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Brief communication (Original)

Safety of equine rabies immunoglobulin injection into fingers and toes

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Background: International guidelines recommend infiltration of Rabies Immunoglobulin (RIG) into and around animal bite wounds in category III potential rabies exposures. This is followed by vaccination with an approved tissue culture rabies vaccine.
Objective: We assessed the feasibility and safety of injecting Equine Rabies Immunoglobulin (ERIG) into anatomical sites with less space for expansion.
Methods: A prospective study on 195 patients having category III animal bites over fingers, toes, nose, ear lobule, and eyelids was carried out at the Anti-Rabies Clinic of Maharaja Krushna Chandra Gajapati Medical College, Berhampur, Orissa, India. All patients received Equine Rabies Immunoglobulin (ERIG).
Results: No major side effects were observed. Minor side effects included induration (67.1%), pain (53.8%), and pruritus (29.2%). No compartment syndrome was seen.
Conclusion: Injecting ERIG into and around bite wounds following WHO and US-CDC guidelines in areas where no ample space is available, such as fingers, is a safe procedure.

Keywords: Equine rabies immunoglobulin, finger injury, rabies

International guidelines recommend infiltration of Rabies Immunoglobulin (RIG) into animal bite wounds as a life saving measure in all severe rabies exposures. It must be carried out as soon as possible after a potential exposure and not later than 7 days after the start of a vaccine series [1].

This is particularly important when the bite wounds are in highly innervated regions like hands, fingers and face. These anatomical sites have limited space for expansion. Hence injecting RIG under pressure into these sites may induce a risk of inducing compartment syndrome. WHO recommends administration of the calculated dose of RIG (of human or purified equine origin) as much as possible into and around the wounds. The rest, if any, is injected into the lateral thigh muscle [1-3]. Previous studies have documented the safety of purified equine RIG. There are many studies carried out in India and abroad about the safety of Equine Rabies Immunoglobulin (ERIG) as a whole [4-7]. However, injecting the tip of a finger or toe is not only a painful procedure but also a technically difficult process. We conducted a prospective study of patients with Category III (severe) animal bite exposures over fingers, toes, nose, ear lobule, and eyelids to assess the safety of ERIG administration into closed spaces.

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Materials and methods

The Anti Rabies Clinic (ARC) of MKCG Medical College Hospital Berhampur, Orissa, India has a long history in anti-rabies treatment. It is the second center to start Intra-dermal Rabies Vaccination (IDRV) in the country in 2007 and administration of ERIG is routine for severe exposure (using the WHO criteria) since 1997. Over the last two years, all category III cases have also received purified ERIG (EQUIRAB, Bharat Serums and Vaccines Pvt. Ltd, Mumbai, India) as recommended by WHO. They also were vaccinated with Purified Vero cell Rabies Vaccine using the updated Thai Red Cross intradermal given free by the Government of Orissa. Suturing of wounds is avoided or delayed. If it could not be avoided, the wounds are first infiltrated with ERIG followed by minimal suture after two to three hours. We are aware that early suturing of rabies-infected wounds increases

the risk of treatment failures [8]. Tetanus prophylaxis using tetanus toxoid was routinely given to all. Antibiotics were advised whenever indicated. All Category III cases underwent a skin test as per the ERIG manufacture's guidelines. An insulin syringe or a syringe with 26-gauge needle was used for infiltrating fingers, toes, nose, ear lobule, and eyelids. Once blanching of the site was noted, injection was stopped. No anesthetic or analgesic agents were used during the procedure. This study was carried out among cases registered between January 2010 and April 2010. This study was approved by the ethics committee of our institution. All samples and data were collected with informed consent from the participating subjects.

Results

During the study period, 2362 patients were registered for post exposure treatment. Of these 2051 (86.8%) had Category III exposure. Among all category III animal bites, 195 (9.5%) patients were bitten over fingers, toes, nose, ear lobules, eyelids, or at the perineal region. A majority (67.7%) was males, 44.1% were in the productive age group of 15 to 45 years and 13.8% were children below five years of age. Dogs were the main biting animal i.e. in 73.3% cases; out of which 99 (69.2%) were stray dogs and 44 (30.8%) pet dogs. Only four patients were bitten by wild animals. A majority (64.1%) reported to the ARC between 24 and 72 hours after the exposure. Only 34 patients (17.43%) reported within the first 24 hours and 13 patients (6.6%) reported after seven days. Seven patients experienced multiple bites.

Almost all body sites, except fingers, toes, the bridge of the nose, ear lobule and eye lids, have ample space for retaining immunoglobulin without possibly compromising local blood supply.

Among all above mentioned sites, bites over fingers accounted for 55.9%, toes 17.9%, and eyelids 19.4%. Only two patients (one child <5 years and an adult of 32 years) had bites at the perineal region, which, unless it is penile, has an adequate tissue space. Children below 15 years of age had exposure to eyes. Site of bite over fingers and toes were higher in the age group above 15 years of age (69.7% and 74.2% respectively) as shown in **Table 1**.

The volume of ERIG injected locally depends not only on the site of bite but also on the type of wound. In all age groups, the majority site was on fingers. Calculated per body weight, it was 6.01±2.39 ml out of which only 0.77±0.38 ml could be safely injected locally at fingers' bite sites and 0.44□0.15 ml at toes. For bites over eyelids, eyebrows and nearby, a maximum of 1.33 ml of ERIG could be injected locally (0.66±0.3 ml). The range of volume of ERIG administered locally over all above-mentioned sites varies from 0.2 ml to 2 ml. The remainder of the calculated body dose of ERIG was usually injected intramuscularly elsewhere.

Adverse side effects that we encountered after administration of ERIG into the study sites were induration (67.1%), pain (53.8%) and pruritus in 29.2%. Systemic side effects such as low-grade fever were observed in 24 cases (12.3%). None presented with wound infection as we provided appropriate wound care before and after injection. We did not suture any bites. There were no compartment syndromes. All injuries healed without complications and required no further intervention. All 195 cases have been followed for one year and none developed rabies. None of our patients experienced anaphylaxis-like reactions, delayed serum sickness reactions were seen in three subjects (1.53%) and 97 patients (49.74%) had early local ERIG injection site reactions mainly moderate to severe pain.

Table 1. Age distribution of site of bites

Age group (years)	Body weight (kg) (avg±SD)	Site of Bite					
		Fingers	Toes	Nose	Ear lobule	Eye lids	Perineal region
1-5	12.81±4.27	19	0	0	1	6	1
6-14	24.61±8.29	14	9	0	2	19	0
15-45	52.8±9.96	54	16	4	1	10	1
46-60	58.03±10.9	13	7	3	0	3	0
>60	55.25±13.09	9	3	0	0	0	0
Total	41.75±19.24	109 (55.9%)	35 (17.9%)	7 (3.5%)	4 (2.05%)	38 (19.4%)	2 (1.02%)

Discussion

RIGs are life saving biological but scarce and expensive. Worldwide less than 3% of at risk exposure cases receive RIGs and it is often not injected into wounds [2, 9]. Fear of anaphylaxis and the cost of RIG are the main barriers. Nevertheless, our institution has been using ERIG where appropriate since 1997. The demography of our study cases is similar to a study by MK Sudarashan and M Vinay [10, 11]. Our study only included patients who had Category III animal bites over fingers, toes, ear lobules, eyelids, nose and perineum. It was found that in 55.9% of cases the bites were over fingers. There are no Indian studies that specifically mentioned the site of bite as fingers or toes. A result of study in Thailand on the safety of RIG administration into bite areas like fingers or toes and no compartment syndromes or other serious complication were noted [12]. **Table 2** shows the amount of ERIG required, calculated by body weight and how much of it was possible to inject into fingers and toes. The range of volumes of ERIG injected locally over the bite areas varied from 0.2 ml to 2 ml. Vinay M et al in their study mentioned that 17 patients (6.1%) received all RIG intramuscularly (IM), even though the wounds were in the face, tip of fingers, palms, and soles of feet [11]. A previous study reported patients that died of rabies due to non-administration of RIG or not into all wounds [8]. Nine patients among our series presented with infected wounds. We injected ERIG locally as usual, but also provided appropriate wound care and antibiotics before and after ERIG injection. All wounds healed without complications. Wilde H and K. Bhanganada found, in a study of severe animal bite wounds and a control group of severe lacerations that that injecting such wounds did not increase the incidence of infection and complications [13, 14]. It has been suggested to use local anesthesia for injecting finger and toe wounds before the use of RIG. However, a study by Fescharek R et al. [15] found no role for anesthesia in decreasing the pain of RIG infiltration. Inserting a digital block is equally painful. Infiltrating the wounds with an anesthetic agent would create an added risk of spreading any virus throughout the bite site. We suggest that any patient with severe wounds, usually small children, where severe pain or emotional trauma would be expected, should receive a short general anesthetic for wound injection.

Conclusion

This prospective study of 195 patients with category III animal bites over fingers, toes, nose, ear lobules, and eyelids suggested that carefully injecting ERIG locally in these areas is a safe procedure

Therefore, it is concluded that careful infiltration with ERIG over bite sites on fingers, toes, nose, ear lobules, eyelids, and the perineal region are safe procedures and should be performed with care for prevention of Rabies.

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Table 2. Volume of ERIG injected per site of bite

Site of Bite (n)	Body weight (kg) (avg±SD)	Total ERIG required (in mL) (avg±SD)	Amount of ERIG injected (in mL)	
			Locally (avg±SD)	Systemically (avg±SD)
Fingers (109)	45.52 ±18.05	6.01±2.39	0.77±0.38	5.24±2.16
Toes (35)	48.74±15.85	6.5±2.1	0.44±0.15	6.05±2.01
Eye lids (38)	30.34±17.01	4.05±2.26	0.66±0.3	3.38±2.25
Nose (7)	51.42±7.93	6.86±1.05	0.62±0.25	6.23±0.9
Ear lobule (4)	16±11.1	2.13±1.48	0.52±0.34	1.61±1.15
Perineal region (2)	38.5	5.13	0.7	4.43

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