Title: CLINICAL SAFETY OF AN EQUINE RABIES IMMUNOGLOBULIN

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Keywords Rabies, ERIG, Safety of ERIG, adverse reactions, inj SupERIG

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Objective: To study the clinical safety of injection SupERIG.

Methods:A prospective study on 217 patients having category III animal bites using an ERIG (InjSupERIG, B.No SRS0115), manufactured by ViNSBioproducts Limited, Hyderabad, India and marketed by Synergy Diagnostics Pvt. Ltd, Mumbai, India with a potency of 300 IU/ml) was carried out at the Anti-Rabies Clinic of Sriram Chandra Bhanja Medical College,Cuttack, Odisha, India during March 2016.

Results:73% were males and 32% were children. Dog bite cases accounted for 82%, stray dogs (97%), unprovoked bites (37%). 65% had bite over lower limb followed by upper limb (24%). 10.8% of cases showed positive to skin test dose of supERIG. Allcases had complained of local induration and pain on day 0. 67% complained of local pruritus on day 3 and 21% on day 7. Other systemic side effects were fever and malaise. Neither anaphylaxis shock nor serum sickness like symptoms was observed.

Conclusion: Despite 10.8% of patients showing positive skin test to ERIG,SupERIG was administered FRIG, SupERIG after giving pre-medications like antihistamines. Children showed more local and systemic side effects than adults. The local complaints of pain and induration decreased with progress of time with simple medications of analgesics. Thus SupERIG was found to be a safe ERIG like other brands and can be used in category III animal bites..

Original Article

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ABSTRACT:

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INTRODUCTION:

Among all human infections, rabies is the tenth most common cause of death[1]. Human rabies is endemic in India and annually an estimated 20,000 persons die of this disease[2].The RIGs in particular are life saving in severe (WHO Category III) rabies exposure. The prohibitive cost of Human Rabies Immunoglobulin (HRIG) and its irregular market availability restricts its use. ERIGs which are indigenously produced are less expensive, affordable and more widely available; still its use is limited to only 2% (APCRI WHO survey in India)[3]. The other causes of its non use are lack of awareness among professionals & public, non-availability in rural areas, time constraint (case overload) and fear of anaphylaxis & severe side effects in the minds of the physicians.

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[3]. WHO recommendsadministration of the calculated dose of RIG (of human or purified equine origin) as much as possibleinto and around the wounds. The rest, if any, is injected into the lateral thigh muscle[3,4]. Previous studies have documented the safety of purified equine RIG. There are many studies carried out in India and abroad about the safety of ERIG as a whole[5-9].

There are instances of treatment failure (Deaths due to rabies) because of non use of RIG in those patients. The hypersensitivity to ERIG is reported in 1-11%[3,5,6,9]. But there are no scientific grounds for performing a skin test prior to administration of ERIG because testing does not predict reactions and ERIG should be given whatever the result of the test[10]. Still it is mandatory to do a skin test and if it is positive (> 10 mm in diameter after 15 minutes) special precautions should be taken if ERIG are used and the patient observed for at least one hour after the injection. Different authors used different pre-medication protocols. In this background the present study was undertaken to assess the safety and efficacy of the ERIG (Inj. SupERIG) newly available in the country for its use at the Anti-Rabies Clinic of SCB Medical College Cuttack, Odisha, India.

Materials and Methods-

The present study was conducted in the Anti Rabies Clinic (ARC) of the Community Medicine Department at S.C.B Medical College & Hospital, Cuttack, Odisha in March 2016.

Two hundred and seventeen (217) cases of category III animal bite were advised to purchase Inj. SupERIG (manufactured by ViNSBioproducts Limited, Hyderabad and marketed by Synergy Diagnostics Pvt. Ltd, Mumbai) because of non-availability of ERIG at Govt. Set-up. Inj. SupERIG was given at the site of bite at 40 IU/kg body weight after skin test. The intradermal

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test was carried out by injecting 1:10 dilution with Normal Saline (0.1ml) in flexor aspect of left forearm and observing for induration after 15 minutes. Induration of > 10 mm in diameter indicated positive skin test.

All patients were also administered IDRV according to Modified Thai Red Cross regimen using PVRV (Inj. Indirab, manufactured by Bharat Biotech Ltd).

All patients were tracked for adherence to treatment & observed for any adverse effects on days 3, 7& 28. They were followed up for 150 days.

RESULTS-

Among the study population, 71.89% were males and females accounted only for 28.11%. Majority of study subjects (57.14%) were from urban areas. Children aged 14 years & below contributed to 35.94% of the study subjects.

Out of all the animal bite cases included in the study, most were due to dog bite (73.73%). Out of those, 75% were stray dogs bites, among which 64.17% were provoked bites. 10% of the stray dogs were reported with abnormal behaviour or killed or died. Among the 25% cases of pet dog bite, 85% were of provoked bites with no immunization history. Other animal bite cases were due to cat (16.13%), monkey (9.22%) and others (0.92%).

Almost all body sites, except fingers, toes, the bridge of the nose, ear lobule and eye lids, have amplespace for retaining immunoglobulin without possibly compromising local blood supply. Among all above mentioned sites, Majority of the study subjects (55.76%) had the bite site over the lower limb followed by upper limb (25.34%). 12.45% of cases had bite injuries over multiple sites. Only two patients (one child <5 years and an adult of 32 years) had bites at the perineal region. (**Table I**)

Table I:
Distribution of site of bite

Site	Number	Percentage (%)
Upper limb	55	25.34
Lower limb	121	55.76
Trunk	8	3.69
Head & Neck	6	2.76
Multiple sites	27	12.45
Total	217	100

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 lower limb. Calculated per Kg of body weight, it was 6.73 ± 2.40 ml out of which only 2.88 ± 2.11 ml could be safely injected locally over the site of bite and rest 3.83 ± 2.88 ml injected over thigh.

For bites over upper limb a maximum requirement of 5.45 ± 2.88 ml of SupERIG was calculated and 1.34 ± 1.45ml could be injected locally and 4.09 ± 2.86ml injected over thigh. The range of volume of ERIG administered locally over lower limb and upper limb varies from 0.1ml to 9.3ml & 7.3ml respectively whereas over the head & neck the range was very less from 0.2 ml to 3.3 ml. Over multiple bite sites the local administration of SupERIG varies from 0.5 ml to 7 ml. The remainder of the calculated body dose of SupERIG was usually injected intramuscularly elsewhere (thigh). (**Table- II**)

Table II:
Volume of Inj. SupERIG injected per site of bite

Site of Bite(s)	Body weight (kg) (Avg± SD)	Total ERIG required (in ml) (Avg± SD)	Amount of ERIG injected (in ml) Locally (Avg± SD)	Amount of ERIG injected (in ml) systemically (Avg± SD)
Lower limb (121)	50.95±18.74	6.73±2.40	2.88±2.11	3.83±2.88
Upper limb (55)	41.92±23.73	5.45±2.88	1.34±1.45	4.09±2.86
Multiple sites (27)	40.44±21.04	5.36±2.77	5.48±1.9	1.88±2.03
Trunk (8)	33.87±20.44	4.52±2.7	5.06±1.8	0.88±1.25
Head & Neck (6)	43±27.2	5.41±3.83	1.45±1.07	3.97±3.39

All the cases had complained of local edema/induration and pain on day 0. Majority of cases (95.85%) complained of local pruritus on day 0. Other adverse reactions were generalised pruritus, malaise and fever.

Local adverse/side effects that we encountered after administration of ERIG (Inj.SupERIG) into the bite sites on the day of administration were local edema/induration (100%), pain (100%) and pruritus in 95.85%.

Systemic side effects such as low-grade fever were observed in 93 cases (42.86%), malaise in 108 cases (49.77%) and generalised pruritus in 14.74%. None presented with wound infection as we provided appropriate wound care before and after injection. We did not suture any bites. All injuries healed without complications and required no further intervention. All 217 cases have been followed for 150 days and none developed rabies. None of our patients experienced anaphylaxis-like reactions nor delayed serum sickness like reactions. (**Table- III**)

Table III:
Day wise adverse reactions after administration of injection SupERIG

Adverse reactions	Day 0	Day 3	Day 7	Day 28
Local edema/induration	217 (100%)	177 (82%)	137 (63.1%)	4 (1.84%)
Local pruritus	208 (95.85%)	103 (47.5%)	63 (29.03%)	2 (0.92%)
Local pain	217 (100%)	206 (94.93%)	116 (53.47%	16 (7.37%)
Generalised pruritus	32 (14.74%)	12 (5.53%)	2 (0.92%)	0 0
Malaise	108 (49.77%)	58 (26.73%)	25 (11.52%)	0
Fever	93 (42.86%)	33 (15%)	0	0

All the local and systemic side effects subsided with or without minor medications on subsequent follow up days.

Table IV:
Comparison of local reactions with skin test on Day 7

Adverse reactions	Skin test Non reactive (n=194)	Skin test Reactive (n=23)	P value
Local edema/ induration	130	7	<0.001
Local pruritus	60	3	0.073
Local pain	110	6	<0.001

Among all local adverse reactions in both skin tests reactive and non reactive to test dose of InjSupERIG, local pruritus did not show any significant association. However the local edema and local pain were marked in patients with skin test non reactive to test dose of InjSupERIG by day 7 following ERIG administration.

All local adverse reactions in both age groups of less than 14 years, and more than 14 years showed a significant association. Local reactions were significantly higher among children aged 14 years and below than among the higher age groups when compared on day 7. **(Table- V)**

Table V:
Comparison of local reactions with age on Day 7

Adverse reactions	< 14 years (n=78)	>14 years (n=139)	P value
Local edema/ induration	70	67	<0.001
Local pruritus	60	3	<0.001
Local pain	72	44	<0.001

All local adverse reactions in both sexes showed a significant association. Among all local reactions edema and pain were more observed among males and these local side effects subsided with simple medications like analgesics. **(Table- VI)**

Table VI:
Comparison of local reactions in both sexes on Day 7

Adverse reactions	Male (n=156)	Female (n=61)	P value
Local edema/ induration	122	15	<0.001
Local pruritus	58	5	<0.001
Local pain	108	8	<0.001

DISCUSSIONS:

As per WHO guidelines RIGs are mandatory for treating category III animal bite cases. There are evidences of deaths following vaccine administration and non administration of RIGs in category III bites because of vaccine failure. HRIGs are available in India by importing but are very expensive and limited. So the alternative is ERIG which is available in our country. Due to apprehension of side effects among doctors its use is limited.

The authors in their previous studies have proved the clinical safety of different marketed ERIG at the ARC of MKCG Medical College Berhampur, Odisha[3,4].

In our present study 10.6% of the patient showed positive (reactive) to the skin test dose of inj. SupERIG. The skin test positive to the test dose of ERIG was found to be 2.6% in 2003 (Inj. Equirab) and 12.6% in 2009 (Inj. VINRIG) in previous studies by the authors[3,4]. The hypersensitivity to different brands of ERIG in India and other countries is reported to be varying from 1-12%[3,5,6,7]. The Anti Rabies Serum produced by CRI Kasauli, India had reported a reactogenecity of 2.4%[8].

Despite positive to skin test dose of ERIG the authors administer SupERIG after simple medication of antihistamine (Tab Levocetrizine) to those 10.6% of patients. The authors in their previous study have proved use of antihistamine (Tab Levocetrizine) as a premedication to patients with skin test positive[4]. M K Sudarshan et al in their study on a premedication protocol for administration of ERIG in patients with hypersensitivity categorised four grades of skin test and used injectable forms of anti histamine, H_1 blocker and short acting steroids[9]. In another study by TR Behera et al among 465 patients with category III animal bites at M K C G Medical college, Berhampur, Odisha found 12.6% positive skin test, to test dose of a new equine rabies immunoglobulin (inj. Vinrig) and administered the ERIG to those patients with a simple premedication of oral antihistaminic for 5 days[4].

Our study included the patients who had category III animal bites where 55.7% of cases had bite over lower limb, 25.3% over upper limb, 3.6% over trunk , 2.7% over head and neck and 12.4% over multiple sites. The amount of ERIG (InjSupERIG) was given as per calculated body weight (40 IU/kg) as much as anatomically feasible and rest was injected over thigh. In our study, the amount of ERIG injected locally in bites of lower limb is 2.88 + 2.11 ml and 3.83 + 2.88 ml systemically over thigh. Similarly in other bite sites less amount of ERIG could be injected locally to avoid any complications like wound infection and compartment syndrome. Wilde H and K. Bhanganada found, in a study of severe animal bite wounds and a control group of severe lacerations that injecting such wounds did not increase the incidence of infection and complications[11,12]. A previous study reported patients that died of rabies due to non administration of RIG or not into all wounds[13]. We injected ERIG locally as usual, but also provided appropriate wound care and antibiotics before and after ERIG injection. All wounds healed without complications. T. R. Behera et al. In a study of 195 patients with category III exposure over fingers toes etc also showed that minimal amount of ERIG could be injected locally without local

anaesthesia to avoid compartment syndrome[18].

In the present study among different local side effects following administration of ERIG local pain and local induration / edema were observed in all patients on day of administration followed by local pruritus in 95.8% . All these local side effects gradually decreased by day 7 with simple medications like anti histamine and analgesics. None of the patients reported with any of the local side effects on day 28. Behera TR et al in a study among children using ERIG reported local Induration was the most common (91.8%) local side effect followed by Erythema (43.1%), pruritus (29.8%) and pain was the least common (19.9%)[21]. The authors in their previous study using injVinrig among 465 patients in 2009 found local reactions like edema, pruritus and pain on day 0 in almost all patients which subsided with simple medications like analgesics by day 28. These local reactions were significantly higher among children (< 15 yrs) when compared on day 7 as in the present study[8].

CONCLUSION-

The present study highlighted the scope of using the newly marketed ERIG (injSupERIG, manufactured by ViNSBioproducts Limited, Hyderabad and marketed by Synergy Diagnostics Pvt. Ltd, Mumbai); despite being skin test positive to test dose of ERIG (in 10.6% of cases) and also using the same in those patients. The local side effects were the same as encountered with other brands of ERIG and these resolved with use of simple analgesics. There were no cases of anaphylaxis nor serum sickness like symptoms with use of injSupERIG in the present study. Thus we are of the opinion that ERIG (injSupERIG) is safe as other brands of ERIG and can be used for treatment of category III animal bite.

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