ORIGINAL RESEARCH ARTICLE

INTRAMUSCULAR RABIES IMMUNOGLOBULIN (IM-RIG) FOR POST-BITE RABIES PREVENTION IS WORSE THAN USELESS

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Abstract

Rabies, a zoonosis that is 100% fatal once symptoms of the disease appear, however Rabies is almost 100% preventable if the prophylactic measures with proper wound wash, vaccines and Immunoglobulins are taken soon after exposure to animal bite. A general tendency has been noticed among clinicians all over to inject Rabies Immunoglobulins (RIG) intramuscularly, mostly in the gluteal muscle, despite the guidelines to infiltrate the wounds. This has resulted in failures of Post Exposure Prophylaxis in many countries leading to death of the patients due to Rabies. Here we discuss how giving any amount or even large amount of RIG intramuscularly (IM) is not going to neutralize rabies virus at the wound site especially during window period, exposing the patients to the risk of Rabies. Whereas small volume of RIG injected into the wound/s are lifesaving intervention as they neutralize the virus there and then in the wound/s especially during initial window period, when the exposed person is unprotected, as the response to concurrent vaccination is awaited and may take 10-14 days after exposure.

Keywords: Rabies, Rabies Immunoglobulins, Post Exposure Prophylaxis.

Introduction

Rabies is a viral zoonotic disease responsible for an estimated 59,000 human deaths and over 3.7 million disability-adjusted life years (DALYs) lost every year .Most cases occur in Africa and Asia, with approximately 40% of cases in children aged <15 years. Dogs are the most important reservoir for rabies viruses and dog bites account for >99% of human cases . Rabies can be prevented if timely prophylaxis is given to the bite victims in the form of rabies vaccine and Rabies immunoglobulin (RIG) injection into the bite wounds , . The pathophysiology of rabies virus after inoculation/bite is to seek a nerve ending that it can invade and advance centrally to the brain within an immune protected nerve. If infection occurs within a week and before sufficient circulating antibodies appear due to vaccination, such a patient is at risk of rabies. There is no viremia and therefore virus remain in the surface of wound/d. Effective post-exposure prophylaxis (PEP) after being bitten involves; a) flushing of virus from wounds

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through effective washing with soap and water and applying any disinfectant; b) active immunisation with vaccine; and c) most importantly, neutralisation of any residual virus within the wounds itself with local wound injection of RIG.

Short incubation periods in Rabies are a known reality especially in children where bites are mostly closer to head and neck due to short stature. After being bitten, even after wound washing some rabies virus is present at the site of bite for varying periods of time and need neutralization by passively administered antibodies into the wound. Rabies vaccine takes about 10-14 days to mount an effective immune response achieving a protective titer of near 0.5 IU/ml of serum. This 10-14 days of window period need to be bridged to protect the patient from rabies. To bridge this window of risk, WHO recommends that passive immunization with readymade antibodies called Rabies Immunoglobulins (RIG) need to be done as early as possible after exposure to rabid animal by injecting RIG into the wound/s.

Recently WHO has recommended only wound infiltration of rabies Immunoglobulins (RIG) without IM administration except in rare circumstances where wound is not available for infiltration e.g. aerosol exposure etc. New guidelines by National Centre for Disease Control (NCDC), India also endorse only wound infiltration as per WHO guidelines . Still some doctors prefer giving RIG intra muscular (IM), in the mistaken belief that it is equally effective and less painful than injecting RIG into the wound(s) as gathered from the focus group discussions with the doctors. Neither of these beliefs is true, and this is still resulting in failures of Post Exposure Prophylaxis (PEP),. Here we present evidence from one case study that even full calculated volume of RIG based on weight of the patient, when injected intramuscularly (IM) did not have neutralizing antibodies in the blood of the patient at day 3 and thereby exposed the patient to the risk of rabies. On May 2014, a 24 years male had gone to nearby city Chandigarh and was bitten by a stray dog on the Rt. Lower leg. The dog was suspected to be rabid and had bitten other people as well. He went to a government anti- rabies clinic and was given a dose of rabies vaccine IM and also full dose of equine RIG (eRIG) calculated based on his body weight (62Kg) i.e. 8.5 ml into gluteus muscle IM, no wound infiltration was done contrary to guidelines. The patient reported to us at our Shimla clinic at DDU Hospital on day 3 for next dose of vaccine injection. He was anxious to know if he is protected or not. He got his serum sample tested for rabies antibodies by Rapid Fluorescent Focus Inhibition Test (RFFIT) from a reference lab at National Institute of Mental Health & Neurosciences (NIMHANS), Bengaluru, India. The report from NIMHANS said only traces of antibodies are there and no measurable antibodies were present on day 3 even after full IM injection of eRIG to the patient at Chandigarh. Later on he was given local wound infiltration of eRIG on day 6 when a vial of eRIG could be made available after long search as RIG was not available in the market. This case study clearly shows that IM injection of full calculated dose of RIG is not going to give protective titers at the wound site during window period thus exposing the patient to the risk of rabies if the rabies virus attaches with the exposed nerve ending within this initial window period and in that case no amount of vaccine or RIG can save the patient subsequently as virus then becomes immune protected within the nerve. Many other studies show the failure to give protective antibody levels in human serum by RIG injected IM.

Animal model studies have clearly shown that any amount of RIG given IM is of no use as no effective titers of antibodies (i.e. >= 0.5 IU/ml of serum) are achieved during the unprotected window period of 10-14 days while vaccine begins to produce an effective endogenous immune response. A four times dose as prescribed by weight for RIG could not help rabies antibodies appear in blood of mice injected IM Human RIG (HRIG) in a study done by China CDC recently. Study says, To evaluate the relationship between the dose of RIG given via systemic injection and the level of specific antibody in serum, mice were injected with different doses of RIG via the intramuscular route for the first immunization (day 0), together with purified Vero-cell rabies vaccine (PVRV) (obtained from Liaoning Chengda Biological Technique Co. Ltd, China). The authors conclude “Importantly, no significant differences were found in the titers between the six groups administered various doses of systemic RIG,

indicating that the systemic injection of RIG rarely influences the level of neutralizing antibody against rabies virus generated during adaptive immunization. This result emphasizes that the main function of RIG in PEP is to rapidly neutralize the rabies virus via local infiltration and to prevent its spread to the nervous system. All of these results indicate that the administration of RIG via systemic injection does not detectably contribute to the passive or adaptive immunization effects of rabies vaccination, suggesting that local wound infiltration of RIG is of paramount importance for severe cases (exposure severity, category III), and provides an immediate supply of antibodies to neutralize rabies virus ."On the other hand only local wound infiltration of RIG has saved many lives not only in Human being bitten by lab confirmed rabid dogs but also lives of animals bitten by lab confirmed rabid dogs and mongoose where small amounts of eRIG injected into the wound/s along with vaccination in cows and buffaloes saved their lives.

It is difficult to know how much virus is there in the wound that needs to be neutralized with local wound injection of RIG. Some of the earlier studies conducted have shown that the quantum of virus present in salivary glands of rabid dogs vary from as low as 10^2 to as high as 10^4 LD^{50} per gm [i],[ii]. Further it has been shown clearly that a dose of 10^4 FFD^{50} of virus has been neutralized 100% by RIG in quantities as low as 0.025 IU. On the other hand a virus dose of 10^3 FFD^{50} has been neutralized 100% in all dilutions of both HRIG and ERIG [iii]. Theoretically speaking, as the value of 0.5 IU/ mL (IU/ml) of rabies antibodies in serum has been recommended by WHO as indicative that a vaccinated person has responded to rabies vaccine , therefore to protect a patient we need 0.5 IU/ml of RIG at wound site to neutralize whatever load of virus is inoculated there inside the wound. That means we can dilute 1 ml of eRIG (300 IU/ml) up to 600 times, HRIG (150 IU/ml) up to 300 times for local wound infiltration at wound site to have 0.5 IU/ml for protection by virus neutralisation. This evidence generated enough confidence in our team at DDU Hospital Shimla, Himachal Pradesh in India to inject a minimum dose of 0.025 ml (7.5IU) of eRIG into the scratches/wounds of our patients at DDU Hospital Shimla who had small nail puncture wounds and this small volume of eRIG was enough to kill any amount of virus that could have been present there in the wound as all our patients, some of them bitten by lab confirmed rabid dogs, survived. WHO advocates that for large and multiple wounds, RIG can be diluted if necessary with physiological buffered saline to ensure the infiltration of all wounds. WHO no longer recommends injecting the remainder of the calculated RIG dose IM at a distance from the wound . Recently in China, a four yrs. eight month old girl child bitten by a confirmed rabid dog and was given wound infiltration of HRIG diluted 15 times and survived .

While RIG given IM fails to reach blood due to large molecular size of the Immunoglobulins and remain deposited in the muscle with the additional risk of serum sickness, swelling, reaction and anaphylaxis. Administration of local injection of eRIG is associated with negligible reaction17 while injecting the remaining eRIG into muscle as per previous WHO guidelines used to have high reaction rate including serum sickness up to 3% recipients5 and anaphylaxis in some of them. Apart from this additional RIG given IM contributes to lower the immune response to rabies vaccine.

Based on our experience of Rabies Immunoglobulins it is worth to study the bio- availability of other Immunoglobulins given IM like Tetanus Immunoglobulin by IM route, Human Gamma-globulin by IM route, Diphtheria antitoxin/ pertussis immune globulin given by IM route, Human Hepatitis B Immunoglobulin and other similar other Immunoglobulins being given IM by the clinicians to generate enough confidence in the clinical outcomes.

Conclusion and Recommendation

Any amount of rabies immunoglobulins (RIG) i.e HRIG, eRIG or RMab given intramuscular (IM) are not going to protect the patient from rabies in a window period and may expose the patient to the danger of contracting rabies if virus attaches to the nerves during the window period and before protective immune response due to rabies vaccination has been developed.

To protect the patient from rabies it is essential that clinicians inject the wounds with local infiltration of RIG by covering the entire surface of the wound/s till the depth so as to neutralize any rabies virus that is present at the surface of the wound/s to save lives. All wound/s need to be infiltrated separately, howsoever small abrasions they may be. Broken skin or abrasions can be assessed by "Spirit Test", if there is doubt about the nature and classification of wound, then a spirit swab is applied on the affected area and if there is tingling/burning sensation, it means that skin is broken and would require local RIG infiltration and vaccination after thorough wound wash and application of antiseptics. Also large amount of RIG at the wound site are not indicated and covering the surface of wound/s till depth is enough for protection, practically mean volume of RIG required for injecting wounds is less18 than total calculated volume based on body weight and remaining volume of RIG in the opened vial can be used to infiltrate the wounds of the remaining patients19. A small volume of RIG injected locally into the wound site(s), which is the only place where it is needed, will suffice to kill a large load of virus inoculum and therein lies the importance of confining the infiltration of RIG products to the wound(s) only than improvidently injecting them IM.

References

1. *Hampson K, Coudeville L, Lembo T, Sambo M, Kieffer A, Attlan M, et al. Estimating the global burden of endemic canine rabies. PLoSNegl Trop Dis 2015; https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0003709*

2. *Fooks, A., Cliquet, F., Finke, S. et al. Rabies. Nat Rev Dis Primers 3, 17091 (2017). https://doi.org/10.1038/nrdp.2017.91; https://www.nature.com/articles/nrdp201791#rightslink*

3. *Anderson DC. WHO guidelines dealing with immunoglobulin use impede rabies prevention Available from. Asian Biomed 2007;1(1):103–7; https://www.semanticscholar.org/paper/WHO-guidelines-dealing-with-immunoglobulin-use-Anderson/5dca196b5e952af49fba56119e307857c6ff830e?p2df*

4. *Bharti OK, Madhusudana SN, Gaunta PL, Belludi AY. Local infiltration of rabies immunoglobulins without systemic intramuscular administration: an alternative cost effective approach for passive immunization against rabies. Hum VaccinImmunother. 2016; https://pubmed.ncbi.nlm.nih.gov/26317441/*

5. *WHO Expert Consultation on Rabies: WHO TRS N°1012, Third report. Available at: https://apps.who.int/iris/bitstream/handle/10665/272364/9789241210218-eng.pdf?ua=1%20Accessed%20on%20September%2023,%202019%20*

6. *National Guidelines for Rabies Prophylaxis, 2019; https://ncdc.gov.in/WriteReadData/linkimages/NationalGuidelinesforRabiesprophylaxis2019.pdf*

7. *Wilde H. Failures of post-exposure rabies prophylaxis. Vaccine 2007;25:7605–9.; https://pubmed.ncbi.nlm.nih.gov/17905484/*

8. *Wilde H et al. Failure of postexposure treatment of rabies in children Available from. https://pubmed.ncbi.nlm.nih.gov/8838177/*

9. *Pranee Chomchay, Pakamatz Khawplod, Henry Wilde, Neutralizing Antibodies to Rabies Following Injection of Rabies Immune Globulin into Gluteal Fat or Deltoid Muscle, Journal of Travel Medicine, Volume 7, Issue 4, 1 July 2000, Pages 187–188, https://doi.org/10.2310/7060.2000.00057; https://academic.oup.com/jtm/article/7/4/187/1842907*

10. *Rasooli A, Pourhossein B, Bashar R et al; Case Report: Investigating possible Etiologies of Post-Exposure Prophylaxis Failure and Deaths from Rabies Infection: Case Reports; https://journals.sbmu.ac.ir/ijmtfm/article/view/27378; https://journals.sbmu.ac.ir/ijmtfm/article/view/27378/25853*

11. *Weichen Wu, Shuqing Liu, Pengcheng Yu et. al; Role of systemic injection of rabies immunoglobulin in rabies Vaccination; Arch Virol (2017) 162:1701–1703; https://link.springer.com/article/10.1007/s00705-017-3263-y*

12. *Bharti OK, Madhusudana SN, Wilde H. Injecting rabies immunoglobulin (RIG) into wounds only: a significant saving of lives and costly RIG. Hum VaccinImmunother 2017;13(4):762–5. https://pubmed.ncbi.nlm.nih.gov/28277089/*

13. *Bharti, OK. , Sharma, UK. , Kumar, A. and Phull, A. (2018) Exploring the Feasibility of a New Low Cost Intra-Dermal Pre & Post Exposure Rabies Prophylaxis Protocol in Domestic Bovine in Jawali Veterinary Hospital, District Kangra, Himachal Pradesh, India. World Journal of Vaccines, 8, 8-20. https://www.scirp.org/journal/paperinformation.aspx?paperid=82278*

14. *Fekadu M, Shaddock JH, Baer GM. Excretion of rabies virus in the saliva of dogs. J Infect Dis 1982; 145:715 - 9; https://academic.oup.com/jid/article-abstract/145/5/715/863535?redirectedFrom=fulltext*

15. *Vaughn JB Jr., Gerhardt P, Newell KW. Excretion of street rabies virus in the saliva of dogs. JAMA 1965; 193:363 - 8; Available from https://jamanetwork.com/journals/jama/article-abstract/656160*

16. *Madhusudana SN, Ashwin BY, Sudarsahan S. Feasibility of reducing rabies immunoglobulin dosage for passive immunization against rabies; results of in vitro and in vivo studies. Hum Vaccine Immunother 2013; 9:1914-7; Feasibility of reducing rabies immunoglobulin dosage for passive immunization against rabies; results of in vitro and in vivo studies*

17. *Background paper; PROPOSED REVISION OF THE POLICY ON RABIES VACCINES AND RABIES IMMUNOGLOBULINS; Prepared by the SAGE Working Group on Rabies vaccines and immunoglobulins and the World Health Organization (WHO) Secretariat September 22, 2017; https://www.who.int/immunization/sage/meetings/2017/october/1_Background_paper_WG_RABIES_final.pdf*

18. *Bharti OK, Thakur B, Rao R. Wound-only injection of rabies immunoglobulin (RIG) saves lives and costs less than a dollar per patient by "pooling strategy". Vaccine; https://www.sciencedirect.com/science/article/pii/S0264410X19310084?via%3Dihub*

19. *Weekly Epidemiological Record, World Health Organization; No 16, 2018, 93, 201–220; http://apps.who.int/iris/bitstream/handle/10665/272371/WER9316.pdf?ua=1*

20. *Zhenggang Zhu, Shichun Huang, Sha Lu, Man Zhang, Shengli Meng, Quan Hu & Yuan Fang (2020) Severe multiple rabid dog bite injuries in a child in central China: Continuous 10-year observation and analysis on this case, Human Vaccines & Immunotherapeutics, 16:4, 904-906, DOI: 10.1080/21645515.2019.1676630; https://www.tandfonline.com/doi/abs/10.1080/21645515.2019.1676630?journalCode=khvi20*

21. *Saesow N, Chaiwatan T, Mitmoonpitak C, Wild H; Diffusion and fate of intramuscularly injected human rabies immune globulin; Acta Tropica; Volume 76, Issue 3, 2 October 2000, Pages 289-292; https://doi.org/10.1016/S0001-706X(00)00107-8*

22. *Quiambao et. al; Single visit intradermal (ID)rabies vaccination induces robust immune responses 5 years after 1 – week, 4 site ID primary post-exposure prophylaxis in the Phillipines; vaccine, http;/doi.org/10.1016/j.vaccine.2020.03.043; https://www.sciencedirect.com/science/article/pii/S0264410X20304229?via%3Dihub*

23. *J. Lang, G.H. Simanjuntak, S. Soerjosembodo, C. Koesharyono Suppressant effect of human or equine rabies immunoglobulins on the immunogenicity of post-exposure rabies vaccination under the 2-1-1 regimen: a field trial in Indonesia. MAS054 Clinical Investigator Group Bull World Health Organ, 76 (1998), pp. 491-495; https://pubmed.ncbi.nlm.nih.gov/9868840/*

24. *Bharti OK, Chand R, Chauhan A, Rao R, Sharma H, Phull A. "Scratches/Abrasions without bleeding" cause rabies: A 7 years rabies death review from medical college Shimla, Himachal Pradesh, India. Indian J Community Med2017; 42:248-9. https://www.ijcm.org.in/article.asp?issn=0970-0218;year=2017;volume=42;issue=4;spage=248;epage=249;aulast=Bharti*