Title: EPIDEMIOLOGY OF ANIMAL BITES IN BERHAMPUR, ODISHA, AND SAFETY OF EQUINE RABIES IMMUNOGLOBULIN

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Keywords Rabies, Equine rabies immunoglobulin, ERIG, adverse events, Inj., Premirab, animal bites

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APCRI Journal

Volume XVIII ● Issue III ● January 2017

Original Article

EPIDEMIOLOGY OF ANIMAL BITES IN BERHAMPUR, ODISHA, AND SAFETY OF EQUINE RABIES IMMUNOGLOBULIN

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ABSTRACT

Objective: To study the present epidemiology of animal bites and safety of equine rabies immunoglobulin (Premirab) in an outpatient setting

Materials and Methods: This observational study was conducted over a fortnight at the Anti-Rabies Clinic (ARC) of the MKCG Medical College Berhampur. 230 cases of category III animal bites, who gave consent were administered ERIG after a test dose. Incidence of adverse reactions was observed.

Results: Skin test to the ERIG was positive in 3(1.3%) of the cases. The most common adverse reaction reported was pruritus in 4 cases on day 0, and 1 case each on days 3 and 7. There were no cases of anaphylaxis or any serious adverse reaction. 17(7.4%) were cat bites and 49(21.3%) were due to monkeys and 69.5% were dog bites. 79.6% patients (213 of 230) were brought to hospital within 24 hours of bite. Only 18 patients (7.8%) had no wound toilet performed prior to ARC visit. 195 (84.7%) had their wound cleaned with soap and water and/or antiseptics and only 17 (7.4%) used local methods

Conclusions: Inj. Premirab, an ERIG, was found to be well tolerated, during mass use in the rabies clinics. The awareness amongst lay public about early bite management is on the rise.

Key words: Rabies, Equine rabies immunoglobulin, ERIG, adverse events, Inj. Premirab, animal bites.

INTRODUCTION

Rabies, an invariably fatal viral disease, is transmitted to humans through animal bites, most commonly dogs. The disease is preventable through timely pre-and post-exposure vaccination. However, once the disease occurs, death is inevitable The annual estimated number of dog bites in India is 17.4 million, leading to an estimated 18 000– 20 000 cases of human rabies per year. Based on available evidence, a fair estimate of rabies burden in India is 2.74 rabies cases per 100 000 people annually.[1] Almost all human deaths caused by rabies worldwide originate from Asia and Africa with 56% of the deaths estimated to occur in Asia and 44% in Africa[2].

Rabies immunoglobulin (RIG) serves to neutralize virus at the inoculation (i.e. bite) sites. It reduces the virus load that can replicate in muscle cells and later invade nerve endings. RIG thus closes the gap until endogenous antibodies elicited by active immunization appear. It is for these reasons that the World Health Organization (WHO) Expert Committee on Rabies recommended the use of RIG in all severe rabies exposures such as single or multiple transdermal wounds regardless of body site. RIG must be injected into and around the wounds, ideally at the time of the first vaccine dose. Equine Rabies Immunoglobulin (ERIG) and Human Rabies Immunoglobulin (HRIG) have therefore been placed on the WHO list of essential drugs and biologicals.[3]

Equine Rabies Immunoglobulin (ERIG) is of heterologous origin produced by hyper immunisation of equines. Currently manufactured ERIGs are highly purified Fab 2' fragments and the occurrence of adverse events has been significantly reduced.

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Table 1
Distribution according to gender and residence

Sex / Residence	Male	Female	Total
Rural	78	39	117
Urban	76	37	113
Total	154	76	230
Chi^2= 0.01; p=0.92			

Table 2
Distribution of cases according to residence and culprit animal

	Animal				
Residence	Dog	Cat	Monkey	Others	**Total**
Rural	84	12	18	3	117
Urban	76	5	31	1	113
Total	160	17	49	4	230

Due to its heterologous origin, ERIG does carry a small risk of anaphylactic reaction (1/150,000). However, literature supports that there is no scientific ground for performing a skin test prior to administering ERIG because testing does not predict reactions, and ERIG needs to be given irrespective of the result of the test.[4] The fear of anaphylaxis with equine rabies immunoglobulin (ERIG) among the physicians is a factor of its non-use. According to the APCRI-WHO survey in India, the use of RIG is less than 2 %. There are instances of treatment failures (death due to rabies) because of non-use of RIG in those patients[5].

With such a high incidence of dog bites, many of whom receive ARS, one would expect heavy reporting of adverse events. With this in mind we conducted this Post Marketing surveillance to gather data in a systematic manner after administration of an ARS, marketed by Premium Serums (Premirab). This will also add to the national pool of pharmacovigilance data. We also gathered information on the epidemiology of animal bite cases in the region.

Figure-01 : Distribution of site of bite according to animals

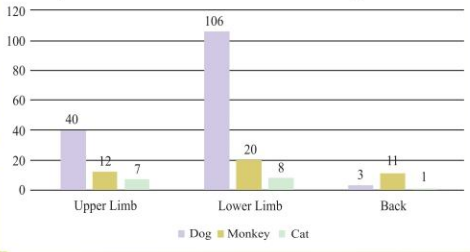

Table 3
Frequency of cases with prior wound management according to residence

Wash	**None**	**Soap and water**	**Antiseptics**	**Other methods**	**Total**
Residence					
Rural	7	76	27	7	117
Urban	11	66	26	10	113
Total	18	142	53	17	230

Table 4
Most common Reaction to RIG

Time	**Reaction**	**Frequency n,(%)**
Immediate	Pruritus	4 (1.7%)
	Pain	1 (0.4%)
Day-3	Pruritus	1 (0.4%)
	Swelling	1 (0.4%)
	Discomfort (Non-Specific)	3 (1.2%)
Day -7	Pruritus	1 (0.4%)
	Serous discharge	6 (2.5%)
Day- 28	NONE	

MATERIALS AND METHODS

This was a cross sectional post marketing survey conducted at the Anti Rabies Clinic (ARC) of MKCG Medical College, Berhampur. Institutional Ethical Committee clearance was obtained prior to starting the study.

299 cases of animal bites visited the out-patient Anti Rabies clinic of department of community medicine, MKCG medical college Berhampur, Odisha, between 18th and 28th May 2016 and they formed the patient pool from which study candidates were recruited using the following inclusion criteria:

1. Patient attending the ARC for the first visit between the study enrolment period,
2. Patient belonging to category 3 animal bite,
3. Patient willing to regularly visit for follow up
4. Patient/Guardian willing to sign a written informed consent form.

This criterion yielded a total of 230 candidates. A written informed consent was obtained from all. Case report forms were filled by research associates and post-exposure prophylaxis was administered to them as per institutional protocol.

This included local treatment of wound, anti-rabies vaccination and rabies immunoglobulin administration. Intra dermal regimen of Purified Vero cell Rabies Vaccine (PVRV ID regimen) was followed for anti-rabies vaccination.

Equine Rabies Immunoglobulin (Inj. Premirab, Premium Serum & Vaccines Pvt Limited, India; (Batch # 191024 with a Potency of 300IU/ml) was given at a dose of 40 IU/Kg on day 0 after skin testing to rule out allergy to the equine product.

The skin test for Inj Premirab was performed by injecting 0.1 ml of ERIG (diluted 1:10 by normal saline) on ventral (flexor) aspect of left forearm and control (0.1 ml normal saline) was injected on right forearm. Transverse diameter was measured after 15 minutes for sensitivity status. A diameter of >10mm was considered positive skin test. Adequate precautions were taken to manage any anaphylaxis reactions.

As much as possible of ERIG was injected in & around the bite wounds, with the remainder being given by deep injection into the gluteal region.

They were observed for an hour for local and systemic reactions and followed up further when they visited for the subsequent vaccine doses on days 3, 7 and 28.

RESULTS

A total of 230 patients participated in the study. The mean age of the subjects was 30.90 years (Range: 2-85 years). 154 (67%) were males and 76(33%) were females. The mean age of patients was significantly less for males (28.67 years) as compared to females (35.43 years) (p=0.016).

117cases (50.9%) were from rural areas and the rest, 113 (49.1%) from urban areas. There was no significant difference in the distribution of cases as per gender and residence (**Table - 1**).

27% subjects reported to the ARC on the same day of the bite where as 52.6% and 13.0% reported on day-2 and day-3 respectively. The culprit animals in most cases were stray dogs followed by monkeys (**Table - 2**).

Cat bites were more common in rural areas (OR=2.54) and monkey bites were more common in urban areas (OR=2.07). There was no significant difference regarding dog bites and the residence of cases, but bites were significantly more common in males (117 out of 154) as compared to females (43 out of 76) with an Odds ratio of 2.42.

Only 3 cases (1.30%) were from animals that were suspected of having died of rabies. In a majority of 191 cases (83.04%), the status of the animal was not known.

The most common site of bite was Lower limb (59.57%) followed by upper limbs (25.65%).

However, a relatively greater proportion of monkey bites were on the back (22.4%). (Figure-01)

79.6% patients (213 of 230) were brought to hospital within 24 hours of bite .As shown in table-03, 61.7% cases had washed the wound with soap and water prior to visiting ARC and 23.04% had used some sort of antiseptics on the wound. Only 7.83% cases had not been given any first aid to the wound. There was no significant difference regarding wound first aid between those residing in urban and rural areas. ($Chi^2 = 2.07; df=3; p=0.56$)

SAFETY EVALUATION:

Skin test to the ERIG was positive in 3(1.3%) of the cases. The most common adverse reaction reported was pruritus (Table-04). No cases of Severe Adverse Events were reported. Only a single case reported continuing pruritus till day 7.

Out of 230 cases, 11 did not complete the full treatment course. 3 cases each were lost to follow up on day-03 and day-07 respectively. 5 subjects were lost to follow up on day 28.

DISCUSSION:

Post exposure prophylaxis using rabies immunoglobulin along with a full course of vaccine is now the proven method of managing category III animal bites. Immunoglobulins of both human and equine origin are available. The later are more in use due to the affordability. However, with the Equine Rabies Immunoglobulin (ERIG), being of heterologous origin, allergic reactions and even anaphylaxis are expected. Better purification during manufacturing tends to reduce their incidence. This trial was a post marketing safety

study on Premirab, the brand of ERIG produced by Premium Serums and Vaccines Ltd.

Although WHO or the national guidelines do not recommend skin tests, these are often conducted so that at least in those who elicit a positive response to the skin test, one can pre-medicate with antihistamines and steroids. In this study also, the test was performed and only 3 of 230 (1.3%) cases were seen to be positive. These were administered human immunoglobulin. In 2007, Sudarshan MK reported a skin positivity of 11.2%.[6] Behera TR et al used ERIG of the same brand but different batch numbers. The skin positivity in this study ranged from 2.6% -10.2%[7].

On day 0 only 4 cases (1.7%) complained of pruritus. Pain and local swelling were commonly seen but since these are manifestations of local injury itself they were disregarded. On day 3, pain, pruritus and swelling was reported by 1 case each, and 3 had other non specific symptoms like discomfort. On day 7, one case reported pruritus and 6 had serous discharge from the wounds. Discharge may be attributed to the normal healing process of the wound. Behera T R et al have also reported pain and swelling in almost 100 % cases[7]. In that study, pain was complained of by 67% on day 3 and 33% on day 7, whereas pruritus was 39% on day 3 and 19% on day 7.

There was no case of anaphylaxis or delayed reaction by 28 days. Until 28 days no case showed signs of rabies. Although the incubation of rabies could be many months to years, for the duration evaluated, Premirab was effective and well tolerated.

In our study, it was interesting to note that 17(7.4%) were cat bites and 49(21.3%) were due to monkeys. The monkey bites were mainly on the torso. In earlier studies from the same location, MKCG medical college, the incidence of monkey bites was 6.5%, 8.6% and 7.2%[8,9,10].

Monkey bites were more in urban areas and a report on wild animal bites by Haldar et al in Berhampur came to similar conclusions[9]. This was possibly because of a well-known temple near Berhampur with a known history of monkey menace contributing to the load.

79.6% patients (213 of 230) were brought to hospital within 24 hours of bite. In a study of over one year on late reported cases, from the same centre, 70% cases had reported within 24 hours[11]. Only 18 patients (7.8%) had no wound toilet performed prior to clinic visit. 195 (84.7%) had their wound cleaned with soap and water and/or antiseptics and only 17 (7.4%) used local methods like turmeric, neem, calotropis juice. In an earlier study from the same institute, Behera TR[12] reported that 53% cases had no wound toilet, 25% had turmeric application and 4.5% had bitter gourd. Further, in our study, there was no difference between urban and rural areas in wound first aid. This possibly indicates the success of public awareness programmes carried out by the government in this area.

CONCLUSION :

To conclude, Premirab an ERIG, was found to be well tolerated during mass use in the rabies clinics. The awareness amongst lay public about early bite management is on the rise.

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