SPECIAL ARTICLE

Safety of rabies immunoglobulin (RIG)/ rabies monoclonal antibody (RMAb) for Post-exposure Prophylaxis in Patients with Potential Rabies Exposure

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Abstract

Background: RIG/ RMAb are life-saving, readymade anti-rabies antibodies; which offer immediate protection for all category III animal exposures.

Objectives: 1.To describe the type of exposures and post exposure prophylaxis provided at the anti-rabies clinic 2. To assess the safety of rabies immunoglobulin/ monoclonal antibody given for post exposure prophylaxis.

Methodology: The study was conducted at the anti-rabies clinic, Department of Community Medicine, KIMS, Bangalore from Jan to June, 2018. All the animal bite victims who came for post exposure prophylaxis with category III exposures and gave informed written consent were included in the study. The details regarding socio-demographic profile, characteristics of animal bites, post exposure prophylaxis provided focusing on type and site of RIG/ RMAb administration were recorded. Assessment of safety was done by recording the ADEs both local & systemic after observing the subjects for 30 minutes & also subsequently upto day 28.

Results: 550 animal bite victims were included in the study; 33.6% of them were < 15 years, 57.8% from 15 - 59 years and 8.5% of them were elderly. Majority received either equine rabies immunoglobulin (51.5%) or rabies monoclonal antibodies (42.7%); only few (5.8%) received human rabies immunoglobulin. Overall, 7.1% ADEs were reported among the study subjects i.e., 6.3% from HRIG, 7.4% from ERIG and 6.8% from RMAb. The common ADEs reported were pain, erythema, itching, body ache, fever, nausea and malaise. All the ADEs resolved with symptomatic treatment, without any complications.

Conclusion: RIG/ RMAb is safe for post-exposure prophylaxis in patients with potential rabies exposure.

Key words: rabies, prophylaxis, safety, rabies immunoglobulin, monoclonal antibodies.

Introduction:

Animal bites to humans is a public health problem; posing a potential threat of rabies to over 3.3 billion people worldwide.1 These exposures occur mainly in the underserved populations, both in rural and urban areas and has been documented for more than 4000 years.2 Most cases occur in Africa and Asia; where a close habitation of large human and dog population is seen.3 World Health Organization's (WHO) South East Asia Region has more exposures, than in any other part of the world; nearly 1.4 billion people are at risk.4 In India, an estimated 17.4 million animal bites occur annually, with an incidence of 1.7 %.5

Rabies is a preventable disease and is most amenable to control, as the appropriate tools for prevention i.e., post exposure prophylaxis (PEP) are available.[6] In rabies endemic country like India, where every animal bite is potentially suspected as rabid exposure, the exposed individuals should seek early and proper health care; simultaneously, PEP should be started immediately at the health care facility.[7] Wound washing with soap/ detergent & water, followed by application of virucidal agents to reduce the viral inocu¬lum at the wound site; complete course of post-exposure vaccination to induce antibodies which prevents the risk of virus entering peripheral nerves and wound infiltration of rabies immunoglobulin (RIG)/ rabies monoclonal antibodies (RMAb) in all category III exposures to neutralize the virus at the wound site.[8]

RIG/ RMAb are readymade anti-rabies antibodies, which provide passive immunity and offer immediate protection for all Category III exposures; since, anti rabies vaccine stimulates production of neutralizing antibodies by immune system, and the protective levels of antibodies are seen only after 7 - 14 days from the 1st dose of vaccine. Therefore, patients are vulnerable during this window period of 7 - 14 days despite the timely and full course of any ARV. Infiltration of RMAb/ RIG into & around all the bite wounds after thorough wound wash will neutralize virus at the site of bite & thus saves the life of bite victim.9 RIGs have to be infiltrated as early as possible & to all types of wounds (RIG can be administered upto 7 days after 1st dose of vaccine/any day if vaccine not started).

Rabies immunoglobulin is derived from the horses or humans and has several limitations relating to supply, cost and quality. Equine rabies immunoglobulin (ERIG) is economical as compared to human rabies immunoglobulin (HRIG), however, ERIG has potential to cause ADRs and thus, physicians are hesitant to use it; whereas, HRIG is costly and not affordable to most of the animal bite victims.10 Monoclonal antibodies produced through recombinant DNA technologies could potentially overcome these limitations.11,12

Since, many pharmaceutical companies have started manufacturing RIGs/ RMAbs, there is a need for constant monitoring of their safety in exposed patients. Therefore, the present study was conducted to describe the type of exposures and post exposure prophylaxis provided at the anti-rabies clinic and to assess the safety of rabies immunoglobulin/ monoclonal antibody given for post exposure prophylaxis.

Material and Methods:

The present study was conducted at the anti-rabies clinic, Department of Community Medicine, Kempegowda Institute of Medical Sciences (KIMS) Hospital and Research Centre, Bangalore after getting Institutional Ethical Committee clearance. It was a descriptive study conducted from January to June 2018.

All the animal bite victims with Category III bites and had come for post exposure prophylaxis to the anti- rabies clinic were included in the study after taking their informed consent. They were ruled out for taking any rabies vaccine either as post exposure prophylaxis (PEP) or pre- exposure prophylaxis (PrEP) and history of any animal bite in the past. A standard case record form was maintained for each bite victim, which included details on socio-demographic profile, characteristics of animal bites including severity of exposure and details of PEP provided, focusing on type and site of RIG/ RMAb administration.

PEP was provided to all cases as recommended by WHO and the standard intramuscular anti-rabies vaccination schedule (Essen regimen) was followed i.e., one dose of vaccine on Days 0, 3, 7, 14 & 28; simultaneously rabies immunoglobulin i.e., either human rabies immunoglobulin (HRIG), equine rabies immunoglobulin (ERIG) or rabies monoclonal antibody (RMAb) was administered as per the calculated volume to all category III exposures. The details regarding RIG/ RMAb required for local infiltration, as much as anatomically possible was recorded and the remaining RIG/ RMAb, if any was infiltrated intramuscularly as per present recommendation of WHO.

Assessment of safety was done by recording the adverse drug events (ADEs) both local & systemic after observing the subjects for about 30 minutes after administration of RIG/ RMAb and also subsequent upto day 28 when they came for subsequent doses of vaccination or through telephonic conversation. All the ADEs, if any, was treated

free of cost in the hospital. The obtained data from the study was entered into Microsoft excel sheet and analyzed using mean and percentages.

Results:

The present study included 550 animal bite victims with Category III potential rabies exposure who came for PEP at the anti-rabies clinic, KIMS, Bangalore. Among the bite victims, 33.6% of them were < 15 years, 57.8% were from 15 - 59 years and 8.5% of them were elderly. 61.1% of the study subjects were males and 38.9% were females. Majority completed their schooling (57.5%) and was either professional/ semi- professional (25.1%) or unskilled/ skilled worker (24%) by occupation **(Table 1).**

Table 1: Distribution of study subjects according to socio- demographic profile

Socio - demographic characteristics (n=550)		Frequency
Age (in years)	<15	185 (33.6)
	15-59	317 (57.6)
	≥60	48(08.7)
Sex	Male	336 (61.1)
	Female	214 (38.9)
Educational Status	Illiterate	77 (14)
	School	316 (57.5)
	Graduate/Post-Graduate	157 (28.6)
Occupation	Professional/ Semi-professional	138 (25.1)
	Clerical/Skilled worker	108 (19.6)
	Unskilled/ Semi- skilled worker	132 (24)
	Unemployed	62 (11.3)
	House wife	110 (20)
Residence	Urban	522 (94.9)
	Rural	28 (05.1)

*Figures in parenthesis indicate percentages

The bite wounds were located on lower limbs (51.6%), upper limbs (38.7%) head and neck region (9.3%), trunk (6.5%) and genitalia (1.8%) with abrasions (58.9%), lacerations (40.1%) and puncture wounds (33.5%).

All the study subjects were advised to wash wound with soap and water and all of them received 1st dose of anti rabies vaccine. All category III exposures were infiltrated with passive immunization; majority received either ERIG (51.5%) or RMAb (42.7%) and only few (5.8%) received HRIG. Rabies immunoglobulin/ rabies monoclonal antibody were mostly administered into and around the wound site. It was given locally in 68% of the subjects **(Table 2).**

Table 2: Distribution of study subjects according to route of RIG/ R-Mab infiltration

Site of infiltration of RIG/ RMAb	HRIG	ERIG	R-MAb	Total
Local	26 (81.2)	173 (61.1)	175 (74.5)	374 (68.0)
Both local & Systemic	06 (18.8)	110 (38.9)	060 (25.5)	176 (32.0)
TOTAL	**32 (100)**	**283 (100)**	**235 (100)**	**550 (100)**

*Figures in parenthesis indicate percentages

The study subjects reported various adverse drug events (ADEs), both local and systemic, after RIG/ RMAb administration. Overall, 7.1% ADEs were reported among the study subjects i.e., 6.3% from HRIG, 7.4% from ERIG and 6.8% from RMAb. The local adverse events reported were pain (8.5%), erythema (7.3) and itching (5.8%)

following infiltration and the systemic adverse reactions were headache (5.3%), bodyache (5.3%), fever (4.5%), malaise (3.6%) and nausea (2.2%) (Table 3). All the ADEs were treated symptomatically and subsided without any complication.

Table 3: Adverse Drug Events following post exposure prophylaxis among the study subjects

Adverse Reaction	HRIG (n=32)	ERIG (n=283)	R-Mab (n=235)	Total (n=550)
Local				
Pain	04 (12.5)	31 (10.9)	12 (05.1)	47 (08.5)
Erythema	02 (06.3)	28 (09.9)	10 (04.3)	40 (07.3)
Itching	01 (03.1)	21 (07.4)	10 (04.3)	32 (05.8)
Systemic				
Headache	02 (06.3)	18 (06.4)	09 (03.8)	29 (05.3)
Nausea	01 (03.1)	07 (02.5)	04 (01.7)	12 (02.2)
Bodyache	02 (06.3)	18 (06.4)	09 (03.8)	29 (05.3)
Fever	03 (09.4)	13 (04.6)	09 (03.8)	25 (04.5)
Malaise	02 (06.3)	11 (03.9)	07 (02.9)	20 (03.6)
TOTAL	**02 (6.3)**	**21 (7.4)**	**16 (6.8)**	**39 (07.1)**

*Figures in parenthesis indicate percentages **multiple response

Discussion:

In India, animal bites are a major public health problem and an estimated 17.4 million bites occur annually.[5] Therefore, in rabies endemic country like India, where every animal bite is potentially suspected as a rabid animal bite, the treatment should be started immediately which includes wound management and simultaneous administration of rabies immunoglobulin in all category III exposures combined with anti-rabies vaccine, which is almost invariably effective in preventing rabies, even after high-risk exposure. Individuals with category III exposures (single or multiple transdermal bites or scratches or contamination of mucous membrane with saliva from licks, licks on broken skin, exposure to bat bites or scratches) are at more risk and should receive early passive immunization.

The present study showed that, the common sites of exposures were lower limbs (51.6%) and upper limbs (38.7%). Another study from Himachal Pradesh showed that, majority (61.1%) were bitten in lower extremities.13 Similar findings were also seen in a study done in Tamil Nadu by Sangeetha S et al., where majority had animal bites on legs 42 (60.87%), hands 18 (26.08%), body 5 (7.25%), face & neck 2 (2.9%) and trunk 2 (2.9%).[14]

In the present study, the severity of bite wounds was abrasions (58.9%) and lacerations (41.1%). Likewise, other study also showed that abrasion (59.4%) was the most common bite wound followed by laceration (28.1%) and puncture wound (3.1%) in the study conducted by Chandana K et al. in Tumkur.15 Similarly, abrasions (54.4%) were also the common type of wounds reported in a study by Shivalingaiah AH et al. followed by punctured wounds (34.5%) and lacerations (31.5%).[16]

All the category III exposures in the study were infiltrated with RIG/ R-Mab; majority (68%) of the subjects were given exclusive local infiltration to all the wounds. Similarly, in a study at Himachal Pradesh by Omesh K Bharti et al. including 269 cases, it showed that all of them were infiltrated locally with ERIG, without any systemic administration.[17]

The ADEs in the present study were 7.1% viz. 6.3% from HRIG recipients, 7.4% from ERIG and 6.8% from RMAb. Likewise, in a study by Minhas A et al. in Himachal Pradesh, only 8% of the participants had adverse reaction to the immunoglobulin.13 Similarly, a study on safety of ERIG in children including 938 subjects from anti rabies clinic,

KIMS, Bangalore showed that, 1.6% reported minor adverse drug reactions after ERIG usage.[18]

In conclusion, RIG/ RMAb is safe for post-exposure prophylaxis in patients with potential rabies exposure. Therefore, this study will install confidence among the treating physicians to infiltrate life saving RIG/ RMAb to all category III exposures; thereby completing the PEP which is essential to prevent and eliminate rabies by 2030.19

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