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Case Series

Should Favipiravir be Used as an Additional Drug in Case of Severe Animal Bites on the Face Especially into the Eyes/ Lips or Aerosol Exposure to Rabies Virus to Prevent Rabies PEP Failures?

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How to cite this article:

Bharti OK, Bansal A, Mehta U. Should Favipiravir be Used as an Additional Drug in Case of Severe Animal Bites on the Face Especially into the Eyes/ Lips or Aerosol Exposure to Rabies Virus to Prevent Rabies PEP Failures? J Adv Res Med. 2022;9(4):1-4.

Date of Submission: 2022-10-10

Date of Acceptance: 2022-11-09

A B S T R A C T

Rabies is a zoonotic viral disease that affects the central nervous system leading to respiratory or cardiac failure. Dogs are a major source of rabies infection in human beings. Rabies is 100% fatal but largely preventable if proper and timely Post-Exposure Prophylaxis (PEP) is availed in the form of immediate wound wash with soap and water and injections of vaccine and rabies immunoglobulins, the first week being the most important. Here we describe four cases of PEP failure despite complete prophylaxis with vaccine and Rabies Immunoglobulins (RIG) over the past year in Himachal Pradesh. All failures were due to suspected rabid dog bites on the face, especially on cheeks, lips, or eyes where complete infiltration of RIG may not have been possible leading to PEP failure. We, after extensive research and discussion, are of the opinion that in such situations, we may add another viricidal oral drug favipiravir along with rabies PEP that could help prevent PEP failures in situations where complete RIG infiltration into wounds is difficult to achieve.

Keywords: PEP Failure, Favipiravir, Rabies Vaccine, Rabies Immunoglobulins, Virus

Introduction

Rabies is a zoonotic viral disease that affects the central nervous system leading to respiratory or cardiac failure. Dogs are a major source of rabies infection in human beings. Rabies is 100% fatal but largely preventable if proper and timely Post-Exposure Prophylaxis (PEP) is given to the victims, the first week being the most important.¹ Failures in PEP have been reported even after complete PEP was administered due to various biological reasons. There are a few cases that we have recorded that could

have benefited if additionally an antiviral drug was provided as given below. A strange observation is that the same rabid dog biting different people had different outcomes with reference to rabies after complete prophylaxis was provided to them.

Case I

A 60 years old male patient near Shimla town was bitten by a stray dog on the lower lip and base of the thumb of right hand. The lower lip had a bleeding laceration and was

sagging down and had some scratches. A dog bite happened suddenly on the morning of Nov 23, 2022 at 09:30 am while the patient was going to the agricultural fields for work. The patient after washing his face and hands with soap and water rushed to the nearby Government Primary Health Centre. He reached within 2 hours (11 am) and was given 3 doses of Intra-Dermal (ID) vaccine 0.1 mL on bilateral deltoid skin on days 0, 3 and 7 along with 7.5 mL local wound infiltration of equine Rabies Immunoglobulins (eRIG) covering all surfaces of all the wounds till depth. The laceration on the lip was 1 cm long and the wound on the base of the thumb of right hand was 4 x 3 cm in size. With eRIG infiltration, bleeding in the lip increased and the patient was asked to visit the ENT Department of Indira Gandhi Medical College (IGMC), Shimla. The patient was rushed to IGMC at about 12:30 pm and was administered 2 separate stitches on the lower lip to stop bleeding and approximate sagging lower lip flap. On Dec 11, 2022, after 18 days of the dog bite and PEP with stitches, the patient arrived at IGMC with a history of vomiting for 3 days, tremors in the bitten hand, and hydrophobia. The patient was examined and further referred to PGI Chandigarh for further management. The patient later died at PGI Chandigarh in the evening at 4 pm on Dec 11, 2022. The medical certificate of cause of death listed cardiac arrhythmia and type 1 respiratory failure as the immediate cause of death, autonomic dysfunction and aspiration pneumonia as the antecedent cause, and rabies as the contributing condition. Another person bitten by the same dog has not been reported to be dead. The same dog had bitten some cows and buffaloes and other dogs that were given PEP and no death was reported.

This is the fourth PEP failure since last year in patients bitten on the face in Himachal Pradesh despite complete PEP.

Case 2

A lady aged 39 years was attacked by a suspected rabid dog in the market of village Cheogin Matiana block in Shimla District of Himachal Pradesh on March 29, 2022. She was bitten on the face multiple times injuring her left eye (Figures 1 and 2), which collapsed due to puncture wounds, therefore she was immediately referred to Indira Gandhi Medical College, Shimla for further management and specialist eye care. After 3 weeks, she died of rabies on April 21, 2022 having symptoms of hydrophobia and aerophobia. The same rabid dog also attacked a 43-year-old male in the face and a 9-year-old female child who was given PEP in the nearby PHC Bani and survived. Later the dog was killed by the villagers.

Case 3

In December 2021, a 51-year-old lady from Jari village of Kullu District was bitten on the upper eyebrow of her

right eye. She took a vaccine the same day, however, eRIG was taken on day 3 at district hospital Kullu as it was not available at Jari health centre. The lady died on Dec 23, 2021 after 3 weeks, due to suspected rabies with symptoms of hydrophobia and aerophobia, although another person from the same village was bitten on the nose by the same dog and took injections on similar days, but survived.



Figures 1 and 2. A Lady bitten on Face Puncturing Her Left Eye who died due to Rabies Despite Complete PEP in Shimla District of Himachal Pradesh Case 4

An 8-year-old boy from Paunta Sahib village of Sirmour district of Himachal Pradesh was bitten on the face including a lower eyelid puncturing the orbit and eyeball (similar to Figure 3 from West Bengal). The vaccination was done and all wounds were infiltrated with eRIG except the eye as the treating physician thought the patient would go blind if the eye is infiltrated with RIG. The boy developed hydrophobia and aerophobia after 2 weeks and died.



Figure 3. Child Bitten on Lower Eye Puncturing the Lower Orbit of Eye Leading to Collapse of Eyeball (Image by Dr Soumya Sengupta from West Bengal)



Figure 4. Wounds on the Face Inflicted by a Clinically Rabid Dog after being Stitched on the Cheek of a Female Patient. Later, we thoroughly Infiltrated them with eRIG without Opening Stitches after the Application of a Local Anaesthetic Xylocaine around the Wounds as One Circle, and the Patient Survived

Discussion

PEP failures despite timely and complete PEP have been reported all over the world and the exact cause is difficult to ascertain.² As in case 3 above, patients having been bitten on the face and getting PEP in similar situations on the same days (delay) are having different outcomes as one dies and the other survives. Some authors have stressed the need for more concentrated rabies antibodies in case of exposure to head and neck regions so that PEP failures are prevented.³ However, practical experience does not warrant such a revision in WHO classification as patients having wounds thoroughly infiltrated even in the head and face have survived despite being bitten by laboratory-confirmed rabid dogs.⁴ The discussion on case 1 above revolved around the fact that stitches were applied soon after eRIG infiltration and may have resulted in failure or in case 3 a delay of 3 days may have been the cause of PEP failure however we have infiltrated wounds on the face after 3 days of the bite of a clinically rabid dog after they were stitched on the cheek and lower lip of a female patient (Figure 4) referred from Kullu district and she survived.⁵ Similarly, no stitches were applied to a third child bitten on the cheek and she died of rabies despite complete PEP in the hospital near Shimla⁶ though she was 17 hours late to get PEP and no immediate wound washing was done, however, case 1 we reported here had arrived within hours of dog bite and given complete and timely PEP that failed.

Similarly, case 2 was also timely referred to IGMC Shimla and given complete PEP and eye care, but died of rabies.

Therefore, it is difficult to point out the exact causes of PEP failures, especially in wounds that are on the head and face, particularly in the eyes and lips. Trauma to nerves caused by the needle during infiltration may cause rabies if wound infiltration is insufficient or inadequate to cover the entire surface of the wounds, especially on highly innervated areas like the eyes and lips. Maybe re-infiltration with RIG is required in case we apply stitches after the patient arrives even after RIG infiltration had been done on the first contact. Maybe the lip surface should have been thoroughly rinsed with a gauze drenched in eRIG rather than repeated lip infiltration with the needle. Maybe to avoid such situations, PEP in endemic areas having high-risk groups is required.⁷ Universal PEP apart from saving lives in the above situations may be a cost-effective option in rabies-endemic countries like India.^{8,9}

Way Forward

Keeping these cases in mind, a pertinent question we have raised is, could concurrent use of an antiviral drug favipiravir help in the survival of these patients? Favipiravir is a viricidal drug and its use in COVID-19 patients has been well-established. A recent review provides insights into the evidence-based evolving role of favipiravir in the management of COVID-19 infection with emphasis on the benefits of initiating an early antiviral therapy.¹⁰ In a recent study,¹¹ the use of favipiravir along with the rabies vaccine provided complete protection against rabies-related death in 100% of mice, even after RABV propagated to the central nervous system during infection. This prompted the authors to think of concurrent oral use of favipiravir along with the rabies vaccine and thorough local wound infiltration of severe facial wounds, especially into eyes/lips or aerosol exposure to rabies virus to prevent rabies PEP failures. Since favipiravir is well-trying in human viral diseases like COVID-19 and influenza, its use for severe rabies exposure does not warrant any ethical dilemmas. The dosing regimen is an important part of successful antiviral therapy. The approved favipiravir dosing regimen for influenza in Japan is a loading dose of 3200 mg on day 1, followed by a maintenance dose of 600 mg twice daily on days 2-5. The currently recommended regimen of favipiravir is 1800 mg of loading dose BID on day 1 followed by 800 mg BID from day 2 to a maximum of day 14.¹² The pharmacological effects of favipiravir on coronavirus and other viruses and its side effects with doses have well been described in a study by Tejaswi et al.¹³

We hope that concurrent early oral use of favipiravir in rabies PEP along with vaccine and RIG, in cases of severe exposure to rabid dogs may help avert recurrent PEP

failures in Himachal Pradesh and elsewhere,¹⁴ especially in situations where the treating doctor feels that RIG infiltration may not have been sufficient to cover the entire surface of wounds till its depth¹⁵ as in the cases mentioned above or there is an inordinate delay to infiltrate RIG on facial wounds.

Conflict of Interest: None

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