ORIGINAL RESEARCH ARTICLE

A STUDY ON CLINICAL SAFETY OF RABIES MONOCLONAL ANTIBODY AMONG CHILDREN IN COMPARISON WITH EQUINE RABIES IMMUNOGLOBULIN

Prof Durga Madhab Satapathy[1], Dr. Sangeeta Das[2], Dr. Sanjaya Kumar Sahoo[2], Dr. Nivedita Karmee[3], Dr. Smitanjali Samal[4*]

[1]Professor and HOD, Department of Community Medicine, MKCG Medical College, Berhampur, Odisha
[2]Assistant Professor, Department of Community Medicine, MKCG Medical College, Berhampur, Odisha
[3]Associate Professor, Department of Community Medicine, MKCG Medical College, Berhampur, Odisha
[4]PG Student, Department of Community Medicine, MKCG Medical College, Berhampur, Odisha

Abstract:

Background: Rabies is an acute zoonotic disease, which significantly impacts global public health. Worldwide India is reported to have the highest incidence of Rabies. Death from rabies can be prevented by timely and appropriate post exposure prophylaxis including wound cleaning, active and passive immunization. Three classes of biological product are available for passive immunization: human rabies immunoglobulin, equine rabies immunoglobulin and Rabies Monoclonal Antibody. HRIG is expensive and ERIG has limitations like irregular availability and allergic reactions related to it. Monoclonal antibodies produced through recombinant DNA technologies could potentially overcome these limitations. Objective: To compare adverse reactions of equine rabies immunoglobulin and monoclonal antibody. Methods: A prospective observational study was done on 233 children having Category III animal bite attending Anti -Rabies Clinic, M.K.C.G. Medical College and Hospital, Berhampur, Odisha, and those who were willing to purchase R'Mab were administered R'Mab. These cases were followed up for both local & systemic side effects during subsequent visits in April and May 2019. Result: - Out of the total children, 62% were Male and 54% were from rural area. Majority (79%) were due to dog bite. Most of the bites were in lower limb (58%) followed by upper limb (24%). There was no serious complaint after R'Mab administration except local swelling and pain on day 0 and 3, whereas 96.4% children who were given ERIG presented with local pain and swelling on day 0. Pruritus was complained by 82% and 74% of children had erythema. Malaise & mild fever were the most common systemic side effects seen in 42% of ERIG recipients on Day 0. Conclusion: Rabies monoclonal antibody potentially offers a safe alternative to ERIG with less adverse reactions for the passive component of post-exposure prophylaxis and could significantly improve the management of bites from suspected rabid animals.

Keywords: Anti rabies vaccine, Post exposure prophylaxis, Rabies Monoclonal antibody (R'Mab)

Introduction:

Rabies is invariably fatal. It kills around 50,000-70,000 people per year1. More than 99% of all human deaths from rabies occur in the developing world2, and rabies still remains a neglected disease throughout most of Asia3. About 56% of the total deaths in Asia and 44% in Africa is due to rabies4. Human rabies is endemic in India, mainly caused

***Corresponding Author:** Dr. Smitanjali Samal PG Student, Department of Community Medicine, MKCG Medical College, Berhampur, Odisha, Email id: smitanjalisamal@gmail.com

Received : 20.11.2020 **Revised :** 15.12.2020
Accepted : 31.12.2020 **Published :** 28.01.2021

by dog bites. Annual incidence of dog bite in our country is 1.7% and incidence of animal bite is 17.4 per 1000 population5. India contributes to 59.9% of human rabies deaths in Asia and 35% of human rabies deaths globally6. Approximately 40% of animal bite cases are seen in children aged <15 years7. Recently in 2015, WHO declared the global goal of achieving dog mediated human rabies free world by 2030 to which India is also committed8.

There are three categories of exposure to suspected rabid animals. WHO recommendations for category III exposures include thorough wound cleaning and deep irrigation, application of a potent virucidal agent, as well as timely administration of rabies vaccine and immunoglobulin9. Around the world, rabies kills around 100 children every day because they cannot afford the vaccine10. There are three types of blood derived RIG products licensed for rabies post exposure prophylaxis (PEP): Human rabies immunoglobulin (HRIG) derived from the sera of humans immunized against rabies; Equine rabies immunoglobulin (ERIG) derived from the sera of horses immunized against rabies; and highly purified F (ab')2 fragments11. Globally an estimated 29.2 million people take rabies PEP each year1. Immunoglobulin is highly efficacious when administered correctly.

Although ERIG carries a risk for severe allergic reactions, it is more commonly used due to availability and lower cost, in comparison to HRIG which is too expensive. A study showed that only 21 out of 783 (2.7%) patients with category III bites were prescribed HRIG, and only 10 could afford to obtain it12. It is therefore not surprising that mortality from rabies remains high.

To address this critical issue, a human monoclonal antibody against rabies virus glycoprotein (G) was developed by recombinant DNA technology13. This antibody, 17C7 (also known as RAB1), which was later designated SII R'Mab binds to a conformational epitope of the glycoprotein of rabies virus and is manufactured by Serum Institute of India Pvt. Ltd (SIIPL), India.

The present study assessed the clinical safety of SII R'Mab when compared with ERIG for PEP in children bitten by suspected rabid animals.

Materials and Methods:

A prospective observational study was conducted in the month of April and May 2019 in the Anti Rabies Clinic of Department of Community Medicine, M.K.C.G. Medical College and Hospital, Berhampur, Odisha. Amount of Inj. R'Mab required was calculated as 3.3 IU/Kg body weight. Children less than 14 years with category III bites were our study participants. Parents of these children were explained about all the three alternatives of passive immunization. They were counseled about availability, cost, effectiveness and side effects associated with them. As Inj. R'Mab is costly and not supplied by the government, parents of 38 children out of the total 233 participants agreed to purchase R'Mab and rest were given government supplied ERIG and rabies vaccine. R'Mab `or ERIG was infiltrated locally into all wounds as much as anatomical feasible. The remaining volume was administered intramuscularly at a site distant from the vaccine injection site. Participants were then followed up regarding any local or systemic side effects during their subsequent visit to ARC OPD for active immunization on 3rd, 7thand 28th day. Data was collected using pre-tested, pre-designed and semi-structured questionnaire, analyzed using SPSS version 17.

Written consent was taken from the parents of these 233 respondents for participation in the study.

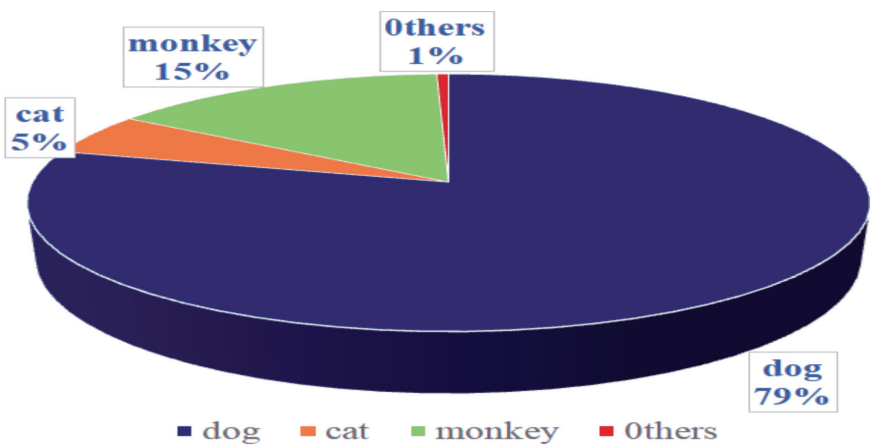
Results:

Parents of 233 children with Category III animal bite had given consent to participate in the study. Out of them, 38 were given R'Mab after counselling and rest were given ERIG. From the total study population, 62% were male and 38% were female. 54% were from rural areas and 43% belonged to low socio-economic status.

Table 1: Socio-demographic profile of study population (n=233)

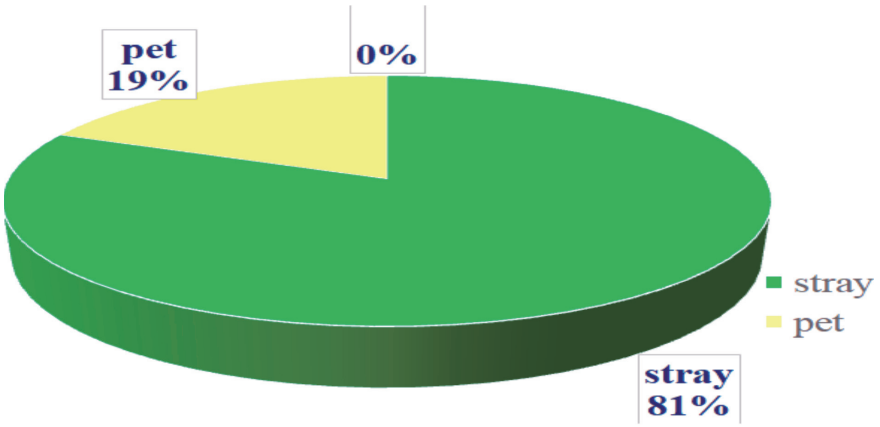
Variables		Frequency (%)
Sex	Male	144(62)
	Female	89(38)
Residence	Rural	126(54)
	Urban	107(46)
Education of father	Illiterate	23(10)
	Primary	33(14)
	Middle	16(7)
	High school	51(22)
	Post high school	37(16)
	Graduate	72(31)
Occupation of father	Labourer	52(22.3)
	Business	62(26.4)
	Cultivator	51(21.7)
	Service	69(29.6)
SES(modified BG Prasad scale)	Upper	20(8.5)
	Upper Middle	64(27.5)
	Middle	49(21)
	Upper Lower	75(32.2)
	Lower	25(10.8)

Fig. 1: Distribution of cases according to site of bite



Out of the total animal bite cases, majority i.e. 184 (79%) were dog bites, 35(15%) were monkey bites and remaining were by cats and other animals.

Fig 2: Type of Dog bite



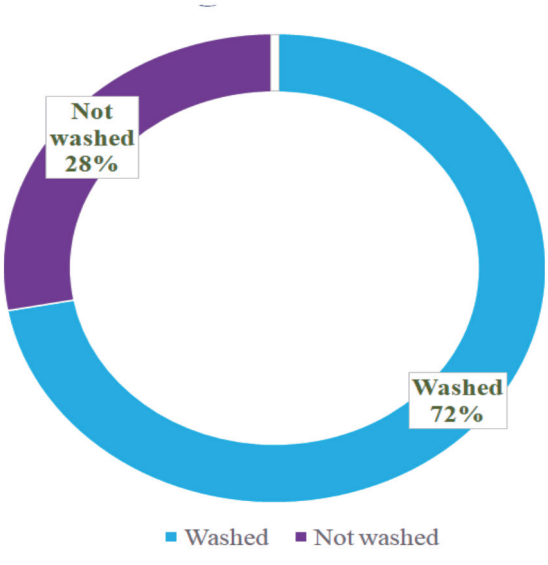
Majority i.e. 81% cases were by stray dog and 19% cases by pet dog.

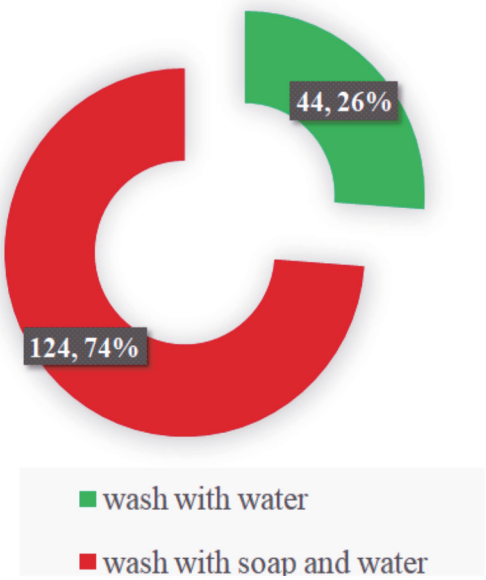
Table 2: Distribution of site of bite

Site	Number	Percentage
Lower limb	135	58
Upper limb	56	24
Head and neck	10	4.3
Multiple sites	32	13.7

About 58% (135) of the bites were seen on lower limbs followed by 24% (56) on upper limbs and the least i.e. 13.7% (32) involved multiple sites.

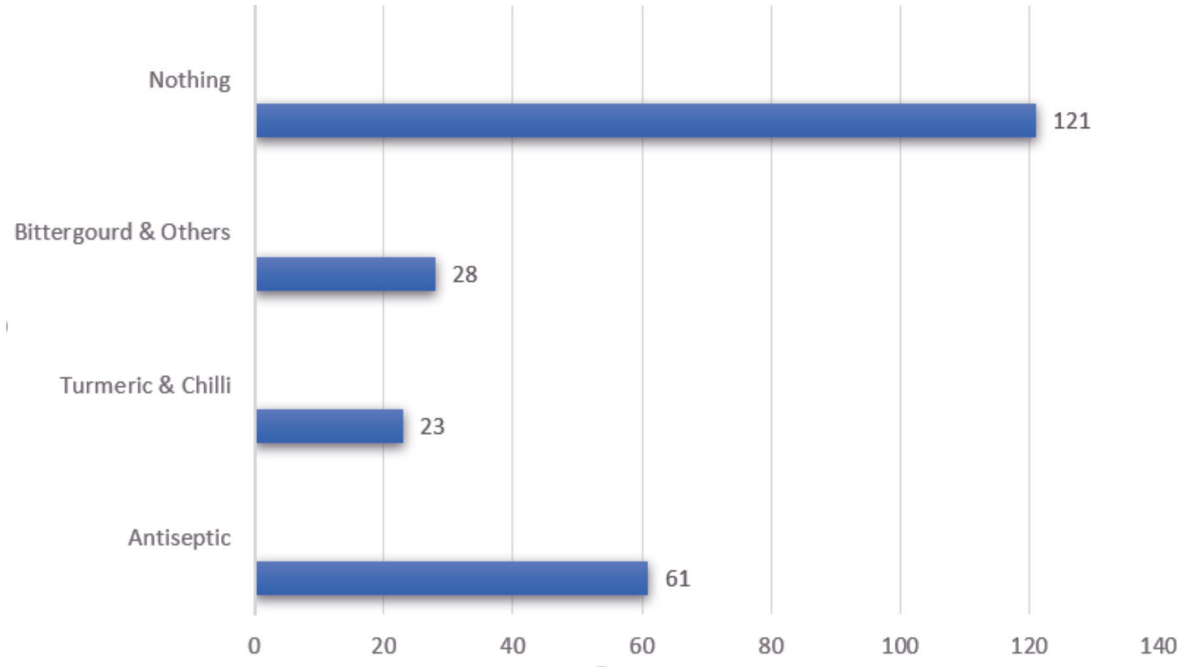
Fig. 3 and 4: Wound Management





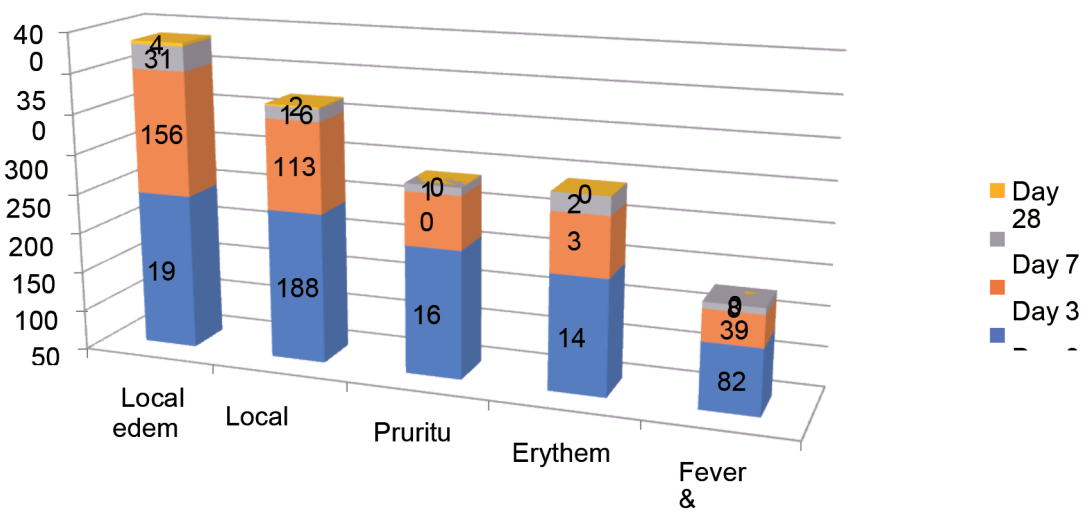
Proper wound wash was done by 72% and 28% of cases had not washed the bite site before coming to hospital. From among them who had washed, soap was used for cleaning the wound by 74% patients.

Fig. 5: Wound Application



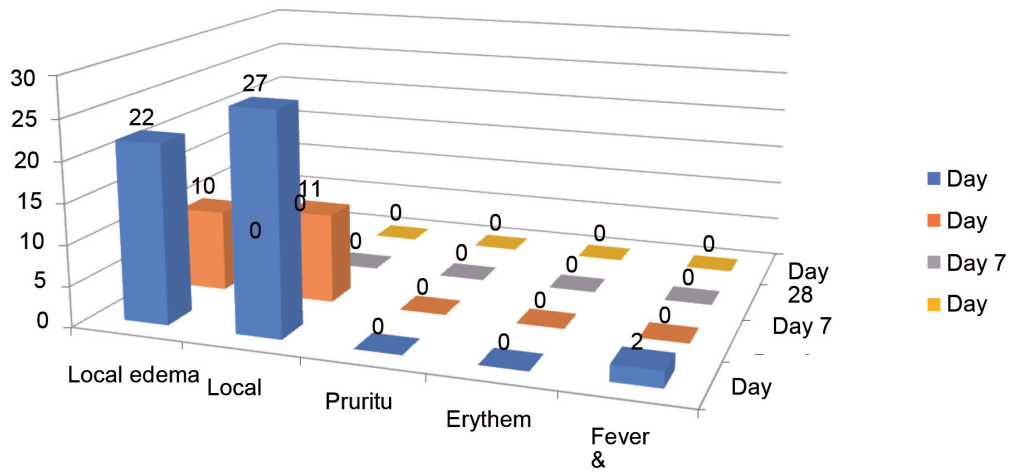
Out of the total study population, 61 cases had applied antiseptic cream on their wound followed by 28 who had applied bittergourd leaves and 23 cases had applied turmeric and chilli. However 121 children had applied nothing on their wounds before coming to hospital.

Fig.6: Day wise adverse reaction of ERIG



Out of the 195 recipients of ERIG, all the cases had complained of local edema, 96.4% had experienced pain at the injection site, 82.05% (160) complained of pruritus and 73.8% had erythema on day 0. On day 3, 80% complained of swelling, 58% pain, 34% pruritus and 38% erythema. About 16% children had edema, 8.2% cases still experienced local pain, and 11.79% had erythema on day 7. Systemic side effects like fever and malaise were observed in 42.05% of cases on day 0 and 20% of children developed fever on day 3.

Fig.7: Day wise adverse reaction of R'Mab



In the 38 children who were given R'Mab, on day 0 local edema was seen in 57.89% and pain was experienced by 71.02% of children. On day 3 pain and edema was observed in 28.9% and 26.31% of children respectively. All these side effects gradually subsided with symptomatic treatment. Only 2 children suffered from fever on day 0 which was subsided by antipyretics.

Discussion:

Death in rabies is inevitable and it does not allow the second chance to treat, so the post exposure prophylaxis protocol has to be very methodical and accurate. National guidelines should be followed strictly. As per **WHO** guidelines passive immunization is mandatory for treating category III animal bite cases. There are evidences of deaths following vaccine administration and non administration of RIGs in category III bites. HRIGs are available in India but very expensive and limited. Similarly ERIGs carry risk of adverse events. So the alternative can be Monoclonal antibody, which is available in our country since 2017.

The present study conducted in 233 children, among which 79% of cases were dog bite and 58% of cases presented with bite over lower limb. The amount of R'Mab or ERIG administered, as per the calculated body weight was injected around the bite site as much as anatomically feasible and rest was injected over thigh. In a study done by Kaware A et al, dog was the most common (93%) biting animal and 44.35% bites were on the lower limb which were similar to our study14. Similarly Behera TR *et al* in their study reported that 73.73% cases were due to dog bite and the most common site of bite was over the lower limb (55.76%) which was similar to our finding15.

In our present study 38 children were given R'Mab and rest were given ERIG. Among all the recipients of ERIG, localised pain was experienced by all children followed by swelling in 96.4% cases, itching by 82.05% and erythema by 73.8% of children. Whereas following administration of R'Mab, only local edema and pain was observed in 58% and 71% of the recipient respectively. In a study by Behera TR *et al* local adverse effects encountered after administration of ERIG on the day of administration were local edema and pain in 100% cases and pruritus in 95.85%15, which was quite similar to our study. Satapathy DM *et al* in their study found

that local pain and edema was present in 11.32% of patients at the site of administration16. In another study by Verma R K *et al* local swelling was found in 41.5% of the participants15. All these local side effects gradually decreased with simple medications like anti histaminics and analgesics.

Only 2 cases had complained of mild fever after R'Mab administration and 42% cases presented with malaise and fever on day 0 and 20% on day 3 of ERIG administration in this study. In a study by Behera TR et al, the systemic side effects of patients receiving ERIG like low grade fever and malaise were 34.8% and 29.5% respectively, which was quite high17.

Limitation of the study was only children less than 14 years were included, so the findings cannot be generalised. ERIG and R'Mab recipients were not of the same proportion i.e. less children were given R'Mab.

Conclusion: Rabies monoclonal antibody potentially offers a safe alternative to ERIG and HRIG with less production cost and less adverse reaction for the passive component of post- exposure prophylaxis and could significantly improve the management of bites from suspected rabid animals. So it is recommended to ensure wider access of R'Mab for passive immunization at a reduced cost.

References:

1. *Rabies [Internet]. [cited 2020 Sep 22]. Available from: https://www.who.int/news- room/fact-sheets/detail/rabies*
2. *Mnyone L, Mazigo H, Okumu F, Kweka E. Retrospective analysis of suspected rabies cases reported at Bugando Referral Hospital, Mwanza, Tanzania. J Glob Infect Dis [Internet]. 2010 [cited 2020 Sep 22];2(3):216. Available from:/pmc/articles/PMC2946675/?report=abstract*
3. *Fooks AR. Rabies remains a "neglected disease". Vol. 10, Euro surveillance : bulletin européen sur les maladies transmissibles = European communicable disease bulletin. 2005. p. 211–2.*
4. *Rabies-World Health Organization*
5. *Gogtay NJ, Nagpal A, Mallad A, Patel K, Stimpson SJ, Belur A, et al. Demographics of animal bite victims & management practices in a tertiary care institute in Mumbai, Maharashtra, India. Indian J Med Res [Internet]. 2014 [cited 2020 Sep 22];139(MAR):459–62. Available from: /pmc/articles/PMC4069742/?report=abstract*
6. *WHO | Epidemiology and burden of disease. WHO [Internet]. 2018 [cited 2020 Sep 22]; Available from: http://www.who.int/rabies/epidemiology/en/*
7. *Afakye K, Kenu E, Nyarko KM, Johnson SAM, Wongnaah F, Bonsu GK. Household exposure and animal-bite surveillance following human rabies detection in Southern Ghana. Pan Afr Med J [Internet]. 2016 [cited 2020 Sep 22];25(Suppl 1):12. Available from: /pmc/articles/PMC5257017/?report=abstract*
8. *New global strategic plan to eliminate dog-mediated rabies by 2030 [Internet]. [cited 2020 Sep 22]. Available from: https://www.who.int/news- room/commentaries/detail/new-global-strategic-plan-to-eliminate-dog-mediated- rabies-by-2030*
9. *WHO Expert Consultation on Rabies Third report [Internet]. 2018 [cited 2020 Sep 22]. Available from: www.who.int/bookorders*

10. *Rabies is killing more than 55,000 a year | The Independent [Internet]. [cited 2020 Sep 22]. Available from: https://www.independent.co.uk/life-style/health-and- families/health-news/rabies-is-killing-more-than-55000-a-year-2360517.html*

11. *Sparrow E, Torvaldsen S, Newall AT, Wood JG, Sheikh M, Kieny MP, et al. Recent advances in the development of monoclonal antibodies for rabies post exposure prophylaxis: A review of the current status of the clinical development pipeline. Vaccine. 2019 Oct 3;37:A132–9.*

12. *Gogtay NJ, Munshi R, Narayana DHA, Mahendra BJ, Kshirsagar V, Gunale B, 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 [Internet]. 2018 Jan 18 [cited 2020 Sep 22];66(3):387–95. Available from: https://academic.oup.com/cid/article/66/3/387/4159363*

13. *Ilina EN, Larina M V., Aliev TK, Dolgikh DA, Kirpichnikov MP. Recombinant monoclonal antibodies for rabies post-exposure prophylaxis [Internet]. Vol. 83, Biochemistry (Moscow). Maik Nauka Publishing / Springer SBM; 2018 [cited 2020 Sep22].p.1–12.Available from: https://link.springer.com/article/10.1134/S0006297918010017*

14. *Kaware A, Rokade H, SK M. Epidemiological study of patients attending anti-rabiesvaccination clinic of tertiary care hospital of Southern Maharashtra, India. Int J Community Med Public Heal. 2016;865–8.*

15. *Behera T R, Mohanty S PN. Clinical safety of an equine rabies immunoglobulin. Apcri J. 2018;XIX(II):9-12[cited 2020 Sep 24]; Available from: www.apcri.org*

    Verma R K MJ. Assessment of Hypersensitivity Reactions Following Equine Anti Rabies Immunoglobulin Inoculation Among Category-III Bite Cases Attending Rural Tertiary Care Institute in Haryana.Apcri J. 2018;XIX(II):24-27. [cited 2020 Sep 24]; Available from: www.apcri.org

16. *Satapathy DM, Panda D, Pradhan SK, Patro SK. Clinical safety of rabies monoclonal antibody. APCRI J. 2019;XX(II):26-29.[cited 2020 Sep 24]; Available from: www.apcrijournal.com*

17. *Behera T, Satapathy DM, Pratap A, Tripathy RM. Post-exposure prophylaxis for rabies with ERIG and IDRV in children. [cited 2020 Sep 24]; J Commun Dis.2011 Mar;43(1):31-7*