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Safety and clinical efficacy of human rabies immunoglobulin in post exposure prophylaxis for category III animal exposures

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ABSTRACT

The human rabies immunoglobulin (HRIG) is a life-saving immune biological essential for all category III animal exposures. It provides neutralizing antibodies at the site of exposure until the body can produce vaccine-mediated antibodies. We conducted this study to determine the safety and clinical efficacy of an HRIG being used presently for post-exposure prophylaxis (PEP) and to strengthen the existing evidence for its further usage. We conducted a prospective cohort study in 123 subjects with category III animal exposures at the KIMS Hospital and Research Center, Bangalore, India. Post-exposure prophylaxis (PEP) with wound toilet, a single application of HRIG, and a full course of anti-rabies vaccination were provided to all the study subjects. The volume of HRIG was calculated according to the body weight, and all the wounds were infiltrated as was anatomically feasible. All the study subjects were followed up for immediate and delayed adverse events (AE), both local and systemic. Subsequently, all the subjects were followed up for 6 months to demonstrate the clinical efficacy of PEP. The incidence of AEs was 11.4% including local pain, erythema, itching, headache, body ache, fever, and malaise. All AEs were mild and subsided without any complications. All the study subjects were healthy and alive after 6 months following the administration of HRIG, along with a full course of anti-rabies vaccine. Our study provides evidence of safety and clinical efficacy of HRIG for category III animal exposures and supports its continued usage.

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Introduction

Animal exposures among humans is a public health problem, posing an impending threat of rabies to over 3.3 billion people worldwide.[1] These exposures occur largely in the underserved populations, both in rural and urban areas, and have been documented for more than 4000 years.[2] They are mostly seen in Africa and Asia, where a close habitation of large human and dog populations is reported.[3]

The World Health Organization's SouthEast Asia region, which includes Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, and Timor-Leste, have reported the most animal exposures worldwide, with 1.4 billion people at risk.[4] Therefore, in these countries, whenever there is an exposure to an animal that is suspected or confirmed to be rabid or when there is doubt about the circumstances that led to the exposure, post-exposure prophylaxis (PEP) should be initiated immediately and completed to prevent rabies.[5]

In category III animal exposures, defined as single or multiple transdermal bites, scratches or licks on broken skin, and contamination of mucous membrane with animal saliva, the PEP consists of a thorough wound wash with soap and water, followed by the application of a virucidal agent to reduce the viral inoculum, a complete course of post-exposure anti-rabies vaccination to induce antibodies that prevent the risk of the virus entering the peripheral nerves and a timely infiltration of rabies immunoglobulin (RIG) to neutralize the virus at the wound site.[6,7]

If the modern anti-rabies vaccines are given immediately after the bite, they are capable of producing neutralizing antibodies with a sero-positive titer of ≥0.5 IU/ml in the bitten person only after 7–14 days from the first dose of vaccine, thus leaving the person vulnerable to rabies during this window period.[8,9] Therefore, the infiltration of RIG into and around all the wounds in category III exposures serves to neutralize the virus at the site of the bite and save the life of the victim.[10]

Rabies immunoglobulins have proved their efficiency when administered at the site of viral entry (wounds/exposed areas) in association with a rabies vaccine. There are two types of RIGs available viz. equine rabies immunoglobulin (ERIG) and human rabies immunoglobulin (HRIG).

Human rabies immunoglobulin (HRIG) is prepared from the pooled plasma of human donors who are hyper-immunized with a rabies vaccine. Since HRIG is homologous in origin, it is relatively free from the side effects encountered with a serum of heterologous origin (such as ERIG) and provides passive immune protection at half the dose of ERIG owing to a longer half-life of 21 days.[7]

The human rabies immunoglobulin (HRIG) manufactured by CSL Behring, Germany, has been used for PEP against rabies in many countries across the globe since 1992. The

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present study was conducted to substantiate the existing evidence of its safety and clinical efficacy in the PEP of category III animal exposures across all ages.

Materials and methods

We conducted a prospective study from January 2021 to December 2021 at The Kempegowda Institute of Medical Sciences (KIMS) Hospital and Research Center, Bangalore, India, after clearance from the institutional ethics committee. Our study included 123 category III animal bite victims who presented to the anti-rabies clinic in the hospital for PEP.

Sample size

The sample size was calculated based on the incidence of adverse events (AEs) in subjects with category III animal exposures who received HRIG in a recent study, i.e. 16.7%.[11] Assuming a confidence interval of 95%, α = 0.05, and absolute precision (d) of 10%, the sample size was calculated as follows:

$$n = \frac{Z_{(\alpha/2)^2} pq}{d^2} = \frac{(1.96)^2 \times 0.167 \times 0.833}{0.01} = 53.42$$

Using the design effect of 2, 53.42 × 2 = 106.84, and assuming a 15% non-response rate, 106.84 + 16.02 = 123. n = sample size; Z = level of confidence according to the standard normal distribution; for a level of confidence of 95%, it is 1.96; p = 16.7% (AE); q = 1-p (83.3%); d = 10% (absolute precision).

Data collection

We enrolled 123 apparently healthy male and female subjects of any age with category III animal exposures who signed the written informed consent to participate in the study. Those with a history of prior animal exposures, rabies vaccination, or rabies immunoglobulin administration, those with a history of allergy to chicken egg, vaccines, or any other medicines, and persons with preexisting medical illnesses, immunocompromised status, and pregnant or lactating women were excluded from the study.

A detailed history was recorded including the sociodemographic profile and the details of animal exposure, such as the type of animal and whether the attack was provoked or unprovoked. Bites inflicted on a person attempting to feed or handle an apparently healthy animal were regarded as provoked. An unprovoked attack indicates that the animal was more likely to be rabid. Simultaneously, a history of current or past medical issues, past medications, and allergy to any medicines were also noted. A detailed clinical examination was conducted to evaluate all the wounds present in the study subjects. The number and site of the wounds (viz. upper limb, lower limb, head, neck, trunk, and abdomen) and their severity (viz., abrasions, lacerations, and punctured) were recorded. The size of each wound was measured at its maximum length by a non-stretchable measuring tape. For patients who had multiple sites of exposure, different types of wounds, and different size of wounds per patient, the size of only the largest wound was recorded for analysis.

PEP was provided to all the study subjects according to the National guidelines.[7] It included a thorough wound wash with soap and running water for 10–15 minutes, irrespective of any wound care given before presentation to the hospital, and a complete course of intramuscular anti-rabies vaccination by the Essen regimen, i.e. one dose each, on days 0, 3, 7, 14, and 28. A simultaneous infiltration of HRIG was done on day "0", in a single dose not exceeding 20 IU/kg body weight into all the wounds, as was anatomically feasible, i.e. until it oozes out of the wound, indicating a successful infiltration. Any remaining volume was injected deep intramuscularly away from the site of vaccination. For multiple or extensive wounds, the calculated dose of HRIG was diluted with normal saline as was clinically required and infiltrated to cover all the wounds. The doses of HRIG needed for infiltration of bite wounds were recorded for all the patients.

The human rabies immunoglobulin (HRIG) Berirab P, available in 2 ml prefilled syringe, manufactured by CSL Behring, Germany, and marketed in India by Bharat Serums and Vaccines Ltd. with potency of 150 IU/ml of market Batch No. P100123647, with manufactured date 06.2019 and expiry date 05.2022, was used in this study.

All the patients were assessed for AEs following PEP. The subjects were observed for an hour to record possible immediate solicited local AEs such as pain, erythema, pruritus, and induration and/or systemic reactions like shivering, malaise, asthenia, faintness, dizziness, headache, myalgia, arthralgia, nausea, abdominal pain, and hypersensitivity or allergic reactions such as urticaria, rash, and anaphylaxis.

Follow-up cards indicating the dates for the next doses of vaccination were issued to all the patients to note down unsolicited late AEs such as itching, fever, serum sickness, arthralgia, and any others. These cards were checked during subsequent hospital visits on days 3, 7, 14, 28, and 180. Each instance was counted as a separate event, even if the patient reported the same even more than once during the 6-month period.

The causality and severity of the AE was adjudicated by the principal investigator (physician).

The AEs were graded as Mild (Grade 1) - with noticeable discomfort without interference with daily activities; Moderate (Grade 2) - which interferes with daily activities; and severe (Grade 3) - which prevents daily activities.

All the study subjects were followed up via phone calls every month after complete PEP, and at the end of 6 months, they were called to the hospital to confirm their health and survival status. Those who were unable to come to the hospital were visited at their homes. The survival of the exposed persons after the completion of the rabies PEP and beyond the usual incubation period of the disease, i.e., six months, is an indicator of the clinical efficacy of the treatment.

The data collected was statistically analyzed using MS Excel and IBM-SPSS statistics software package version 21.0. The frequency and percentages were computed for analyzing the AEs, and chi-square test was used to find out the relationship of AEs to different characteristics of the study subjects.

Results

The present study included 123 subjects with category III animal exposures across all age groups. Most of them (56.1%) were children; 32.5% were adults; and 11.4% were elderly. The majority of the bites were from dogs (92.7%), followed by cats (4.9%) and monkeys (2.4%). The bites in the study subjects were present on lower limbs (39.1%), upper limbs (23.6%), head, neck, and face (17.8%), trunk (7.3%), and some had bites on multiple sites (12.2%). The most common type of wound was abrasions (43.9%) followed by lacerations (35.8%) and punctured wounds (20.3%). The wound size varied from as small as <0.1 cm to as large as >10 cm, with most of the wounds being 1–5 cm in size (55.4%) (Table 1).

HRIG was infiltrated locally into or around the wound in all the subjects. Additionally, in some patients, the HRIG remaining after infiltration was administered deep intramuscularly at a site away from the anti-rabies vaccination (Table 2).

Among the 123 study subjects, 14 (11.4%) reported minor AEs. The common local AEs were pain at the injection site, erythema, itching and the systemic AEs included fever, malaise, headache and body ache (Table 3). All the AEs were mild in nature and subsided spontaneously and completely, without any complications. Some (3.2%) patients had applied irritants like lime, turmeric and coffee powder before coming to the clinic but none of them reported any AEs after PEP.

The age of the patients and the type of concomitant vaccine used did not have a significant correlation with the occurrence of the AEs; however, the dose of HRIG administered was significantly associated with occurrence of local AEs (Table 4). None of the study subjects reported a severe AE or an AE leading to discontinuation of the study. There were no missed visits or dropouts during the course of the study.

Table 1. Details of exposure among study subjects (n = 123)*.

Details of exposure	Frequency	Percentage
Biting animal:		
Dog	114	92.7
• Stray	79	69.3
• Pet	35	30.7
Cat	6	4.9
Monkey	3	2.4
Circumstance of bite:		
Provoked	43	34.9
Unprovoked	80	65.1
Type of wound:		
Abrasion	54	43.9
Laceration	44	35.8
Punctured wound	25	20.3
Size of wound:		
<1 cm	50	40.6
1–5 cm	68	55.3
>5 cm	5	4.1
Site of Exposure:		
Lower limb	48	39.1
Upper limb	29	23.6
Head, neck, and face	22	17.8
Trunk	9	07.3
Multiple sites	15	12.2
Wound wash practiced:		
Yes	95	77.2
No	28	22.8

*For patients who had multiple sites of exposure, different types of wounds, and different size of wounds per patient, the size of only the largest wound was recorded for analysis.

Table 2. Usage of rabies immune biologicals (n = 123).

Rabies immune biologicals	Frequency	Percentage
Anti-rabies vaccine used:		
PCECV	59	48
PVRV	64	52
Site of HRIG administration:		
Local	99	80.5
Local and systemic	24	19.5
Median volume of HRIG infiltrated into the wound (ml):		
<1 cm (n = 50)	1.1 (0.7–1.9)	
1–5 cm (n = 68)	2.5 (2–3.1)	
>5 cm (n = 5)	5.2 (3.2–7.4)	

PCECV Purified chick embryo cell vaccine; PVRV purified vero cell rabies vaccine.

Table 3. Number of adverse events following post exposure prophylaxis.

Types of adverse events*	Frequency	Percentage
Local:		
Pain	5	4.1
Erythema	2	1.6
Itching	2	1.6
Systemic:		
Head ache	2	1.6
Body ache	1	0.8
Fever	1	0.8
Malaise	1	0.8
Total	14	11.4

*Multiple response.

Table 4. Adverse events related to different characteristics of the study subjects.

Adverse events	Present	Absent	X^2, p-value
Age:			
<18 years (n = 69)	8 (11.6)	61 (88.4)	0.196;
18–60 years (n = 40)	4 (10)	36 (90)	0.90
>60 years (n = 14)	2 (14.3)	12 (85.7)	
Concomitant vaccines:			
PCECV (n = 59)	8 (13.5)	51 (86.5)	0.533;
PVRV (n = 64)	6 (9.4)	58 (90.6)	0.46
Site of HRIG administration:			
Local (n = 99)	10(10.1)	89 (89.9)	0.826;
Both local and Systemic (n = 24)	4 (16.6)	20 (83.4)	0.36
Dose of HRIG administration:			
0.7–1.9 ml (n = 50)	4 (80)	46 (20)	12.36;
2–3.1 ml (n = 68)	7 (10.3)	61 (89.7)	0.002
3.2–7.4 ml (n=5)	3 (60)	2 (40)	
Timing of adverse events:			
Immediate	14	109	

Figures in parenthesis indicates percentages; HRIG: human rabies immunoglobulin; X^2 = chi-square value.

In the present study, all the subjects were healthy and alive throughout the period of 6 months after receiving PEP, thereby proving the clinical efficacy of HRIG when used along with the vaccine.

Discussion

Passive immunization has been an essential component of PEP to prevent rabies since decades. From the first recorded preparation of rabies immune serum described by Babes & Lepp in 1889, to WHO adapting its guidelines in 1957, recommending a combination of a single serum application and a course of 14 daily vaccinations as the optimal post-exposure treatment, multiple studies have

proven the efficacy of combined administration of vaccine and serum after animal bite.[12–14] The benefit of RIG in combination with vaccination in PEP of patients with severe bite wounds has since then been established as scientific evidence.[9–15–17]

Hosty et al.[18] in 1959 and Winkler, Schmidt & Sikes[19] in 1969 described efforts to prepare rabies immune globulin of human origin, further to which, a study by Cabasso et al.[20] led to a dose of 20 IU/kg proven to provide early protection without interfering with the active antibody response to anti-rabies vaccination.

The present study was conducted as a post-marketing evaluation of Berirab P, since there were no published studies on this therapy despite more than 30 years of its usage. Our study provides the clinical evidence of the safety and efficacy of HRIG in combination with a full course of anti-rabies vaccination for PEP and contributes for the evidence supporting the use of HRIG in all category III animal exposures. The study subjects were representative of both sexes and varied age groups. The incidence of AEs was found to be 11.4%, and all were mild in nature and subsided spontaneously without any complications.

These findings are similar to other studies evaluating different rabies immunoglobulins/rabies monoclonal antibodies for passive immunization. A phase 3, randomized, non-inferiority trial evaluated the anti-rabies monoclonal antibody cocktail (twinrab^{tm}) and HRIG in 308 patients of category III exposure from a suspected rabid animal. 27.7% patients from the antibody cocktail group and 21.1% from the HRIG group experienced local reactions during the study. Most of these reactions were local, such as pain and swelling, in both the groups. All the AEs subsided without complications.[21]

In another study, a human monoclonal antibody against rabies virus glycoprotein G, developed by recombinant DNA technology, was administered to 199 subjects. A total of 461 AEs were reported, of which 83.7% were solicited events and 16.3% were unsolicited events, all of which were found to be unrelated to the product under study. There were no serious AE reported during the study period.[22] A study from USA also showed that HRIG was well tolerated and safe for PEP administered concomitantly with rabies vaccine.[23]

Likewise, a study of safety and efficacy of rabies immunoglobulin in 30 children with suspected exposure showed no serious AEs. Twelve subjects experienced a total of 13 AEs deemed treatment-related.[24] Similarly, in Odisha, India, a comparative safety study of ERIG and HRIG in children at a tertiary care hospital showed that 42.2% in the ERIG group had AEs, whereas only 5% in the HRIG group developed AEs, and the difference was statistically significant.[25]

In our study, all the subjects recovered completely and were alive at the end of the study period of 6 months after receiving PEP, proving the clinical efficacy of HRIG in PEP. The efficacy of HRIG in the present study is consistent with the real-world usage results for this product at our center, where it has been used for more than two decades. The efficacy is consistent with the results of other studies, including one from Bangalore, India, with 717 subjects having category III animal exposures, and another study on 95 subjects.[10,26]

Our study was limited by logistical issues which prevented the follow-up of the biting animals to ascertain if they were rabid. Likewise, the Rabies Virus Neutralizing Antibody (RVNA) analysis for the immunogenicity of the anti-rabies vaccine could not be done due to the costs involved. However, as the maximum incubation period of rabies is 6 months, the survival status of all the study subjects beyond 6 months was indicative of the clinical effectiveness of the PEP administered.

In conclusion, this study provides robust evidence of the safety and clinical efficacy of human rabies immunoglobulin in category III animal exposures and supports its continued usage to prevent rabies in humans.

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References

1. WHO Expert Consultation on Rabies. Third report, technical report series 1012. Geneva: World Health Organization; 2018.
2. Tarantola A. Four thousand years of concepts relating to rabies in animals and humans, its prevention and its cure. Trop Med Infect Dis. 2017;2(2):e5. doi:10.3390/tropicalmed2020005.
3. World Health Organization. WHO South East Asia Region: Strategic framework for elimination of human rabies transmitted by dogs in the South–East Asia region. Regional Office for South East Asia, World Health Organization; 2012.
4. Knobel DL, Cleaveland S, Coleman PG, Fèvre EM, Meltzer MI, Miranda ME, Shaw A, Zinsstag J, Meslin F-X. Re-evaluating the burden of rabies in Africa and Asia. Bull World Health Organ. 2005;83(5):3608. doi:10.1590/S0042-96862005000500012.
5. World Health Organization. Weekly epidemiological record. Rabies Vaccines: WHO position paper No. 16. Wkly Epidemiol Rec 2018;93:201–20.
6. Kalappa Sudarshan MK, Haradanhalli RS. Facilities and services of postexposure prophylaxis in anti-rabies clinics: a national assessment in India. Indian J Public Health. 2019;63(1):s26–30. doi:10.4103/ijph.IJPH_367_19.
7. National Guidelines for Rabies Prophylaxis. National rabies control programme. National Centre for Diseases Control. New Delhi (India): Ministry of Health and Family Welfare; 2019. p. 618.
8. Zero by 30. The global strategic plan to end human deaths from dog mediated rabies by 2030. Geneva: Food and Agriculture Organization of the United Nations, World Organisation for Animal Health, World Health Organization and Global Alliance for Rabies Control; 2018.
9. Habel K, Koprowski H. Laboratory data supporting the clinical trial of anti-rabies serum in persons bitten by a rabid wolf. Bull World Health Organ. 1955;13:773–79.

10. Haradanhalli S R, Krishna C, Kumar P, Siddareddy I, Annadani RS. Safety, immunogenicity and clinical efficacy of post exposure prophylaxis in confirmed rabies exposures. Global Vaccines Immunol. 2016;1(3):56–59. doi:10.15761/GVI.1000116.
11. Shivalingaiah AH, Shankaraiah RH, Hanumanthaiah AND. Safety of new indigenous human Rabies Monoclonal Antibody (RMAb) for Post Exposure Prophylaxis. Indian J Comm Health. 2018;30:196–201.
12. Gerber F, Tetchi M, Kallo V, Léchenne M, Hattendorf J, Bonfoh B, Zinsstag J. Rabies Immunoglobulin: brief history and recent experiences in Côte d'Ivoire. Acta Trop. 2020;211:105629. Epub 2020 Jul 11. PMID: 32659281. doi:10.1016/j.actatropica.2020.105629.
13. Habel K. Public Health Weekly Reports for MAY 18, 1945. Public Health Rep. 1945;60(20):545–76. doi:10.2307/4585257.
14. Atanasiu MB, Baltazard M, Fox JP, Habel K, Kaplan MM, Kaplan MM, Kissling RE, Komarov A, Koprowski H, Lepine P, et al. Rabies neutralizing antibody response to different schedules of serum and vaccine inoculations in non-exposed persons. Bull World Health Organ. 1956;14(4):593–611.
15. Baltazard M, Bahmanyar M. Field trials with rabies vaccine on persons bitten by rabid wolves. Bull World Health Organ. 1955;13:747–72.
16. Rabies, W.H.O.E.C.o., World Health, O. Expert committee on rabies: third report 694. Geneva: World Health Organization; 1957.
17. Dean DJ, Baer GM, Thompson WR. Studies on the local treatment of rabies-infected wounds. Bull World Health Organ. 1963;28:477–86.
18. Hosty TS, Kissling RE, Schaeffer M, Wallace GA, Dibble EH. Human antirabies gamma globulin. Bull World Health Organ. 1959;20:1111–19.
19. Winkler WG, Schmidt RC, Sikes RK. Evaluation of human rabies immune globulin and homologous and heterologous antibody. J Immunol. 1969;102:1314–21.
20. Cabasso VJ, Loofbourow JC, Roby RE, Anuskiewicz W. Rabies immune globulin of human origin: preparation and dosage determination in non-exposed volunteer subjects. Bull World Health Organ. 1971;45:303–15.
21. Kansagra K, Parmar D, Mendiratta SK, Patel J, Joshi S, Sharma N, et al. A phase 3, randomised, open-label, non-inferiority trial evaluating anti-rabies monoclonal antibody cocktail (TwinrabTM) against human rabies immunoglobulin (HRIG). Clin Infect Dis. 2020 June 17: ciaa779. Epub ahead of print. PMID: 32556113. doi:10.1093/cid/ciaa779.
22. Gogtay NJ, Munshi R, Ashwath Narayana DH, Mahendra BJ, Kshirsagar V, Gunale B, Moore S, Cheslock P, Thaker S, Deshpande S, et al. Comparison of a novel human rabies monoclonal antibody to human rabies immunoglobulin for postexposure prophylaxis: a phase 2/3, randomized, single-blind, noninferiority, controlled study. Clin Infect Dis. 2018;66 (3):387–95. doi:10.1093/cid/cix791.
23. Matson MA, Schenker E, Stein M, Zamfirova V, Nguyen HB, Bergman GE. Safety and efficacy results of simulated post-exposure prophylaxis with human immune globulin (HRIG; KEDRAB) co-administered with active vaccine in healthy subjects: a comparative phase 2/3 trial. Hum Vaccin Immunother. 2020;16 (2):452–59. doi:10.1080/21645515.2019.1656967.
24. Hobart-Porter N, Stein M, Toh N, Amega N, Nguyen H-B, Linakis J. Safety and efficacy of rabies immunoglobulin in pediatric patients with suspected exposure. Hum Vaccines Immunother. 2021;17(7):2090–96. doi:10.1080/21645515.2020.1854000.
25. Priyadarsini Debta S, Ranjan Behera T, Routray D. 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. J Commun Dis. 2020;52(2):63–68. doi:10.24321/0019.5138.202012.
26. Haradanhalli RS, Kumari N, Sudarshan MK, Narayana DHA, Prashanth RM, Surendran J. Defining the volume of rabies immunoglobulins/rabies monoclonal antibodies requirement for wound infiltration of category III animal exposures - an exploratory study. Hum Vaccin Immunother. 2021;17(12):5355–60. doi:10.1080/21645515.2021.2013079.