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SHORT REPORT

Injecting rabies immunoglobulin (RIG) into wounds only: A significant saving of lives and costly RIG

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ABSTRACT

An increasing number of dog bite victims were being presented to public hospitals in Himachal Pradesh in 2014 amidst virtual non availability of any rabies immunoglobulin (RIG). Only a small quantity of equine rabies immunoglobulin (eRIG) was available from the government owned Central Research Institute (CRI) Kasauli. This available eRIG was used in 269 patients as an emergency response and only for local infiltration of severe bite wounds by suspected rabid dogs. This was followed by rabies vaccination, using the WHO approved intra-dermal Thai Red Cross Society vaccination schedule. A subgroup of 26 patients were later identified who had been severely bitten by laboratory confirmed rabid dogs. They were followed for more than one year and all were found to be alive.

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Rabies is an invariably fatal disease. An unknown number of humans die of rabies every year worldwide. News media often estimate 40,000 to 60,000 annual human cases worldwide. India alone reports approximately 20,000 deaths annually.[1] One major barrier to Post Exposure Prophylaxis (PEP) continues to be the high cost of rabies immunoglobulins (RIG) which can be bridged by injecting RIG into the wounds only, and omitting intramuscular administration of the remaining part that was not used for wound injection.[2] An increasing number of dog bite victims were being presented to public hospitals in Himachal Pradesh, India in 2014 amidst virtual non availability of RIG.[2] Only a small quantity of eRIG was available from the government owned Central Research Institute (CRI) Kasauli. We were 'forced' to do this study given limited availability of eRIG. It was decided to inject it only into bite wounds and share the rest of the calculated WHO prescribed dose with the next rabies exposed patient. This was based on evidence that it can be a potentially lifesaving alternative.[3-5]

WHO recommended post exposure prophylaxis (PEP), using WHO recognized rabies vaccines, induces an effective circulating virus killing serum antibody level, but only after a delay of 10–14 days.[3,4] Short incubation periods, particularly from bites close to sites containing many peripheral nerves, can allow entry of virus into nervous tissue before there is a neutralizing circulating serum antibody level that can kill virus at the bite sites. Once inside nerves, virus may be in an immune protected environment.[4]

Current WHO guidelines require that a total dose of RIG is calculated based on body weight: 20 IU/ Kg for human RIG, and 40 IU/ Kg for the equine products. As much as is anatomically possible, is to be infiltrated into bite wounds and the remnant is then injected at a distant site intramuscularly.[3] Evidence for this recommendation to inject the remnant intramuscularly elsewhere, is not based on controlled studies in humans and must be considered observational. Costs of RIG in India, for an average patient of 60 kg, body weight, are approximately US $20 for equine rabies immunoglobulin (eRIG) (which represents 6 d of wages for an Indian laborer). If the human origin immunoglobulin (hRIG) is used, it would costUS $ 500. This is one month's salary of a midlevel employee in Himachal Pradesh.

Immunoglobulin (RIG), obtained from humans (hRIG) or equines (eRIG), are the only immunoglobulins presently available for managing unprotected "Window Periods" in severely rabies exposed patients.[3,4] Human immunoglobulin (hRIG) is expensive and generally not available in poor rabies endemic countries. The equine product is now increasingly available in many canine endemic countries. Some RIG is locally manufactured, highly purified, enzymaticaly treated and almost free from any serious allergic reactions. However, vaccination and treatment with systemic RIG will not prevent all rabies deaths.[4] Treatment failures, when vaccine only is used, are more common when there are multiple bites or deep punctures at locations where there are many peripheral nerves such as on face and hands.[3-8] Published controlled studies in animals demonstrated efficacy of infiltrating rabies infected bite wounds in animals with antiserum or immunoglobulins.[4,6,9] Controlled animal studies demonstrated that antibody is more effective when instilled into wounds than when inoculated parenterally.[3,4,6] It is the RIG injected into bite wounds that can make the difference between life and death. This conclusion is sadly illustrated by reported human treatment failures where only

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intramuscular RIG was administered. In such reported treatment failures, either no RIG was administered, or it was not injected into wounds or, in the case of multiple wounds, not injected into all of them.[5,7,8] In a busy animal bite clinic, where patients are often not fully undressed, it is also possible to miss small wounds. Immunogenicity studies have shown that a total calculated dose of RIG, administered intramuscularly, will provide only a barely detectible circulating antibody level within the critical 10–14 day unprotected "window period." It is unlikely to be sufficient to kill a virus load deposited at the bite site.[10,11] Virus has then time to replicate locally, enter nearby nerve endings and continue centrally toward the brain. D.C. Anderson, during the 2009 WHO Expert Conference on Rabies, presented strong criticism of WHO guidelines for the current use of rabies immunoglobulins.[12] He argued that the calculated dose of RIG, injected intramuscularly at a distant site, may be a waste of this precious product.

During much of 2014, there was a critical shortage or total lack of human and equine rabies immune globulin (hRIG and eRIG) in Himachal Pradesh and adjoining states of North India.[2] Only a very limited supply of locally manufactured eRIG was available from the Central Research Institute (CRI), Kasauli, HP. The government Health Services responded by directing hospital authorities to release this limited amount of eRIG only for local infiltration of bite wounds to save lives in this setting of extreme scarcity.[2] This available eRIG was used in 269 patients as an emergency response and only for local infiltration of severe bite wounds by suspected rabid dogs. The RIG left after injecting wounds, was to be shared with the next rabies exposed patients for wound injection within the same or next day. Application of this emergency protocol was approved by the ethics committee of Jaypee University (Waknaghat, Solan, HP on 23 May, 2014IEC/Project No. 11–2014). It was then reviewed and agreed by hospital authorities as the only available emergency response possible to provide some immune prophylaxis to severely exposed patients. The selection criteria for administering the locally injected eRIG were animal bite victims of any age, a severe potential rabies exposure from a suspected or proven rabid animal, and bleeding transdermal single or multiple wounds at any body site. Patients with history of previous rabies vaccination were excluded and received only WHO recommended booster vaccination. Each patient, parent or care provider was explained the reasons why this protocol was being applied, and asked to provide a written and witnessed signed consent. Illiterate subject had the benefits and possible complications explained in simple terms by a professional health care provider and this was documented.[2]

We later learned that there were cases which had been bitten by laboratory confirmed rabid dogs. The suspected rabid dogs were captured and later upon their death, their brain samples were sent for FAT examination to CRI Kasauli. Further permission of government authority and ethics committee were obtained to follow this subgroup of 26 subjects for at least one more year as a prospective observational study. During this prospective study from June 2014 to July 2016 in just over 2 years time 7,499 patients have been registered at our clinics and research center at DDU Zonal Hospital and Indira Gandhi Medical College (IGMC) Shimla. Out of them, 4531 were type III and were given only local eRIG in and around the wound/s with IDRV. Of these, 244 patients were bitten by potentially rabid dogs and 26 by lab confirmed rabid dogs. Minimum dose of eRIG given to these patients was 0.5 ml and maximum was 6.5 ml and nowhere had we exceeded the limit of 3000 IU of eRIG to avoid possible immunosuppression.[13] We also encountered 117 rabies re-exposed patients and those were given prophylaxis by giving one time 4 site 0.1 ml IDRV booster. They had previous history of rabies vaccination with cell culture rabies vaccine.[14,15]

Table 1, shows the details of these 26 subjects. The age range was 2–58 years, the weight ranged from 10 to 98 Kg. There were 14 males and 12 females including 6 children under 15 years of age. The time lapse between dog bites and RIG injection were aonly 6–12 hours in 22 patients, 3 received PEP on the next day and one on the third day. All of the 26 severely rabies exposed subjects had survived one year or more after the exposure. Due to the retrospective nature of this study, the only measure of results that could be tracked for the 26 patients was survival and no patient developed any form of rabies including paralytic one which has an equal fatality rate.[4]

The results of our study show that injecting only the bite wounds with eRIG in 26 patients exposed to severe trans-dermal bites from laboratory proven rabid dogs, may have prevented as many as 26 human rabies deaths. It allowed local bite wound immunoprophylaxis in an environment of extreme shortage of immunoglobulin and utilized the small amount of available locally manufactured equine rabies immunoglobulin for the maximum benefit of the community.

Wound/s must be injected carefully to cover the entire wound surface till its depth. The rest of the calculated dose, which is usually greater than what is needed for wound injection alone as per WHO guidelines is to be injected intramuscularly into the lateral thigh or gluteal region which is mostly distant from bite site and will not provide desired circulating antibody level at the inoculation site. This strongly suggests that residual RIG, left after injection of wounds, may well be a wasted valuable resource.[9,11,12] Many recent WHO expert consultations, dealing with this subject firmly acknowledged the paramount importance of wound infiltration with RIG.[16]

One weakness of this study is that the actual rabies virus content in saliva of rabid dogs can vary from not detectable to very high. We therefore cannot predicts the actual risk of rabies infection to each of the 26 bitten victims. It is known that oral viral loads may vary from very high to complete absent among clinically furious or paralytic rabid dogs.[4] Similarly, it is difficult to establish the exact amount of RIG that is required to neutralize the virus at the local site. However, in a previous study conducted in experimental mice, it has been clearly shown that there is no basis for calculating the dose based on body weight.[17] In this study there was 100% survival of peripherally challenged mice, which were infiltrated with 1/100 amount of immunoglobulin required calculated based on body weight. In these experiments mice had been challenged with 10^4 LD 50 of CVS. Even doses of ERIG as low as 0.01 IU could neutralize this amount of virus and prevent rabies where as based on body weight the amount of RIG to be used was 10 IU. This study clearly indicates that there is no basis for calculating dosage of RIG based on body weight. Further, these animals were not administered post-

Table 1. Follow up of 26 patients bitten by laboratory proven dogs who received only wound injection of RIG followed by rabies vaccination.

Sl. No.	ID No	Age in Yrs	Sex	Time interval between bite & ERIG(in Days)	Previously Vaccinated	Volume of RIG injected into wound/s	Follow-up interval after RIG injection	Status of the bitten person
1	DDU/529	50	M	1 Day	No	2 ml	70 Weeks	Alive
2	DDU/530	25	F	Within 8 Hrs	No	1 ml	70 Weeks	Alive
3	DDU/534	41	M	Within 8 Hrs	No	6 ml	70 Weeks	Alive
4	DDU/536	16	F	1 Day	No	0.5 ml	70 Weeks	Alive
5	DDU/541	12	F	1 Day	No	3 ml	70 Weeks	Alive
6	DDU/542	06	F	Within 8 Hrs	No	2.5 ml	70 Weeks	Alive
7	DDU/567	33	M	3 Days	No	6.5 ml	70 Weeks	Alive
8	DDU/1531	40	F	Within 8 Hrs	No	5 ml	58 Weeks	Alive
9	DDU/1534	32	M	Within 8 Hrs	No	1 ml	58 Weeks	Alive
10	DDU/1535	20	F	Within 8 Hrs	No	1 ml	58 Weeks	Alive
11	DDU/1542	34	M	Within 8 Hrs	No	0.5 ml	58 Weeks	Alive
12	DDU/1554	48	F	Within 8 Hrs	No	1 ml	58 Weeks	Alive
13	DDU/1566	57	F	Within 8 Hrs	No	1 ml	58 Weeks	Alive
14	DDU/1568	30	M	Within 8 Hrs	No	2 ml	58 Weeks	Alive
15	DDU/1582	51	M	Within 8 Hrs	No	1 ml	58 Weeks	Alive
16	DDU/1585	35	M	Within 8 Hrs	No	0.5 ml	58 Weeks	Alive
17	IGMC/ 56	2	F	Within 8 Hrs	No	400 IU	58 Weeks	Alive
18	IGMC/ 01	5	F	Within 8 Hrs	No	250 IU	58Weeks	Alive
19	IGMC/ 04	58	M	Within 8 Hrs	No	40 IU	58 Weeks	Alive
20	IGMC/ 09	15	F	Within 8 Hrs	No	40 IU	58 Weeks	Alive
21	IGMC/ 10	38	M	Within 8 Hrs	No	40 IU	58 Weeks	Alive
22	IGMC/ 11	34	M	Within 8 Hrs	No	40 IU	58 Weeks	Alive
23	IGMC/ 12	7	F	Within 8 Hrs	No	460 IU	58 Weeks	Alive
24	IGMC/ 16	30	M	Within 8 Hrs	No	40 IU	58 Weeks	Alive
25	IGMC/ 25	46	M	Within 8 Hrs	No	600 IU	58 Weeks	Alive
26	IGMC/26	17	M	Within 8 Hrs	No	300 IU	58 Weeks	Alive

Alive means: Without evidence of the furious/paralytic form of rabies.
Rabies in Dogs was confirmed by FAT test done by Government of India lab,Central Research Institute, Kasauli, Himachal Pradesh, India

exposure vaccination but still there was 100% survival with local infiltration of RIGs alone emphasizing the importance of local infiltration of RIG in prevention of rabies.

Our study, done in a canine rabies endemic field settings, supports previous experimental and observational studies of clinical efficacy that injecting bite wounds only, followed by rabies vaccination, can save patients from rabies deaths.

Abbreviations

CRI	Central Research Institute
eRIG	Equine rabies immunoglobulin
FAT	Fluorescent Antibody test
hRIG	Human origin immunoglobulin
IDRV	Intradermal Rabies vaccination
PEP	Post Exposure Prophylaxis
RIG	Rabies Immunoglobulin
WHO	World Health Organization

Note: Window period: First 7–10 days after rabies vaccination was started.

Dedication

We dedicate this paper to the memory of our late friend Professor Shampur Narayan Madhusudana, whose untimely demise has left a void in rabies research worldwide.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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