Title: INTRA-DERMAL RABIES VACCINATION FAILURE TO PRODUCE ADEQUATE PROTECTIVE ANTIBODY IN A CATEGORY III SUSPECTED RABID DOG BITE CASE

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Keywords Rabies, Intradermal rabies vaccination, rabies Immunoglobulin, Failure of antibody production..

Abstract

Intra- dermal rabies vaccine (IDRV) is a World Health Organisation (WHO) approved cost effective method for prophylaxis in animal bite cases to prevent the 100% fatal disease Rabies. In Category III bite cases apart from IDRV, Rabies Immunoglobulin (RIG) needs to be administered. Most post-exposure treatment failures are due to deviations from WHO standards and delay or not using immunoglobulin. Case report: A 21-year-old male had a Category III bite with a suspected rabid dog on 14.9.2020. The patient had received Tetanus Toxoid (TT), three doses of IDRV on day 0 (Dated-15.9.2020), Day 3 and Day 7 but without administration of rabies Immunoglobulin (RIG) at a peripheral hospital (Government Primary Health Center). The patient reported to the Anti Rabies Clinic (ARC) of SCB Medical College, Cuttack, the level of RVNA was estimated which was found to be non immune.

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CASE REPORT

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ABSTRACT :

Background: Intra- dermal rabies vaccine (IDRV) is a World Health Organisation (WHO) approved cost effective method for prophylaxis in animal bite cases to prevent the 100% fatal disease Rabies. In Category III bite cases apart from IDRV, Rabies Immunoglobulin (RIG) needs to be administered. Most post-exposure treatment failures are due to deviations from WHO standards and delay or not using immunoglobulin. Case report: A 21-year-old male had a Category III bite with a suspected rabid dog on 14.9.2020. The patient had received Tetanus Toxoid (TT), three doses of IDRV on day 0 (Dated-15.9.2020), Day 3 and Day 7 but without administration of rabies Immunoglobulin (RIG) at a peripheral hospital (Government Primary Health Center). The patient reported to the Anti Rabies Clinic (ARC) of SCB Medical College, Cuttack, the level of RVNA was estimated which was found to be non immune. The patient was re-treated with Purified Chick Embryo Cell Culture (PCEC) vaccine through Intra Muscular (IM) route over left upper arm on days 0-3-7-14 &28 with double dose of vaccine i.e 1ml on both arms on day 0 along with Rabies human monoclonal antibody (RMab) (rDNA) administration on Day 0 at the rate of 3.33 IU/kg. After completion of 5 doses of Anti Rabies Vaccine (ARV) reassessment of rabies antibodies was done and the value came to be >4 EU/ml which is Immune. Conclusion: As adequate protective antibody could not be achieved with use of only ARV through intra-dermal route (IDRV), it should be made mandatory to supply and use of RIG/RMab for all category III animal bite cases not only at the district head quarter hospitals but also at designated ARCs at Community Health Centers (CHC). More emphasis should be given for creating awareness among the medical officers for use of RIG/RMab within 7 days of initiation of vaccination for all category III animal bite cases and should be oriented to refer to higher centers in case of unavailability of RIG/RMab.

Keywords: Rabies, Intradermal rabies vaccination, rabies Immunoglobulin, Failure of antibody production

INTRODUCTION

Intra- dermal rabies vaccine (IDRV) is a World Health Organisation (WHO) approved cost effective method for prophylaxis in animal bite cases to prevent the 100% fatal disease Rabies. The Updated Thai Red Cross (TRC) regimen of IDRV method is widely used in the world for treating Category II and III animal bite cases[1,2].In Category III bite cases apart from IDRV, Rabies Immunoglobulin (RIG) needs to be administered. It is recommended that RIG should be given within 7 days of administration of 1st dose of anti rabies vaccine so as to prevent the interference with development of active immunity[3].

Odisha was the 2nd state in India to implement the IDRV with SCB Medical College Hospital, Cuttack being 2nd to start IDRV[4]. As in majority of the peripheral Primary Health Centres (PHCs) and Community Health Centres (CHCs) of the state, Rabies Immunoglobulin (RIG) is scarce or even not in supply so, patients from these areas are being referred to the Anti Rabies Clinic (ARC) of SCB Medical College Hospital for either RIG administration or for further course of treatment.

The acceptable WHO cut-off level, indicating an adequate adaptive immune response, is 0.5 IU/mL[5]; the ACIP cut-off level is 0.1 IU/mL (complete virus neutralization at serum dilution of 1:5)[6]. The virus neutralizing antibody (VNA) titre response ideally should be determined 2–4 weeks (WHO) or 1–2 weeks (ACIP) after the last dose of the anti-rabies vaccine to assess whether an additional dose is needed [5,6]. Very poor or no response to pre- and post-exposure rabies vaccination has been well documented in HIV-infected subjects[7] and is very likely with immuno suppressive drugs and immuno-compromised patients[8];

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Most post-exposure treatment failures are due to deviations from WHO standards and delay or not using immunoglobulin[9].

The present case report is about such a scenario where a Category III bite had not been administered Immunoglobulin within 7 days of 1st dose of ARV and had poor antibody response to ARV. However proper re administration of ARV and RIG administration helped in development of protective level antibodies. Thus this case report may help in guiding doctors while dealing with cases of improper or incomplete post exposure prophylaxis in animal bite cases.

CASE/PATIENT PROFILE

A 21-year-old male was bitten by a stray dog on 14.9.2020 over his left leg which was an unprovoked bite. The dog was abnormal, had bitten 5 more persons and was killed on the same day i.e 14.9.2020. The patient went to the District Headquarter Hospital (DHH) of Jajpur district on 15.9.2020. Though it was a category III dog bite (as mentioned in the prescription), the patient received only tetanus toxoid vaccine (TT) as Intramuscular and anti-rabies vaccine through intra-dermal route on 15.9.2020 but without rabies immunoglobulin (RIG) administration. The patient was also administered Day 3 IDRV on 18.9.2020 and Day 7 IDRV on 22.9.2020at DHH Jajpur.

The patient reported to the ARC of SCB Medical College, Cuttack, on 8.10.2020with the chief complain of local pruritis and tingling sensation. As it was a category III animal bite, the patient was counselled about the necessity of RIG infiltration at the site of bite within the first 7 days of vaccine administration which was not done at the DHH Jajpur. Again, the patient was counselled about the necessity of estimating the antibody titre i.e., RVNA (rabies virus neutralizing antibody) to know whether the required protective antibody titre has been achieved or not. The father of the patient agreed to conduct the test. It was also revealed from the parent of the patient that neither he was on any immunosuppressive drugs nor was he suffering from any chronic immune-compromised diseases.

Sample Collection and Its Result

Blood sample was collected on 8.10.2020 for estimating the RVNA and sent to SRL Diagnostics Mumbai. The method used at SRL Diagnostics was Rabies Virus Antibodies Total (Serum, EIA). The patient reported to the ARC of SCB Medical College Hospital on 12.10.2020 along with the antibody titre report. The RVNA titre response ideally should be determined 2–4 weeks (WHO) or 1–2 weeks (ACIP) after the last dose of vaccine to assess whether an additional dose is needed[5,6]. In our case, the antibody titre was done only after 3 weeks after last dose of vaccine administration. 66

The result of antibody titre was found to be 0.14 IU/mL which was non-immune according to biological reference interval (immune >0.50 IU/mL and nonimmune $\leqslant$ 0.50 IU/mL titre of antibodies). The acceptable WHO cut-off level, indicating an adequate adaptive immune response is 0.5 IU/mL[5]; the ACIP cutoff level is 0.1 IU/mL (complete virus neutralization at serum dilution of 1:5)[6].

Treatment Offered at ARC SCB Medical College, Cuttack

The patient was re-treated with Purified Chick Embryo Cell Culture (PCEC) vaccine (inj. Vaxirab N, Batch number- RV90016, Expiry date-09/2022, Manufactured by Cadila Healthcare Ltd, marketed by Zydus Vaxxicare, Ahmedabad, Gujrat, India) as Essen regimen through intra-muscular (IM) route over left upper arm on days 0-3-7-14-28 with double dose of vaccine i.e 1ml on both arms on day 0. Along with the day 0 anti rabies vaccine the patient was also administered Rabies human monoclonal antibody (RMab) (rDNA) i.e. Inj Rabishield (Batch number- 1879T004, Expiry date-10/2022, Manufactured by Serum Institute of India Pvt. Ltd, Pune, India) as 3.33 IU/kg. The calculated dose of RMab was 226.4 IU (68 kg × 3.33 IU/kg = 226.4 IU). Inj Rabishield contains 100IU in 2.5ml and so the total calculated dose for the patient was 5.66 ml which was infiltrated locally at bite site on 17.10.2020.The patient completed all the five doses of PCEC through intramuscular route at the ARC of SCB Medical College, Cuttack with Day 0 on 17.10.2020, day 3 on 20.10.2020, day 7 on 24.10.2020, day 14 on 31.10.2020 and day 28 on 14.11.2020 and was found to be healthy. The patient was not a non-responder to intra-dermal rabies vaccination as he was not taking any immune-suppressive drugs.

Blood sample was collected after completion of the scheduled antirabies vaccination for assessment of Rabies antibodies (Total) by Serum, EIA method and the value came to be >4 EU/ml which is Immune (>0.5) as per the Biological Reference Interval. The assay detects Rabies IgG antibody. It is a protective response and the titres represent the person's immune status. A level of antibody equal to or superior to 0.5 EU/ml is considered by the WHO as acceptable serocon version level above which the vaccination could be considered as successful. The external evaluation of the kit used by the Laboratory has been performed at Rabies Reference Laboratory, Institute Pasteur de Paris, France (Reference method is RFFIT).

Discussion

There are many studies worldwide in proving the efficacy, immunogenicity and safety of intra-dermal rabies vaccination using both PVRV and PCEC[10-15].

The National Guidelines on Rabies Prophylaxis 2015 under National Rabies Control Programme state that the volume of the diluent of PVRV for ID use should be same as that of the IM dose and vaccine should have the potency of $\geqslant$2.5 IU/IM dose[16].

Sudarashan et al reviewed 66 cohorts of 2,799 vaccines over 27 years collected from six countries (PubMed and Google) where post-vaccination neutralizing rabies antibodies were measured. They studied time intervals between primary and booster vaccination in individuals who had previously received a full course of pre-exposure or post-exposure prophylaxis and were then re-exposed to rabies. The duration of presumed protection by previous vaccination was assessed by using a surrogate marker of adequacy; a neutralizing antibody level above 0.5 IU/mL. They also found poor responders with less than 0.5 IU/mL in 0.07% and 0.14% at the end of the first and third month post primary vaccination. However, all 577 subjects, with previous pre-exposure vaccination, had antibody responses above 0.5 IU/mL at the end of the first and third month post-primary vaccination[17].

Laboratory errors or poor vaccine quality are unlikely to produce inadequate protective antibody production. In a study (6/85) among the Swiss study subjects what could be the cause of the poor responses was assessed. Numbers are small and a small cluster of undetected immune-compromised subjects is one possibility; perhaps the most likely. The suggestion to recommend routine antibody testing on day 21 is not realistic due to cost and lack of specialized laboratories in endemic regions[18]. Detecting a low or absent titre on day 21 may be too late to alter the course, if rabies is already incubating.

Hence it was clearly indicated that the vaccine Indirab (diluted with 1 ml of diluent) which was given as intradermally on scheduled dates as three doses failed to achieve the required antibody titre (>0.5 IU/mL) for the protection of an individual against rabies. So there may be faulty technical procedure adopted for vaccination, i.e., Intra-dermal route at the District Hospital Jajpur or failure of cold chain maintenance of the reconstituted vaccine. The potency of the vaccine used at DHH Jajpur is questionable as documented from the result obtained from SRL diagnostics, Mumbai, which indicates this was a clear-cut case of vaccine failure in producing the protective antibody, i.e., >0.50 EU/mL. There are many studies, where vaccine failure has been documented only in immune-compromised cases like a case report reported by Terapong Tantawichien et al.[7] where IDRV fails in a patient with HIV+ve with low CD4 count. But here the patient was not immune compromised.

Conclusion

As adequate protective antibody could not be achieved with use of only ARV through intra-dermal route (IDRV), it should be made mandatory to supply and use of RIG/RMab for all category III animal bite cases not only at the district head quarter hospitals but also at designated ARCs at CHCs. More emphasis should be given for creating awareness among the medical officers for use of RIG/RMab within 7 days of initiation of vaccination for all category III animal bite cases and should be oriented to refer to higher centers in case of unavailability of RIG/RMab. The study showed that use of RIG, especially RMab, along with IDRV is essential to treat Category III animal bite in children. Therefore, the authors recommend the use of RIG/RMab with IDRV for treatment of Category III animal bite cases in children. Establishing an international registry for failure cases might be appropriate and they should be carefully reviewed for hidden causes. Laboratories able to perform reliable rabies neutralizing antibody tests are few and absent in many endemic countries. However, it would be important if poor responders could undergo a thorough immunological evaluation to identify causes.

Conflict of Interest: None

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