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Research Article

Comparison of Safety Profile of Equine and Human Rabies Immunoglobulin in Children below 15 Years, in a Tertiary Care Hospital of Odisha - an Observational Study

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I N F O

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A B S T R A C T

Background: The incidence of rabies is equally more in children < 15 year of age i.e. 35.3% as found in the APCRI-WHO Survey in India. Out of the two alternatives (Equine Rabies Immunoglobulin: ERIG and Human Rabies Immunoglobulin: HRIG) for treatment for Category III animal bites, HRIG is invariably the preferred intervention mounting to exorbitantly high economic burden. There is paucity of studies comparing their safety profiles especially in children.

Methods: A hospital-based observational study was conducted at the Anti-rabies Clinic of SCBMCH, Cuttack, Odisha from March to April 2019. The enrolment of patients was done in two months period from 1st March to 30th April 2019 and all these patients were followed up for a period of one month till 31st May 2019. New Category III animal bite cases in <15 years of age, taking ERIG and HRIG comprised of two groups A and B, respectively. They were followed up on their subsequent visits on 3rd, 7th and 28th days of treatment to study any local and systemic reactions. Chi square test/ Fischer exact test/ Mann Whitney test were applied to compare the outcomes.

Result: Mean age in ERIG (Group A) is 9.84 (±3.9) years and for HRIG (Group B) is 7.1 (±4.1) years and mean weight for ERIG group is 27.63 (±12.4) kg and HRIG group is 24.2 (±23.8) kg. The total amount of immunoglobulin administered was 3.6 (±1.6) ml in ERIG (Group A) and 2.5 (±1.34) ml in HRIG (Group B). Any type of local reaction was seen in 42% cases in Group A (ERIG) and in only 5% cases in Group B (HRIG). Pain, itching, local swelling, oedema, and tenderness were more marked in Group A (ERIG) but were not found to be statistically significant in all cases. These local reactions were managed symptomatically with medications like analgesics and anti-histaminic. Similarly Systemic reactions in form of arthralgia, fever, malaise and generalized rash were also more observed in Group A (ERIG) which could be managed symptomatically with same medications.

Conclusion: Safety profiles (in terms of local and systemic reactions) of ERIG and HRIG were comparable in children below 15 years of age. The minor side effects of ERIG can easily be managed by readily available drugs like analgesics and antihistaminics in the ARV OPD itself.

Keywords: HRIG, ERIG, Category III Exposures, Safety Profile, Children <15 years of age

Introduction

India estimated to have highest incidence of rabies globally, with 30,000 of the world's 50,000 cases reported each year, that translates to roughly 36 % of global and 65% of Asian rabies case.[1] Out of total cases in Africa and Asia, most cases of rabies about 40% being children age <15 year have a history of contact with infected dog.[2]

Passive immunization is highly recommended to provide immediate protection from development of rabies along with 1st dose of vaccine or as soon as possible or within 7 days of start of antirabies vaccine administration.[3] Passive immunization can be offered by injecting RIG either human (HRIG) or equine (ERIG), which neutralizes the virus at site of bite and prevents its progression into CNS. It offers protection which starts immediately after administration and last 7-10 days during which active immunity to rabies can develop and protect the individual.

ERIG, which are indigenously produced are less expensive, affordable, and more widely available; still, its use is limited to only 2% (APCRI WHO survey in India).[4] However, ERIG has the potential to cause hypersensitivity in 1% to 11% patients and anaphylaxis and allergic reactions are rare and these reactions are controlled with antihistaminics and analgesics.[3,5]

The study was done to access how ERIG can be administered despite some known side effects in comparison to HRIG which is the gold standard for passive immunization against Category III animal bite treatment. However, recent studies (Phase 4 Clinical Trial) show similar efficacy in terms of prevention of clinical rabies and the side-effects like itching, fever, generalized rash, malaise, pain, etc., are more with ERIG.[6] But these side-effects are easily managed in an OPD set up.

Studies comparing the local and systemic side-effect of ERIG and HRIG are lacking in this part of the state especially among children. Hence, the current research was planned to study the comparison of safety profile of ERIG and HRIG in children below 15 years of age.

Materials and Methods

This is a hospital-based observational study conducted at the Anti-rabies Clinic (ARC) of SCBMCH, Cuttack, Odisha over a period of 2 months from March to April 2019. The study subjects were any new Category III animal bite cases among children less than 15 years of age attending the ARC of SCBMCH and with an exclusion criteria of children with acute febrile illness or serious illness or any immune-supressive disease, or having received any blood products within last 3 months or any allergic skin diseases.

A sample size of 80 was taken purposively based on the daily patient load. About 2 to 3 patients were selected randomly from both the groups (Group A: at least one child receiving ERIG and Group B: at least one child receiving HRIG) on lottery method from new cases of Category III animal bite attending ARV OPD each day. So a total of about 30 children receiving ERIG and 30 children receiving HRIG were enrolled with an addition of extra 10 patients from both groups to compensate any dropout or loss to follow up. All the children were followed up during their next visits on Day 3, Day 7, and Day 28 for completion of antirabies vaccine (IDRV). HRIG was given to that patient who had either multiple bites or depth of wound was more or if bite was on face and neck or from a suspected rabid animal or child who had a skin test positive to the test dose of ERIG. After the children were chosen, an informed consent from their respective parent was taken. The antirabies vaccine (PVRV, i.e, Abhyarb Batch No. - 62E18002A, Mfg 8/2018, Exp 5/2021) as per updated Thai Red Cross Regimen (2-2-2-0-2) of an amount of 0.1 ml ID on both the deltoids was administered. The HRIG (Inj. Berirab-P B.N.P100014723) by CSLB Behring, Germany, with a potency of 150IU/ml) was given as 20 IU /kg body weight or ERIG (inj. Rabies antiserum B.N.191049) by Premium Serums with a potency of 300 IU/ml was given 40 IU/kg body weight as prescribed.

The amount of ERIG and HRIG was given as per body weight as 40 IU and 20 IU /kg body weight, respectively, as much as anatomically feasible at the site of bite and the rest was injected on thigh so as to prevent any compartmental syndrome and infection (if the wound is on fingers and toes).

Before administration of ERIG, a skin test was done with the test dose of ERIG (ERIG diluted with normal saline with maximum dilution of 1:10) and the patient was asked to wait for about 30 minutes for observation of any reaction like itching, redness, or swelling. The ERIG was infiltrated around the wound as per the calculated dose as much as anatomically feasible and rest amount if any was given IM over thigh. If the skin test to the test dose of ERIG was positive then the Patient was administered HRIG in place of ERIG as per body weight. The reactions following ERIG administration if any were managed at the ARC by analgesics and anti-hitaminics. The phone numbers of patient's parent were taken and, if any reaction occurred, they were instructed and counseled to inform us. Vital parameters like blood pressure, pulse and temperature were recorded after RIG administration. In every subsequent follow up visits on days 3, 7 and 28, the parent of children were asked again whether any reaction occurred or not. In all selected children, sign and symptoms of local and systemic reaction like itching, fever, malaise, swelling, oedema, arthralgia, rash, induration were observed and, if seen, managed by simple medication available in the OPD. Two children from ERIG group were missed as lost to follow up.

A pretested and predesigned questionnaire was used to collect data.

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Statistical Analysis

Analysis was done using SPSS software (version 21). Descriptive statistics was used for analysis. Chi square test, odds ratio (with 95% confidence interval) were used to show the association. P <0.05 was considered as statistically significant. Results were presented in the form of tables.

Ethical Consideration

Ethical clearance was taken from Institutional Ethics Committee (IEC), SCB MCH, Cuttack. Verbal informed consent was taken from parents of all participants.

Result

The mean age in ERIG group is 9.84 (±3.9) years and in HRIG group is 7.13 (±4·1) years.

Gender, weight, systolic blood pressure, diastolic blood pressure as baseline character had some difference between ERIG and HRIG group but not statistically significant.

Mean volume of total ERIG given was 3.6 (±1.6) ml which was more as compared to HRIG which was approximately 2.5 (±1.34) ml and the difference of administration of total volume of RIG was found to be statistically significant (as child with higher age group had more weight so this total amount also more in ERIG). The amount of RIG infiltrated into and around the wound was as per the depth and severity of bite which was 1.9 (±0.95) ml in ERIG and 1.8 (±0.49) ml in HRIG. The amount of RIG given IM in ERIG group was 1.59 (±1.3) ml which is more as compare to HRIG where mean volume is 0.71 (±1.3) ml only and also it was statistically significant. The HRIG is preferred in multiple bites or severe bites so maximum volume was used locally in the wound site and less or no amount of HRIG was left for IM administration.

In case of ERIG group, any form of local reaction was found in 42.2% cases. In HRIG group, only 5% had developed any type of local reaction and the difference of occurrence of development of local reaction among these two groups was found to be statistically significant. Pain, itching more in ERIG group, i.e., about 34.2% and 28.94%, respectively, as compared to HRIG which was about 5% and 2.5% for pain and itching, respectively, and also statistically significant. Induration (15.78%), tenderness (26.31%) was noticed only in ERIG group as compared to HRIG and it was also statistically significant. But this percentage of induration and tenderness was less and could be managed easily with medication available in our OPD.

Table 1.Baseline characteristics of the two groups

	Group A ERIG (n=38)	Group B HRIG (n=40)	P-value (t-test)
Age in years Mean (±SD)	9.84 (±3.9)	7.13 (±4.1)	0.04
Gender			
Boy	16 (42.1%)	24 (60%)	0.264
Girl	22 (57.89%)	16 (42.1%)	
Mean Weight in kg (±SD)	27.63 (± 12·4)	24.20 (±23.8)	0.548
Mean SBP (±SD)	97.37 (±12.9)	89.7 (±9.7)	0.052
Mean DBP (±SD)	73.6 (±11.2)	69.2 (±6.4)	0.150

Table 2.Details of RIG infiltration locally and IM

	Group A ERIG	Group B HRIG	P-value (t-test)
Amount of RIG in ml (total)	3.6 (±1·6)	2.5 (±1.34)	0.028
RIG given local	1.9 (±0.95)	1.82 (±0.49)	0.573
Rig given IM	1.59 (±1.37)	0.71 (±1.3)	0.04

Table 3.Comparison of the local reaction in the two study groups

Local reaction	ERIG group (n=38)	HRIG group (n=40)	P-value (Chi square test)
Any Local reaction			
Yes	16 (42.1%)	2 (5%)	0.001
No	22 (57.89%)	38 (95%)	
Pain			
Yes	13 (34.2%)	2 (5%)	0.006 OR 13.8 CI (1.5-125.6)
No	25 (65.78%)	38 (95%)	

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Itching			
Yes	11 (28.94%)	1 (2.5%)	0.001
No	27 (71.05%)	39 (97.5%)	
Swelling			
Yes	6 (15.78%)	0	0.06
No	32 (84.21%)	40 (100%)	
Oedema			
Yes	4 (10.52%)	0	0.136
No	34 (89.47%)	40 (100%)	
Tenderness			
Yes	10 (26.31%)	0	0.002
No	28 (73.68%)	40 (100%)	
Induration			
Yes	6 (15.78%)	0	0.03
No	32 (84.21%)	40 (100%)	

Table 4.Comparison of systemic reaction in two study group

		ERIG Group (n=38)	HRIG Group (n=40)	P-value
Systemic Reaction	Yes No	12 (31.57%) 26 (68.42%)	4 (10%) 36 (90%)	0.095
Rash	Yes No	8 (21.05%) 30 (78.94%)	2 (5%) 38 (95%)	0.134
Malaise	Yes No	6 (15.78%) 32 (84.21%)	2 (5%) 38 (95%)	0.267
Fever	Yes No	12 (31.57%) 26 (68.42%)	4 (10%) 36 (90%)	0.095
Arthralgia	Yes No	8 (21.05%) 30 (78.94%)	3 (7.5%) 37 (92.5%)	0.339

Most of the systemic reaction, approximately 31.57%, were seen in the ERIG group as compared to HRIG group. Generalized rashes, malaise, fever and arthralgia were seen more in ERIG group as compared to HRIG, however the occurrence of systemic reaction in both the groups was not found to be statistically significant. Among all systemic reaction maximum had fever (31.5%) in case of ERIG group.

Two children developed rash following HRIG administration on Day 3 and it subsided before next follow up on Day 7 with simple anti-histaminics.

Discussion

As per WHO guidelines, administration of RIG in Category III animal bite is mandatory due to vaccine failure and also due to the variable incubation period of rabies virus. Currently in developing countries only 2% of all post exposure treatment includes both vaccine and serum.[7] This is because HRIG is not widely available and its cost is prohibitive and there is apprehension about side effects of ERIG.

In our study, 42.2% of children with ERIG developed any type of local reaction. Among all local symptoms pain was seen in 34.2%, itching in 28.94 %, tenderness in 26.3% and induration in 15.17% of children which was more with ERIG as compared to HRIG. But in a study by Behera TR et al. conducted at the MKCG Medical college Berhampur, Odisha in Category III animal bite reported induration in 91.8% as the most common local reaction followed by erythema in 43.1%, pruritus in 29.8% and pain as the least common local side effect seen in only 19.9%.[8] Systemic reaction like fever, malaise also present in more children with ERIG as compared to HRIG group. The hypersensitivity to ERIG also depends on the purification of the Ig (different in different brand of ERIG). The hypersensitivity to different brand of ERIG varies from 1% to 12% in India and other countries.[3,5,9]

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According to a previous study by Sikes in 1969, the less purified ERIG had higher chance of any reaction.[10] These minor side effects were managed very easily at the ARVOPD with simple medication like cetrizine, levocetrizine, and paracetamol.

In our study total amount of ERIG administered was 3.6 (±1.6) ml as compared to HRIG which is only 2.5 (±1.3) ml. Also, the amount of ERIG inoculated locally is 1.9 (±0.95) ml in comparison to 1.8 ml in HRIG. The amount of ERIG injected IM over thigh is 1.59 (±1.37) ml as compared to HRIG which was only 0.71 (±1.3) ml as HRIG usually used in severe bite and lacerated wound and multiple bite; so, more amount used locally over biting site. Henry et al. and Bhanganada et al. found, in a study of severe animal bite wounds and a control group of severe lacerations that injecting such wounds did not increase the incidence of infection and complication.[11,12]

HRIG is derived from human protein not foreign species protein (like ERIG) so less chance of any reaction. Purification of RIG leads decreased sensitization of ERIG.[7] In our study, no case of serum sickness was found whereas a study by Moharana et al. at the same center found 0.125% of cases of serum sickness among the recipients of ERIG among children of age 0 to 14 years. In another study by Bhangada K et al. it was found to be 0.086% in 0 to 14 year age group. The reactions like itching, fever, arthralgia were also due to the vaccine component.

No case of anaphylaxis or clinical rabies was seen during this study and also no life threatening complication due to ERIG administration was noticed. Similar finding from another study by Maharana S et al. was also reported earlier at the same center. So use of ERIG is a safe and life-saving procedure. Serum sickness is usually found from day 8th and ends with on day 14th following ERIG administration.[7] However, in our study, we did not find any case of serum sickness.

As we know, the cost of HRIG is much higher about 8 to 10 times than the ERIG which is supplied by Government of Odisha free of cost. The complication due to ERIG was comparable with HRIG in our study, and the few complications of ERIG were managed with simple antipyretics, analgesics and antihistaminics.

Conclusion

From this study we have observed that both ERIG and HRIG have similar efficacy and safety. ERIG has more side effects than HRIG, i.e., both local and systemic. However these reactions were managed with simple drugs like anti-histaminic and analgesics and anti-pyretics. ERIG is more economical than HRIG. So use of ERIG in case of Category III animal bite is safe and reliable. This study can be generalized to the population for use of ERIG in all Category III animal bite cases.

Conflict of Interest: None

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Questionnaire

Name:

Age:

Sex:

Address:

Mobile no.:

Type of animal: provoked/ unprovoked, dead/ living/ UT

Site of bite:

Type & Number of wound:

Weight:

Amount of ERIG/HRIG to be administrated:

Skin test- reactive/ non reactive:

If reactive, any action taken:

Any premedication given:

Amount (in ml) infiltrated around bite site locally:

Amount (in ml) given in thigh:

Any immediate reaction in observing the pt. for 1- 2 hrs:

S/Es –local/systemic/none

S/Es if any-resolved by medications/resolved spontaneously

If resolved by medications-specify the drugs

Which S/Es ↓sed gradually with medications- local/systemic

Which S/Es ↓sed gradually without medications- local/systemic

Any case of anaphylaxis observed:

Any case of serum sickness observed:

Any complain on day 3: (S/E)

Any complain on day 7:

Any complain on day 28:

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