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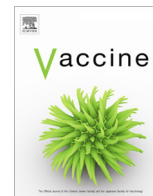
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Wound-only injection of rabies immunoglobulin (RIG) saves lives and costs less than a dollar per patient by “pooling strategy”

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ABSTRACT

Since 2008, we in Himachal Pradesh have used a “pooling strategy” to help patients save money by pooling vials of antirabies vaccine at a centralized hospital and sharing them using the intradermal technique. In 2014, there was an acute shortage of rabies immunoglobulins (RIG) and two patients died after four injections of rabies vaccine were administered without RIG, which was not commercially available. After an extensive literature review and technical and ethical committee clearances, in June 2014 we started to infiltrate equine RIG (eRIG) into wound/s only without the recommended systemic intramuscular (IM) injection. WHO recommended this technique in 2018. During the four-year period June 2014 to June 2018, 7506 of 10,830 patients exposed to suspected rabid animals were injected with eRIG in and around the wounds in a single clinic at DDU Hospital Shimla without any adverse outcomes. The average volume of eRIG used per patient was 0.75 mL and cost US\$ 0.75. Of the 80% of patients who were followed up, all were healthy at the end of a year, including 26 patients bitten by laboratory-confirmed rabid dogs. The reaction rate after PEP administration also declined significantly. Since February 2018, Himachal has started following the new WHO recommendations on PEP regimens of three intradermal antirabies vaccines instead of four, thereby saving hundreds of vaccine vials that became useful during shortages of rabies vaccine in India. To date, more than 700 vaccine vials have been saved in a single clinic at DDU hospital during the past 6 months alone. Not giving PEP to patients who have consumed raw milk from a suspected rabid cow has also saved 62 vials. Currently, 90 “pooling centers” have been established for sharing of vaccine and eRIG vials in Himachal State, generating huge savings that have enabled the government to provide PEP free of charge to all. The new WHO guidelines are a positive step towards a rabies-free world by 2030.

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1. Introduction

Rabies, a dreaded infectious disease, is invariably fatal once symptoms appear, although some survivors have occasionally been reported with functional deformities. Current estimates suggest that approximately 60,000 human deaths occur each year globally; the burden of the disease is primarily borne in Asia and Africa, especially in rural areas [1]. Dogs are the most important reservoir for rabies viruses and dog bites account for >99% of human cases [2]. The pathophysiology of rabies virus after inoculation/bite is to seek a nerve ending that it can invade and advance centrally within an immune protected nerve. If infection occurs within a week and before sufficient circulating antibodies appear due to

vaccination, such a patient is likely to be doomed. Rabies virus induces drastic behaviour modifications in infected hosts as rabies virus glycoprotein, with homologies to snake venom/toxins, has the ability to alter behaviour in animals by inhibiting nicotinic acetylcholine receptors present in the central nervous system [3]. However, rabies can be prevented if timely prophylaxis is given to bite victims in the form of vaccine and by injecting rabies immunoglobulin (RIG) into the wounds. <90% of victims bitten by possibly rabid animals obtain WHO recommended management due to unaffordability which has been known for decades. Injection of RIG is, however, largely ignored worldwide due to cost, antibody products not being available and ignorance or lack of motivation by health care providers to inject wounds. Himachal, a state in India, has instituted injection of bite wounds with available human RIG or equine RIG (eRIG) for all patients at risk of rabies since June 2014. The effectiveness of infiltrating RIG locally into wounds only

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with concomitant vaccination has been well established by the authors [4,5]. To date, more than 38,000 patients have received PEP free of charge since June 2014 across 90 clinics designated as “pooling centers” throughout Himachal State. This has enabled the World Health Organization (WHO) to revise its position paper on RIG use globally [6] after due consideration by the Strategic Advisory Group of Experts (SAGE) on immunization, and to update the recommendations for rabies pre-exposure prophylaxis (PrEP) and PEP. The present study was undertaken to determine the reaction rate and the cost of single PEP using intradermal vaccination and local wound infiltration only of eRIG among patients coming to our clinic at DDU Hospital (pooling center) as per the new WHO protocol (2018) and to compare it with those of the earlier WHO protocol (2010) of additional IM injection of RIG as per weight-based calculations.

2. Material and methods

Since 2008, we have used a pooling strategy for intradermal rabies vaccination in our government clinics at Himachal Pradesh, which started with the first pooling center at DDU Hospital Shimla. The pooling strategy was adopted to maximize patient load and distribute the vaccine vials among patients who used to buy the vaccine [7]. Subsequently, vaccine but not RIG, was made available free of charge to all by the government. In 2014, when RIG was not available commercially we, after careful literature review [8–13], decided to infiltrate eRIG available in the hospital into wounds only while avoiding IM injection to optimize RIG use during scarcity. For this method, ethical clearance for only local wound infiltration of RIG without systemic use was granted by the Ethics Committee (Jaypee University, Wagnaghat, Solan HP dated May 23, 2014 IEC/Project No. 11-2014); subsequent ethics clearance to continue with the methodology was obtained State-wide (IEC/Project no-26-2015 dated 27-11-2015). Patients were asked to complete the consent form after being briefed about the unavailability of RIG commercially. Meticulous wound care was given by



Fig 1. Cat Scratch being infiltrated locally with eRIG at ARCRC Shimla Clinic. All scratches are to be infiltrated separately.



Fig 2. Dog bite wound being infiltrated at Shimla ARCRC Clinic, DDU Hospital Shimla, India. A small dot puncture wound near the thumb would also be infiltrated with a drop of eRIG separately.

washing the wounds with soap and copious amounts of running tap water. The wounds were then cleaned with Betadine and later with spirit and left to dry before injecting eRIG locally to cover the entire wound surface down to its bottom, while avoiding injecting “as much RIG as possible” to minimize wastage. Our objective was to cover the surface of the wound with RIG to neutralize any rabies virus that might be attached to the surface of the wound. After wound infiltration of eRIG (Figs. 1 and 2), patients were asked to wait for half an hour and observed for any adverse events. The data on 10 830 patients given PEP from June 2014 to June 2018 for four years in DDU Hospital, Shimla was entered on an Excel spreadsheet and analysed using Microsoft Excel Software. Patients were proactively asked about any adverse events that occurred during 2016–2017 to account for any minor event that might not have come to the patient’s attention.

3. Results

During the four-period from June 2014 to June 2018, of 10 830 rabies exposed patients attending our clinic, 7506 patients were category III as per WHO classification and received solely wound-injected eRIG along with intradermal rabies vaccination (IDRV); 63.5% (6869) were male and 3961 were female. The median age was 39years (range, 1–92years) and the median weight was 53 kg (range, 9–103 kg). Separate needles were used for each patient or in case more eRIG was required for the same patient. The average eRIG volume per patient was 1.26 mL when we started this method of local wound infiltration in 2014, decreasing to 0.89 mL in 2016 and 0.87 mL per patient in 2017 due to more experience and confidence of the staff nurse in the clinic to infiltrate wounds. The eRIG volume also decreased as we focused on covering the surface of the wound down to its bottom rather than injecting “as much as possible into the wound”. The analysis of the volume distribution of eRIG among 7506 patients (Fig. 3) shows that 70% of patients (5261/7506) required eRIG infiltration volume <0.5 mL. In our clinic the median dose of eRIG injected was 0.5 mL (20 units), ranging from 0.025 mL to 10 mL (1–3000 units). The minimum dose of eRIG given to 66 patients was just 1 unit of insulin syringe (40 units = 1 mL) i.e. eRIG = 0.025 mL, mostly into small dot puncture wounds caused by the nails of monkeys/dogs.

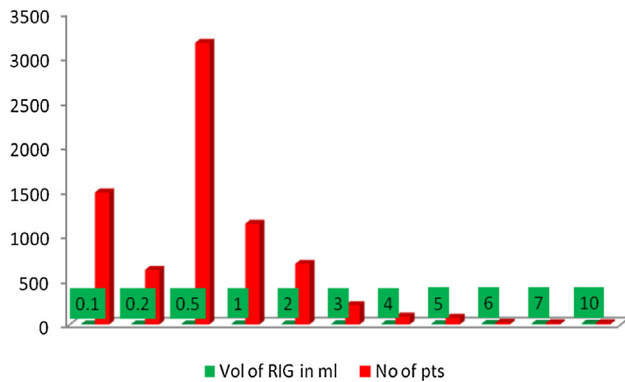


Fig 3. Analysis of 7,506 patients given only local wound eRIG infiltration at ARCRC, DDU Hospital, Shimla, June 2014–2018.

A maximum of 3000 IU (10 mL) of eRIG was given to only 7 patients with large lacerated wounds due to furious stray or suspected rabid dog bites. Some 14 children aged up to one year were given PEP, of which 8 were bitten by pet dogs, mostly on the hands; the volume of eRIG required was 0.1–1.5 mL. Some 22.8% children (2469) aged up to 15 years were given PEP; the average volume of eRIG used was 0.62 mL. Overall, the average eRIG volume used was 0.75 mL per patient, costing US\$ 0.75. The bite wounds were documented on the fingers or thumbs in 7% (714) of patients; the average eRIG dose injected into a finger wound was 0.38 mL. Whereas a dot puncture wound required just a drop of eRIG, say 0.025 mL, a large lacerated wound required a maximum of 10 mL eRIG diluted two to three times with normal saline to infiltrate all wounds to cover the entire surface of the wounds till the depth of each wound. A 1-cm sized wound/scratch required about 0.5 mL of eRIG, whereas a $3 \times 3 \times 1$ cm wound required 1 mL of eRIG; a $5 \times 3 \times 1$ cm wound required 4 mL of eRIG and a $6 \times 3 \times 3$ cm wound required 8 mL of eRIG. There was no correlation of the volume of eRIG used and the weight of the patient: rather, the volume of eRIG was related to the size and the number of wounds. Some 2% of patients (233) had a history of previous vaccination and were given four site one-time intradermal vaccine boosters without RIG, saving both vaccine and eRIG. Of the 10 830 patients, only 15 reported adverse reactions (vomiting, sweating, giddiness and allergy), of which three were possibly due to eRIG infiltration and two due to vaccine; the remainder were nonspecific.

Of the 10 830 patients, 36% (3863) were bitten by pet dogs; 26% of these pet dogs were unimmunized stray dogs kept as pets. Some 28% (2999) were bitten by monkeys, 26% (2909) by stray dogs including 270 by potentially rabid dogs and 26 by laboratory-confirmed rabid dogs; 379 were bitten by cats, nine by leopards, two by wild pigs and the remainder by other stray/wild animals. Rabies in monkeys in Shimla has been laboratory-confirmed by the authors [14]. Rabies due to monkey bites has been reported across India, i.e. from Uttar Pradesh, Haryana and Delhi in the north [15] to Andhra Pradesh [16] in the south. Rabies in monkey has been reported also from Sri Lanka [17].

We carefully documented the details of adverse reactions among patients attending the State Intra-dermal Anti-rabies Clinic and Research Centre (ARCRC), DDU Hospital Shimla in 2016 and 2017. We calculated that with only local wound infiltration of eRIG, the rate of any reaction was 0.41% (8/1923 patients) in 2016 and 0.2% (4/2020 patients) in 2017. As per the old weight-based guidelines for eRIG use, serum sickness used to occur in <1–3% of recipients (WHO TRS 1020). Therefore, the reaction rate for only wound injection of eRIG reduced by up to 15 times without any anaphylaxis. In 2016, the eRIG used was Premi-RAB with a potency of 300 IU/mL, the average volume per patient used was

0.89 mL and the vaccine used was Rabipur with a potency of ≥ 2.5 IU/vial. In 2017, the eRIG used was Premi-RAB with a potency 300 IU/mL, the average volume per patient used was 0.87 mL and the vaccine used was VaxiRab-N with a potency of ≥ 2.5 IU/vial. Fainting and falling blood pressure/pulse were controlled by injecting Avil 2 mL IM stat (22.75 mg Chlorpheniramine maleate) and injecting Decadron 2 mL IM stat (4 mg/mL, Dexamethasone).

4. Discussion

Provision of rabies PEP free of charge is an essential step towards a rabies-free India by 2030 and state governments are struggling to reconcile this situation with the high cost of rabies PEP. In 2008, when we started our intradermal rabies vaccination centre at DDU Hospital Shimla with a pooling strategy, the cost of rabies vaccination fell by 80% relative to IM vaccination practiced previously. First, a government order was issued to all nearby small hospitals to refer all animal bite patients to the central DDU hospital for vaccination after first aid. This way, pooling of patients was ensured. Afterwards, we asked each patient to purchase a vial of vaccine on the first visit and advised that subsequent doses would be given free of charge. Actually it was not free: we divided a vial among four patients using the intradermal technique and refrigerated the remainder of the vaccine vials for individual use by sharing among them on subsequent visits. Later on, we trained doctors and nurses from other districts on how to use the intradermal technique and thereafter throughout the “pooling centers” in Himachal State, mainly community health centers or in some of the high load primary health centers. When the cost of rabies vaccine had reduced five-fold, the Government of Himachal decided to give rabies vaccine free of charge to all in 2010 but not RIG because of its high cost. In 2014, when only local wound infiltration was started in our clinic at DDU Hospital, a single eRIG vial used to be shared between 5 and 10 patients depending on the size and number of wounds, reducing the cost to a few hundred rupees (INR). Today, each patient requires an average of 0.6 mL of vaccine costing US\$ 2 and 0.75 mL of eRIG costing US\$ 0.75. (1 \$ = INR 70). Therefore, the total cost of rabies PEP with three injections of intradermal vaccine and wound-infiltrated eRIG is <US\$ 2.75. We call this the Himachal Model of rabies PEP. Before 2008, five vials for IM vaccine alone used to cost US\$ 45 and eRIG US\$ 5. However, most doctors used to prescribe human RIG (HRIG) for fear of anaphylaxis with eRIG, and HRIG used to cost US\$ 500.

Himachal has also started following the newly recommended three-dose intradermal vaccine regimen for PEP, thereby saving hundreds of vaccine vials that became useful during shortages of rabies vaccine in India. To date, more than 700 vaccine vials have been saved in a single clinic at DDU during the past 6 months. As per the new WHO recommendations, no vaccination is required for people who consume the raw milk of a rabid cow. Not giving PEP to patients who have consumed raw milk from a suspected rabid cow has also saved 62 vials during the past 6 months and more than 1000 vials are expected to be saved throughout the State every year. Currently, 90 “pooling centers” are following the new WHO protocol on PEP by sharing vaccine and eRIG vials in the State.

Interestingly, the reduction in the recommended vaccine dose from four to three visits has highlighted the importance of low-dose immunobiologicals without compromising patient survival. Similarly, we have demonstrated that with 70% patients requiring <0.5 mL of eRIG for wound infiltration even if bitten by laboratory-confirmed rabid dogs, the neutralization of the virus in the surface of the wound with eRIG is important, not the quantity of eRIG injected. Rather than injecting “as much as possible” eRIG in and around the wound, it is important to inject sufficient eRIG to cover

the entire raw surface of the wound until its depth in order to neutralize the rabies virus that is likely to be present at the surface of the wound.

5. Conclusion and recommendations

We have shown that local wound infiltration only of eRIG is safe and affordable, with a lower reaction rate than the traditional method of additional IM injection. Compared to the era before dose-sparing of eRIG, we have reduced the volume of eRIG used per patient by eight times; the overall volume used by the health system has increased 21 times, as the state government is, for the first time, buying and providing PEP free of charge to all patients. This has happened because intradermal vaccination and local wound infiltration only of eRIG has reduced the overall cost below that of only one vial of rabies vaccine for IM administration, as was practiced before 2008 in our clinics. For the first time, the WHO Weekly Epidemiological Record has reported that intradermal rabies vaccine has efficacy equivalent to or higher than that of the same vaccine administered by the IM route [18]. This statement has enabled us to convince medical colleges to agree to intradermal rabies vaccination as well. Omitting IM injections for both vaccine and RIG at our clinics has also minimized the pain and suffering of patients. The new WHO guidelines are therefore a positive step towards a rabies free-world by 2030. Future strategies to optimize PEP should include the “Pooling Strategy of Himachal” as an important component in realizing the goal of a rabies-free world.

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Declaration of Competing Interest

None.

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