Original Article:

SAFETY OF NEW INDIGENOUSLY MANUFACTURED EQUINE RABIES IMMUNOGLOBULIN FOR POST EXPOSURE PROPHYLAXIS

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ABSTRACT

Rabies immunoglobulins are readymade anti rabies antibodies, which provide immediate protection; since, anti-rabies vaccines take 7-14 days to elicit the protective antibody response. Therefore, RIGs has to be infiltrated into all the wounds with category III exposures to neutralize the rabies virus at the site of deposition. The presently available ERIGs are purified, safe and economical for usage. In this regard, a new indigenously manufactured rabies immunoglobulin viz.Premirab has been approved by DCGI and is available in the market. The present study was a non-inferiority study conducted to assess the safety of new indigenously manufactured ERIG in post exposure prophylaxis as compared to the already established brand. A total of 246 animal bite victims with category III exposures were included in the study; randomly divided into 2 groups of 123 subjects viz. Premirab and Equirab group. The study showed that 7.3% of the Premirab group and 6.5% of the Equirab group had SST positivity. Similarly, the incidence of adverse drug reactions was found to be 4.0%in both the Premirab and Equirab group. In conclusion, the new indigenously manufactured ERIG Premirab is safe and non-inferior to the presently established brand.

Key words: safety, equine rabies immunoglobulin, post exposure prophylaxis, prevention, rabies

INTRODUCTION

Rabies is a viral zoonosis which occurs in more than 150 countries of the world.[1] The disease is transmitted to animals and humans through close contact with saliva from infected animals through bites, scratches, licks on broken skin and mucous membranes and poses a threat to more than 3.3 billion people in the world, primarily in Asia and Africa.[2] It is a neglected zoonotic disease which indicates that, it is insufficiently addressed by Governments and the International community. Rabies affects mostly the poor people living in remote rural areas and urban slums of the developing World.[3]

Rabies is 100% preventable; therefore, it is the first zoonosis in the list of neglected diseases targeted for regional and eventually global elimination by 2030 and is the disease most amenable to control, as the tools for prevention i.e., post exposure prophylaxis (PEP) are available worldwide.[4] Timely and complete post exposure prophylaxis, which includes proper wound washing, full course of anti-rabies vaccination (ARV) and local wound infiltration of rabies immunoglobulin (RIG) into all exposed wounds will save the lives of the exposed individuals.

RIGs are readymade anti rabies antibodies, which provide passive immunity and immediate protection. This is an essential part of PEP, since, even the best of modern anti rabies vaccines take 7-14 days to elicit the protective antibody response and thus, RIGs cover this vulnerable period in all Category III exposures.[5] RIGs are of two types i.e., Human rabies immunoglobulin (HRIG) & Equine rabies immunoglobulin (ERIG). HRIG is imported & expensive, not affordable to majority of the bite

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victims and thus, is a major constraint in developing countries of Asia and Africa. World Health Organization (WHO) recommends the use of ERIG for these countries to reduce the cost of PEP.[6]

In India, ERIG was initially manufactured in only one Government facility at Central Research Institute, Kasauli, Himachal Pradesh. Later, because of large number of animal bite cases in the country and subsequent increase in the demand for ERIG, there was a huge gap between supply & demand, which was the major limiting factor for its wider usage. Therefore, there was a need for increase production of ERIG indigenously. In this regard, Drug Controller General of India (DCGI), as per the recommendations of WHO, approved permission to private pharmaceutical companies to manufacture purified ERIG indigenously from 2001.[7] In this regard, few companies started manufacturing ERIG indigenously. In spite of that, as the number of animal bite cases in the country are increasingly coming for PEP and continued demand for RIGs, there is still a scope for other pharmaceutical companies to develop ERIG as per the demands. In this regard, an indigenous pharmaceutical company M/s. Premium Health Care Ltd., Pune has produced new purified equine rabies immunoglobulin viz. Premirab and is there in the market from past 2 years.

Therefore, post marketing safety has to be evaluated for wider usage. Therefore, the present study was a non-inferiority study conducted to assess the safety of new indigenously manufactured ERIG i.e., Premirab in post exposure prophylaxis as compared to the already established brand of ERIG viz. Equirab.

OBJECTIVES

1. To describe the post exposure prophylaxis provided to the bite victims.
2. To assess the safety of equine rabies immunoglobulin in post exposure prophylaxis and to compare with the established brand.

MATERIALS AND METHODS

The present study was initiated after obtaining the Institutional Ethical committee clearance and was conducted at the anti-rabies clinic, Department of Community Medicine, Kempegowda Institute of Medical Sciences (KIMS), Bangalore. All the animal bite victims who came to hospital with category III exposures for post exposure prophylaxis during the study period were included in the study. They were divided into two groups randomly viz., Premirab and Equirab group.

The socio-demographic characteristics & details of exposure were collected from all the study subjects using pre- designed, semi-structured proforma. PEP was provided to all the animal bite victims as recommended by World Health Organization. A signed informed consent was taken from the parents and/or guardians of all subjects before administration of ERIG and prior skin sensitivity test was done for testing hypersensitivity as per DCGI recommendation.

The calculated dose of ERIG was infiltrated to all the wounds as is anatomically feasible and if, any amount remained then it was administered deep intramuscularly. 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

Table - 1
Characteristics of animal bites

Characteristics	Premirab	Equirab
Age range	1-78 years	1-72 years
Sex: Male	83(67.4%)	84(68.3%)
Female	40(32.6%)	39(31.7%)
Biting animal:		
Dog	117(95.2%)	113(91.9%)
Cat	3(2.4%)	3(2.4%)
Monkey	2(1.6%)	2(1.6%)
Others	1(0.8%)	5(4.1%)
Provocation :		
Unprovoked	40(32.5%)	90(73.2%)
Provoked	83(67.5%)	33(26.8%)
Site of bite :		
Lower limb	6(4.9%)	1(0.8%)
Upper limb	31(25.2%)	5(4.1%)
Trunk	3(2.4%)	3(12.4%)
Head & neck	55(44.7%)	12(9.7%)
Multiple sites	28(22.7%)	101(82.1%)
Wound wash :		
Yes	108(87.8%)	105(85.4%)
No	15(12.2%)	18(14.7%)

recorded, only if the subject spontaneously complained of a problem to a question on general well being i.e., unaided recall. The delayed adverse drug reactions which were related to ERIG, were reported by the bite victim, any time after administration of ERIG and were also documented. Data regarding safety was recorded and then transcribed to the case record form. The overall data was analysed using MS Excel. The descriptive statistics was computed for statistical analysis.

RESULTS

A total of 246 animal bite victims with category III exposures were included in the study and were randomly divided into 2 groups, 123 in each group viz. Premirab and Equirab group. The age and sex distribution of the bite victims in both the groups were similar. The most common biting animal was dog in both the groups, followed by cats, monkeys and others. Most of the animal bites were unprovoked and were on the different parts of the body (Table 1).

All the bite victims in both the groups were given thorough wound wash with detergent soap and water in the hospital and all of them were administered intramuscular anti rabies vaccination. Similarly, all of them were given equine rabies immunoglobulin i.e., either Premirab or Equirab. Prior to administration of ERIG, skin sensitivity test (SST) was done for all subjects in both the group as per DCGI protocol and the results showed that 7.3% of the Premirab group and 6.5% of the Equirab group had SST positivity (Table 2).

Table - 2
SKIN SENSITIVITY TEST

Skin sentivity test	Premirab	Equirab
Administered	123	123
Positive SST	9	8
Percentage	7.3%	6.5%

The required quantity of equine rabies immunoglobulin was infiltrated locally, into and around the wound/s; wherever, anatomically not feasible, it was infiltrated both locally into the wound as well as systemic infiltration was done as shown in Table 3.

Table - 3
ROUTE OF ADMINISTRATION OF EQUINE RABIES IMMUNOGLOBULIN

Route of administration	Premirab	Equirab
Local	108 (87.8%)	112 (91.1%)
Local+ Systemic	15 (12.2%)	11 (8.9%)

The incidence of adverse drug reactions (ADRs) was found to be same i.e., 4.0% among both the Premirab and Equirab group. All the ADRs were local in nature and there were no systemic reactions. All the ADRs were mild in both the groups and resolved without any complications. The common ADRs were erythema at the site of injection, itching at the site of injection and pain at the site of injection in both the groups as shown in Table 4.

Table - 4
ADVERSE DRUG REACTIONS

Adverse drug reactions	Premirab	Equirab
Pain	2(1.6%)	3 (2.4%)
Erythema	2(1.6%)	1 (0.8%)
Itching	1(0.8%)	1 (0.8%)
Total	**5 (4.0%)**	**5 (4.0%)**

DISCUSSION

Rabies immunoglobulin is a lifesaving immune-biological,since it neutralises the virus at the site of deposition and is a must for all cases of category III animal exposures, i.e., all transdermal bites or scratches irrespective of site, number and severity.[8]

RIG is more effective when infiltrated immediately or within 24 hours of animal bite along with the first dose of vaccine; whereas, if vaccine alone was started, then RIG can be given up to 7 days after starting first dose of vaccine (minimum 3 doses of vaccine given on days 0, 3 and 7) as this will not interfere with the vaccine effect. However, RIG can be administered anytime if the person has not received any vaccine.

RIGs have to be infiltrated into all the wounds to neutralize the virus locally. Systemic [intramuscular] administration of RIG is of very little value. As much of the calculated dose of RIG, as is anatomically feasible, should be infiltrated into and around all the wounds i.e., RIG shall be

injected into the edges and base of the wound(s) till traces of RIG oozes out. It is preferable to use separate needles for infiltrating different wounds. Multiple needle injections into the wound should be avoided as far as possible.[9]

At present, there are two kinds of RIGs which are available worldwide i.e. Human rabies immunoglobulin (HRIG) and equine rabies immunoglobulin (ERIG). The presently available ERIGs are highly purified, safe and affordable. The study was conducted to assess the safety of new indigenously manufactured ERIG i.e., Premirab in post exposure prophylaxis as compared to the already established brand of ERIG viz. Equirab.

The present study showed that the incidence of positive skin sensitivity test was 7.3% and 6.5% for Premirab and Equirab respectively. The difference between them was not statistically significant ($p > 0.05$). Similarly, the adverse drug reactions in both the groups were similar i.e., 4.0%. This showed that both the ERIGs are safe and well tolerated with minimal ADRs. All the ADRs subsided without any complications.

Similarly, a study from Bangalore on clinical evaluation of safety of different brands of ERIG showed that the skin sensitivity test was positive among 13.2% of the subjects and the adverse drug reactions were 1.5%.[10]

Another study on safety of ERIG in children also showed that the skin sensitivity test was positive among 8.2% of the subjects and the adverse drug reactions were only 1.6%. All the ADRs subsided without any complications.[11]

All these studies showed that the adverse drug reactions for ERIG were minimal and all of them subsided without any complications, thereby showing that, the presently available ERIGs are safe and well tolerated by all age groups.

CONCLUSION

The new indigenously manufactured ERIG (Premirab) is safe and non-inferior to the presently available established brand (Equirab). Therefore it can be recommended for wider usage to prevent and ultimately eliminate human rabies by 2030.

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