

Review Article

Intramuscular Use of Rabies Immunoglobulin may be Dangerously Interfering with Rabies Vaccine Immune Response

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India reports the highest number of dog bites and consequent rabies deaths in the world. Though rabies vaccines (RV) and rabies immunoglobulins (RIG) are covered under the Free Drugs Initiative of National Health Mission (NHM) of Government of India, still their shortages are a regular feature all over the country mainly due to exponential increase in dog bite cases over the years and the use of high dose-high-cost human rabies post-exposure prophylaxis (PEP). In this context, we need to implement the low dose-low-cost human rabies PEP as recommended by the World Health Organization (WHO) in its recent Rabies Prophylaxis Guidelines 2018.¹ High potency of RVs and RIGs available in the Indian market further necessitates using low dose-low-cost PEP.

The benefit of one week, three dose (2-2-2-0-0) intra-dermal (ID) rabies vaccination (IPC Regimen) is now well established in Himachal Pradesh showing high rabies virus neutralizing antibody (RVNA) titers on day 8-14² while simultaneously using only wound infiltration of equine RIG as per the recent WHO guidelines (Table-I). However, the interference of vaccine response by high potency RIG calculated by weight based formula when given IM after wound infiltration³ further underscores the need of only wound infiltration of RIG to an extent that minimal volume of RIG is used just to cover the surface of the wound/s till depth and no intramuscular(IM) injection of remaining RIG is used (Table-II). As evidenced⁴ by potent rabies monoclonal antibodies (RMABs) neutralizing the vaccine endogenous response even on day 7, that can be life threatening to the patients at risk of rabies and possibly contributing to the unexplained PEP failures (Table-III). RIGs are infiltrated into and around the wound/s to cover the window period till endogenous vaccine response is produced. However, if IM administration of RIG/RMAB interferes with the endogenous vaccine response (Table-III) it may obliterate the window period and make the bite victim vulnerable to the risk of rabies defeating the very purpose of using RIG for protection during this window period. This deserves serious attention of Pharma companies and clinicians across the globe. Due to lack of proper trainings in rabies PEP and misclassification of

rabies exposure, PEP failures⁵ are already common⁶ and interference of IM use of RIG and RMAb shall contribute to more PEP failures.

Himachal Pradesh is the first state in India to adopt WHO 2018 guidelines since they were issued in April 2018 and has achieved almost zero rabies deaths from 35 deaths estimated in 2005, using the limited resources available. Till now we have vaccinated about 300,000 patients of dog bites⁷ with only one confirmed PEP failure and thus saving millions of rupees of poor patients and the government. This has been achieved through sustained hands-on trainings to doctors, pharmacists, nurses and health workers and information, education and communication (IEC) regarding importance of wound wash in dog bite up to the level of ASHA workers. Long term estimates of requirements of rabies vaccine and RIG, enhancing storage facilities by providing ordinary refrigerators up to PHC level are immediate steps for improving rabies PEP in rural areas. Negligible rabies deaths in Himachal Pradesh now without sustained dog vaccination is a new emerging model that may be considered by other states of India till we are able to vaccinate the required 70% of the 60 million dogs across India. Lastly, we cannot wait more as we have had enough of rabies deaths in India, especially of children.⁸

Table 1. Rabies virus neutralizing antibody (RVNA) titers following the use of high potency rabies vaccine and only wound infiltration by equine rabies immunoglobulin (only IL the remaining calculated eRIG was not given IM)

Patient ID No.	Day Of Blood Sample	RVNA Titers (IU/ml) by RFFIT (@NIMHANS) after ID administration of rabies vaccine and only wound infiltration/IL using equine RIG
DDU 06	D-08	6.5 2 ml eRIG used I/L
DDU 07	D-12	5.6 1 ml eRIG used I/L
DDU 14	D-12	7.8 2 ml eRIG used I/L
DDU 133	D-10	8.5 8 ml eRIG used I/L after dilution in 20 ml Normal saline
DDU 211	D-14	13.4 0.1 ml eRIG used I/L
DDU 248	D-14	12.5 0.3 ml eRIG used I/L
DDU 319	D-14	12.5 0.25 ml eRIG used I/L
DDU 384	D-08	12.5 2 ml eRIG used I/L

*Source: Bharti OK et al, 2016²

Note: IL means Intra-lesional or only into wound/s. Rabies vaccine used: VAXIRAB –N (PCECV) of potency 7.18 IU/ 1 ml vial (as against the prescribed norm of ≥ 2.5 IU per vial); equine RIG used – Central Research Institute, Kasauli, Himachal Pradesh, of potency 550 IU / ml (as against the norm of ≥ 300 IU/mL) We observed high titers on day 8 for DDU 384, 25 times higher than required protective levels of 0.5 IU/ml

Table 2. Human rabies immunoglobulin (HRIG) when given intramuscularly after wound/s infiltration, interfering with vaccine response

Day Of Blood Sample	RFFIT Titers (GMC) (IU/ML) after IMRV (Rabivax-S) in Cat-III with IL+IM HRIG & (no RIG in parenthesis)	RFFIT Titers (GMC) after IDR (Rabivax-S) in Cat-III with IL+IM HRIG & (no RIG in parenthesis)	RFFIT Titers (GMC) (IU/ ML after IMRV (Rabipur) in Cat-III with IL+IM HRIG& (no RIG in parenthesis)
0	0.25	0.25	0.25
7	1.55 (2.02)	1.34 (2.26)	1.03 (1.64)
14	16.47 (20.57)	19.46 (20.99)	14.13(16.01)
28	22.50 (30.22)	23.20 (27.93)	22.14 (26.59)
42	24.61 (27.64)	24.38 (25.40)	26.24 (29.45)
Diff due to RIG IM on day 7	-0.47	-0.92	-0.61

*Source: Bose A, Munshi R, Tripathy RM, et al, 2016³

Note: (1) Rabies vaccines used – Rabivax –S (PVRV) & Rabipur (PCECV); GMC= Geometric mean concentration rabies virus neutralizing antibody by RFFIT; IMRV = Intramuscular rabies vaccination; IDR = Intradermal rabies vaccination; IM=Intramuscular (2) The figures in parenthesis are GMCs when no RIG is given (3) Difference/ Dip in titers on day 7 is comparable to protective RVNAb titers of ≥ 0.5 IU/ml

Table 3. Rabies monoclonal antibodies (RMAb) and human rabies immunoglobulins (HRIG) when given intramuscularly after wound/s infiltration, interfering with vaccine response

Day of blood sample	RFFIT titers (GMC mean) (IU/mL) after IM (Rabivax-s) in category -III with SII- RMAb – IL+IM (Participants with protective RVNAb titers of ≥ 0.5 IU/ml)	RFFIT titers (GMC mean) (IU/mL) after IDRV (Rabivax-S) in category -III with HRIG – IL+IM (Participants with protective RVNAb titers of ≥ 0.5 IU/ml)
0	0.22 (3/101)	0.23 (1/98)
3	0.22 (4/101)	0.24 (5/97)
7	0.26 (8/99)	0.28 (7/95)
14	23.29 (96/97)	5.65 (87/95)
28	30.77(93/93)	20.61 (89/91)
42	31.12 (86/86)	30.85 (85/85)
84	8.67 (83/83)	9.75 (77/77)

*Source: Gogtay NJ, Munshi R, Ashwath Narayana DH et al, 2018⁴

Note : Rabivax –S (PVRV); SII-RMAb) GMC mean = Geometric Mean Concentration; IM=Intramuscular. Here we observe almost 100% obliteration of the window period (7-10 days) and putting a risk of rabies for patients, defeating the purpose of RIG use, while only wound infiltration of RIG (Table-I) we get very high protective RVNAb titers even on day 8 in some patients.

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