Title: Recommending infiltration of category III wounds with rabies immunoglobulin/ rabies monoclonal antibody following re-exposure to confirmed or strongly suspect rabid animals in individuals previously taken full course of either post exposure prophylaxis or pre-exposure prophylaxis

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Keywords

Preamble

Rabies is almost always fatal and hence, post-exposure prophylaxis (PEP) is life saving. Rabies exposures that are category III (severe) require administration of rabies immunoglobulin (RIG) or rabies monoclonal antibody (RMAb) in addition to rabies vaccines and wound management. The RIG/RMAb is ready made anti rabies antibodies. According to the guidelines of world health organization (WHO), Government of India(GoI) and the product insert/package leaflet of the manufacturer RIG/RMAb are to be thoroughly infiltrated into the wounds to neutralize the virus that is still present there and not removed after washing by soap and water. The vaccines take about 10 to 14 days to produce the desired anti rabies antibodies in the vaccinated individual and for these to reach the wound site to neutralise the rabies virus deposited there. But in some instances the incubation period (time interval between exposure/bite and deposition of the rabies virus and onset of rabies symptoms) could be as short as four days. Hence, in such cases vaccine alone is not sufficient. Also the anti rabies antibodies produced as a result of vaccine response in the individual may not reach or have access to all sites where the virus is deposited in the wounds of the bitten individual and thus exposing the person to rabies. Hence, in category III (severe) rabies exposures, wound infiltration by RIG/RMAb is life saving with human, animal and environmental sectors. Recently launched “National Action Plan for Elimination of Dog Mediated Rabies in India by 2030" (NAPRE) is the right step towards achieving this objective by adopting One Health approach and to have rabies free India by 2030.

SPECIAL ARTICLE

Recommending infiltration of category III wounds with rabies immunoglobulin/rabies monoclonal antibody following re-exposure to confirmed or strongly suspect rabid animals in individuals previously taken full course of either post exposure prophylaxis or pre-exposure prophylaxis

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Preamble

Rabies is almost always fatal and hence, post-exposure prophylaxis (PEP) is life saving. Rabies exposures that are category III (severe) require administration of rabies immunoglobulin (RIG) or rabies monoclonal antibody (RMAb) in addition to rabies vaccines and wound management. The RIG/RMAb is ready made anti rabies antibodies. According to the guidelines of world health organization (WHO), Government of India(GoI) and the product insert/package leaflet of the manufacturer RIG/RMAb are to be thoroughly infiltrated into the wounds to neutralize the virus that is still present there and not removed after washing by soap and water. The vaccines take about 10 to 14 days to produce the desired anti rabies antibodies in the vaccinated individual and for these to reach the wound site to neutralise the rabies virus deposited there. But in some instances the incubation period (time interval between exposure/bite and deposition of the rabies virus and onset of rabies symptoms) could be as short as four days. Hence, in such cases vaccine alone is not sufficient. Also the anti rabies antibodies produced as a result of vaccine response in the individual may not reach or have access to all sites where the virus is deposited in the wounds of the bitten individual and thus exposing the person to rabies. Hence, in category III (severe) rabies exposures, wound infiltration by RIG/RMAb is life saving.

Context

In individuals who are re-exposed (bitten again) by a strongly suspect or confirmed rabid animal, and have previously received PEP or pre-exposure prophylaxis/vaccination (PrEP), the World Health Organization (WHO), Government of India (GoI) and the product inserts of manufacturers of RIG and RMAb recommend only wound management and administration of two doses of rabies vaccine on days 0 and 3 either by IM or ID route and *no RIG/RMAb is needed*. It is because the previous vaccination is known to generate memory T-Cells for life time. Following re-exposure vaccination there is an an aemnestic boosting response in the individual and the anti-rabies antibodies are known to quickly appear in 3 to 5 days.

The problem/issue

But the problem/issue is when the bites are severe like on the head, face, neck, fingers, genitals, multiple wounds, lacerations and avulsions by wild animals, etc. and in instances where the virus is directly deposited in the open nerve ending, hoping for the vaccine induced antirabies antibodies in the bitten individuals to reach all sites and neutralise the virus present there is a very risky proposition. In some cases the immunological effectiveness of the previous vaccination is doubtful for reasons of unreliable history, non-availability of the records, doubtful potency of the vaccine due to poor cold chain, wrong handling, wrong administration, poor health condition of the patient, etc. The dose of RIG/RMAb for local infiltration of wound/s is based

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on the body weight of the exposed individual. Even in those with heavy built of over 100 Kgs despite high volume of RIG/RMAb following its use for wound infiltration and absorption it is not known to interfere with the vaccine response.

Recommendation

Hence, as an "off label" practice it would be prudent to use RIG or RMAb for wound infiltration in such high risk/severe re-exposures for in situ neutralisation of the virus. Care must be taken to infiltrate ONLY wounds and not to inject the remaining RIG/RMAb intramuscularly. Only in case the individual has received previously equine RIG one need to be careful in using again the eRIG where there may be hypersensitive reactions. In such individuals it is recommended to use a different product like human RIG or RMAb. The author's dictum is - it is "wise to over treat in rabies prophylaxis then under treat" as rabies is practically 100% fatal and rabies biologicals like vaccines and RIG/RMAb are largely safe and efficacious. The individual seeking treatment shall be clearly explained about the planned procedure in advance and signed informed consent taken that should be readily forthcoming in such life threatening conditions. This also obviates any litigation later under consumer protection act, though it is likely to be remote.

Conclusion

In conclusion, in cases of PEP following high risk/severe re-exposures to rabies like following bites by confirmed or suspect rabid animal , it is recommended to infiltrate the wounds with RIG or RMAb despite having received either post-exposure or pre-exposure rabies prophylaxis previously though this being not recommended by WHO or GoI or the manufacturer. This recommendation by the author is not to take chances as rabies is practically 100% fatal and RIG/RMAb is practically safe. Though there may not be reports of any failures in the current practice of not giving RIG/RMAb following category III (severe) re-exposures it would be not wise to wait for mishap to occur/ failure to be reported and then act. But, the current Page 3 of 3 recommendation shall be used very discreetly and as an exception in very select high risk /severely exposed cases or as deemed fit by the treating physician and not as a general thumb rule. The author opines that this will stand the legal scrutiny also, even if that happens remotely.

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The author has an experience of over three decades in rabies prophylaxis; and was a member of WHO Geneva, Switzerland, expert consultations on rabies from 2004 to 2019 and GoI/ICMR from 2007 to till date. He has over 50 original publications and other papers on rabies in national, international journals; and author of many guidebooks/manuals on rabies for medical professionals and others. He was elected - fellow of National Academy of Medical Sciences (FAMS), New Delhi and an honorary Fellow of Faculty of Public Health (FFPH) of Royal Colleges of Physicians of United Kingdom. He is the founder President of Association for Prevention and Control of Rabies in India (APCRI) and Rabies in Asia (RIA) foundation.