactions for half an hour.

A list of test results and adverse reactions were made.

Adverse reactions were divided into two categories:

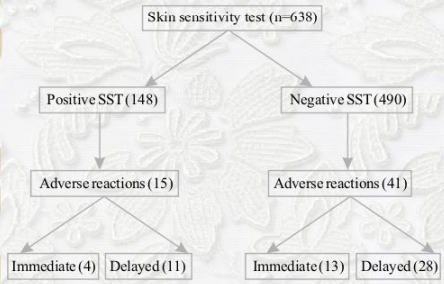
Immediate reactions: The reactions which occurred within 30 minutes of administration of full dose of ERIG. **Delayed reactions:** The reactions which occurred within 28 days of administration of ERIG.

Delayed reactions were assessed by interviewing the patients and observing for any reactions on their subsequent visit that is on day 3, day 7 & day 28.

RESULTS:

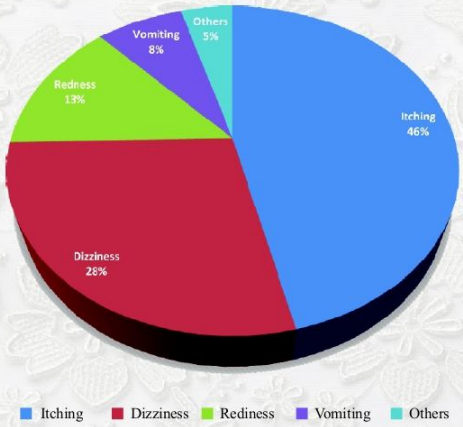
Majority of participants were males (63%) and in the age group of 16-40 years (55.8%).Most of the study population were from rural area (72.33%).Dog was the most common (92%) biting animal. Lower limb was the most common site of bite(68.6%).

FIGURE 1: FLOWCHART DEPICTING NUMBER OF SKIN SENSITIVITY TEST PARTICIPANTS SHOWING ADVERSE REACTIONSTO ERIG:



Out of the total patients who were administered ERIG (638), SST was positive in 148 and negative in 490 patients. Adverse reactions was observed in 15 patients of those who tested positive for SST(148) and in 41 patients who had a negative SST(490).

FIGURE 2: TYPES OF ADVERSE REACTIONSAMONG THE STUDY PARTICIPANTS(N=56):



Itching was the most common adverse reaction seen among the study participants followed by dizziness, redness at the site of injection and vomiting. 5% of the study population had other adverse reactions like abdominal pain or something crawling in the body.

TABLE 1:
RELATION OF ADVERSE REACTIONS TO THE RESULTS OF SKIN SENSITIVITY TEST:

SKIN SENSITIVITY TEST	ADVERSE REACTIONS		TOTAL
	POSITIVE	NEGATIVE	
POSITIVE	15(10.14%)	133(89.86%)	148
NEGATIVE	41(8.36%)	449(91.63%)	490

10.14% of the cases who had positive SST developed adverse reactions whereas only 8.36% of the cases with negative SST developed adverse reactions. 89.86% of cases with positive SST and 91.63% of cases with negative SST did not develop any adverse reactions and this difference was not statistically significant. (P value = 0.5053 and x^2=0.4436).

The sensitivity and specificity of the SST test is low i.e., 26.79% and 77.15% respectively. The positive predicative value & negative predictive value were 10.14% and 91.63% respectively. So performance of skin sensitivity test before administration of ERIG is not that justified.

DISCUSSION :

Equine rabies immunoglobulin is reasonably safe but at times it develops adverse events that are mild to moderate in nature. The immediate reactions that might occur with the use of heterologous sera are mediated by IgE or are triggered by complement activation, non-immunological activation of mast cells or of the modulators of arachidonic acid and do not depend on previous exposure to antigens (anaphylactoid reactions).

An adverse event rate of 10% was observed among the study participants who were positive to SST in our study whereas it was only 3% in a study conducted by panda et al[9].

Most of the adverse events were observed in day 7. Most of the study participants complained about itching on day 7. Levocetrizine was the most common medicine prescribed.

Sensitivity, specificity, positive predictive value and negative predictive value was 32%,77%, 3.1% and 98.03% in a study conducted by panda et al[9] whereas in our study sensitivity, specificity, positive predictive value & negative predictive value was 26.79%,77.15%, 10.14% and 77.15% respectively. As the sensitivity and specificity of skin sensitivity test is very low so testing before administration of immunoglobulin will not be of much help in a clinical setting as it cannot predict anaphylaxis or serum sickness reaction.

The procedure for skin sensitivity test is cumbersome and time consuming, especially in a busy health care facility. This may prompt health care practitioners to give only the vaccine and skip the immunoglobulin which would leave the patient half treated as the vaccine alone cannot guarantee adequate protection.

SST has been abolished in Brazil and WHO also does not advocate SST any more[3]. With this background of adequate evidence and appropriate recommendations, it is time to do a proper review and conduct many more studies so that we can make guidelines and stop using skin sensitivity test before administration of ERIGs. The producers of ERIGs, after approval of the regulatory authority, i.e Drugs Controller General of India (DCGI) should modify the product insert on SST.

RECOMMENDATIONS:

Health care personnel working in these facilities should be prepared to manage anaphylaxis which, though rare,could occur during any stage of administration of ERIG. Administration of ERIG in tertiary hospital alone is highly burdensome.Therefore continuing medical education of doctors of peripheral institutions as well as private hospitals must be emphasized and administration of ERIG envisaged. Proper use of ERIG will help a lot in reduction of burden of mortality and morbidity due to human rabies in India.

DECLARATION:

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Conflict of interest: None declared
Ethical clearance: Approval was taken from the Institutional Ethical Committee prior to start of the study

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