

# **Title: Immunogenicity of Rabies Monoclonal Antibody and Wound Management in a Diabetic Patient With Category III Dog Bite**

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**Abstract** A 57 year old diabetic male with multiple bite wounds over his lower limbs bitten by a stray dog was subjected to infiltration of RMab and FHeal ointment application locally to assess the importance of proper wound management and to test the immunogenicity of RMab. He was provided with proper antibiotic coverage (AmoxyClav for 5 days and Cefuroxime for next 5days) along with oral hypoglycaemics (Metformin 500mg as his FBS found to be 146mg/dl) drugs for healing of the wound. He was administered with rabies vaccine (PVRV) by intramuscular regimen and rabies monoclonal antibody for passive immunization. After the completion of vaccination, his Rabies virus neutralising antibody (RVNA) titre was tested which was found to be above the recommended level protective value (>4 EU/ml).

## **INTRODUCTION**

Rabies following dog bite is a public health problem in India affecting 18,000 to 20,000 cases every year. Many of the patients following dog bite still prefer to attend a private practitioner because of many reasons, may be, lack of confidence over government facilities or more affordability etc. referral from different primary and secondary level of health care centres is a common phenomenon in Odisha, especially because of non-availability of Anti-rabies vaccines and immunoglobulin.<sup>1</sup> In general, low-risk infections following animal bite do not require antibiotics. However, the therapy is recommended for high-risk wounds (bites in hands, crush injuries, multiple lacerated bites, late presentation, and poor general health like in diabetes). Wound care following animal bites with appropriate antibiotics is one of the pillars in its management. The organisms involved tend to originate from oral cavity of the offending animal as well as from the immediate environment. The goal of anti-microbial therapy is to cover organisms found in animal's saliva such as Staphylococcus, Enterococcus, Pseudomonas, Citrobacter and Klebsiella.<sup>2</sup> Rational use of antibiotic in animal bite cases is a less studied area and different studies in Odisha have shown use of Amoxyclav, Levofloxacin, and Cefuroxime etc. the recently launched Rabies monoclonal antibody (Rabishield) has proven its safety and immunogenicity in category III animal bite treatment with respect to its low-cost factor as compared to HRIG.<sup>7,8</sup>

Management of animal bite with lacerated wound in diabetics is less studied.

### **CASE PROFILE:**

A 57 years old male (60kgs by weight and 170cms by height) hailing from, Charbatia, Chowdwar, of Cuttack Dist., Odisha, reported to the physician in Cuttack on 22.11.2019 with the chief complaint of multiple wounds resulting from an unprovoked stray dog bite in the evening of 21st November 2019 (the dog showed some abnormal behaviour and the dog was killed by people). There were a total of three wounds on his right leg- two were abrasions and one lacerated wound situated two inches above the medial tibial tuberosity.

Immediately after the incident, he visited the nearest health facility (PHC) in Charbatia where he was administered with a dose of Inj. TT 0.5ml intramuscularly, one dose of anti-rabies vaccine intramuscularly (PVRV- Inj. Abhayrab).

On the day of visit to the physician, he was administered Rabies Monoclonal Antibody (RMab, Injection Rabishield Batch No 030Z Expiry Date 03-2020, manufactured by Serum Institute of India Pvt Ltd, Pune, India) locally in and around the wound as per his body weight (199.8 IU= 5ml). Additionally, Tab. Amoxicillin + Clavulanic acid (625mg) and ointment Povidone iodine was also prescribed for healing of the wound.

Similarly, on Day 3 i.e. on 24.11.2019, he visited the clinic and took the 2nd dose of ARV (PVRV- Injection Rabivax-S Batch No. T022, expiry date 07-2022, manufactured by Serum Institute of India Pvt Ltd, Pune, India)

On Day 5 i.e. on 26.11.2019, he again reported to the physician with the chief complaint of non-healing of his wound. So, he was advised to get his Fasting Blood Glucose checked.

On Day 7 i.e. on 28.11.2019 he came with his reports which reflected FBS to be 146mg/dl, for which he was started with Tab. Metformin (500mg) once daily. Additionally he was prescribed with Tab. Cefuroxime (500mg) twice daily after food for 5 days and F-Heal cream (Tritium vulgare extract and 2-penoxethanol marketed by Lupin Ltd) for local application over the wound.

On Day 14 i.e. 05.12.2019, when he came for his 4th IM dose of ARV (PVRV- Inj. Rabivax-S), the wound was almost healed when examined.

On Day 28 i.e. 19.12.2019, he came for his last dose of ARV. Upon examination of the wound, it was completely healed. He was then advised to do a RVNA test i.e., Rabies Virus Neutralising Antibody Test to know the antibody titre against the vaccine as a tool to assess his protective antibody.

Sample collection for RVNA Test: Blood sample for estimating antibody titre (RVNA) was collected on 20.12.2019 at SP laboratory, Ranihat, Cuttack. The result of the test was reported on 23.12.2019. The method used was Rabies Virus Antibodies Total Antibody Serum. The result of the antibody titre was found to be >4 EU/ml, which was immune according to the biological reference value of >0.5 EU/ml.

### **DISCUSSION:**

According to WHO there are 3 important steps in the management of a category III animal bite wound viz thorough wound washing for 15 minutes with soap and water or irrigation with Povidone iodine, a complete course of vaccines meeting WHO standards and administration of rabies immunoglobulin or monoclonal antibodies.<sup>6</sup>

In a developing country like India where the government spends a meagre amount for providing health care facilities accounting for 1.5% of GDP, cost-effective options are required regarding administration of immunoglobulin and vaccines following animal bite. While switching to intradermal rabies vaccines reduces the cost of cell culture vaccines by 60 to 80% according to WHO reports<sup>6</sup>, there are a few cases where this regimen fails to induce an effective antibody response. In a study conducted by Behera T R et al<sup>4</sup>, showed that even a full course of PVRV through intradermal regimen for a case of stray dog bite, failed to produce the baseline level of protective antibodies upon testing. Another similar study by Haldar S et al<sup>5</sup>, showed that despite complete administration of Anti rabies vaccine by intradermal route and ERIG administration locally at the wound site, the patient developed clinical rabies due to improper wound management.

Therefore, in our case since the patient had an unprovoked stray dog bite and the dog showed some abnormal behaviour later the dog was killed, we decided to provide him with a complete course of intramuscular vaccine regimen.

Earlier studies by Ashe S et al<sup>1</sup> and Biswas M et al<sup>2</sup>, demonstrated the healing of animal bite wound by using Tab. Amoxicillin+Clavulanic acid (625mg) as the first line of therapy. However, the non-healing of the wound in our case may be attributed to the accidental diagnosis of diabetes mellitus in the patient.

Since the patient also showed resistance to the first line antibiotic therapy, we administered him a combination of oral as well as local treatment. Orally he was provided with Tab. Cefuroxime axetil (500mg) and for local application an ointment containing Tritium vulgare extract and 2-penoxethanol for a duration of 5 days. This showed remarkable results after a week. Another similar study by Behera T R et al<sup>7</sup> showed complete healing of a category III dog bite wound by local application of the same ointment. Similar results of healing of animal bite wounds were described by the same author.<sup>3</sup>

Even though ERIG is available easily only at hospitals especially in urban areas for the management of animal bite wounds, still many physicians are reluctant to use because of fear of higher incidences of anaphylactic reactions as well as local reactions. HRIG have to be derived from immunized human donors which makes it more expensive and relatively less available. To overcome these issues, another alternative is available known as the Rabies Monoclonal Antibodies (RMab) which is produced from mammalian cell lines, relatively lower cost, and requiring lesser volume and reliable for producing adequate protective antibodies. These RMabs are being used in US since 1998<sup>9</sup> and in India the first RMAb was launched in the year 2018<sup>10</sup>.

The patient did not develop any local pain, erythema or pruritus or systemic reactions like fever or generalised pruritus. This result was comparable to the findings of another study conducted by Satapathy D M et al<sup>8</sup> among 59 patients in another Hospital in Odisha. Furthermore; larger studies were being conducted wherein it was demonstrated that RMabs did not produce any serious adverse reactions in the study participants.<sup>11</sup>

In our study, upon measurement of the antibody titre of the patient after completion of the vaccination course, it was seen that sufficient protective antibodies was produced i.e. >4EU/ml. Another larger clinical trials were conducted which demonstrated the efficient immunogenicity of the monoclonal antibodies which was comparable to HRIG.<sup>11,12</sup>

## **CONCLUSION:**

In this case, it is demonstrated that even though Tab. Amoxicillin+Clavulanic acid is widely used for

management of animal bite wounds, there are always exceptions like the accidental diagnosis of diabetes mellitus which delays wound healing. So, alternatively higher antibiotics like Tab. Cefuroxime (500mg) along with a combination of topical ointment containing Tritium vulgare extract and 2-penoxyethanol proved to be highly beneficial.

This study also demonstrates RMab a cost effective and relatively safer alternative to ERIG/HRIG to be used for post- exposure prophylaxis of rabies. Moreover, its immunogenicity is also non-inferior to its other counterparts.

## REFERENCES:

1. Ashe S., Behera T.R., Rampant use of antibiotics in animal bite cases in the era of antibiotic resistance: a cross-sectional study. *Journal of Medical Science and Clinical research*, Volume 08, Issue 1, p 380-387.
2. Mohua Biswas<sup>1</sup>, Durga Madhab Satapathy. Bacterial contamination and antibiotic sensitivity pattern of animal bite wounds: a study in the anti-rabies clinic of SCB medical college, Cuttack, Odisha. *APCRI Journal*, Volume XX Issue I July 2018, p 11-13
3. Tapas Ranjan Behera. Case report of a 58 year old woman presenting with category III dog bite. *Flatrate F. Feel the difference with Fheal, All Speciality*. 2009; (3):1-4.
4. Tapas Ranjan Behera, Gurukrushna Mohapatra, Lomapada Nayak. Failure of antibody production following intradermal rabies vaccination in the management of category III animal bite: a case report; *APCRI journal*, Volume XVII- Issue 2, January 2016, pg. 35-36.
5. Suchitra Haldar, Tapas Ranjan Behera – Treatment failure of a Category III dog bite with IDRV and ERIG; *APCRI journal*, volume XX- Issue 1, July 2018. pg. 32-33.
6. WHO, <https://www.who.int/news-room/fact-sheets/detail/rabies>.
7. Behera T R, Ashe S: Safety and immunogenicity of Rabies Human Monoclonal Antibody (Rabishield) in a Category III Rabid Dog bite case- A case report. *APCRI journal*, Vol XXI, Issue 2, January 2020. Page 40-41.
8. D. M. Satapathy, Devasish Panda, Subrat Kumar Pradhan, Sithun Kumar Patro, Clinical safety of rabies monoclonal antibodies: a follow-up study conducted at ARC, VIMSAR, Burla. *APCRI journal*, Vol. XX, Issue 2, January 2019. Page 26-29.
9. Susan E Sloan, Cathleen Hanlon, William Weldon, Michael Niezgoda, Jesse Blanton, Josh Self et al: Identification and characterization of a human monoclonal antibody that potentially neutralizes a broad panel of rabies virus isolates. *Vaccine*. 2007 Apr 12; 25 (15):2800-10.
10. <https://rabiesalliance.org/resource/first-monoclonal-antibody-replacement-rig-launched>
11. Gogtay N, Thatte U, Kshirsagar N, Leav B, Molrine D, Cheslock P, Kapre SV, Kulkarni PS; SII RMab author group. Safety and pharmacokinetics of a human monoclonal antibody to rabies virus: a randomized, dose-escalation phase 1 study in adults. *Vaccine*. 2012 Nov 26;30(50):7315-20. doi: 10.1016/j.vaccine.2012.09.027. Epub 2012 Sep 23. PMID: 23010601.
12. Gogtay N.J., Munshi R., Ashwath Narayana DH, Mahendra B.J., 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*. 2018 Jan 18;66(3):387-395. doi: 10.1093/cid/cix791. PMID: 29020321.

