8-Site Intradermal Post-Exposure Antirabies Vaccination for Major Animal Bites

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Follow up of 8-site intradermal post-exposure antirabies vaccination for category III (major) animal bites compared to the 2-site regimen with rabies immunoglobulin: a clinical audit.

Abstract

Background: In 2002, the eight-site intradermal reg-imen (0.1ml of purified inactivated vero cell vaccine-VERORAB) was given to the patients with category III (major) exposures, due to the lack of rabies immunoglobulin(RIG) in Sri Lanka. Our objective was to study their incidence of rabies at the end of two years after exposure in comparison to RIG and 2-site intradermal regimen.

Methods: Data were collected prospectively from patients who presented to the Teaching Hospital,
Peradeniya in 2002 and 2003.

Results: We compared 667 patients who received eight-site regimen (study group 1) in 2002 with a group of 670 patients who had both RIG and 2-site intradermal regimen in 2003 (study group 2). The mean age of study group 1 was 25 (SD 18) and study group 2 was 25 (SD 20) years respectively. Parameters such as gender, type of biting animal and the severity of bite were similar in both groups. However, study group 1 had 70.6% of stray animal bites compared to group 2 which had 71.5% domestic animal bites. Most of the bites were on hands and legs in both groups. There were no deaths reported in either groups due to rabies by the year 2005(two years after exposure).

Conclusion: We report a supportive clinical evidence for 8-site intradermal regimen as a post exposure prophylaxis in situations where RIG is not available for management for category III exposures. However, administration of rabies immunoglobulin should remain the best post-exposure therapy for these patients.

Introduction

Rabies encephalomyelitis is caused by a rhabdovirus, transmitted commonly by animal bites. Although human rabies is considered as an invariably fatal disease, it is eminently preventable following an exposure to the virus. Rabies is endemic in Sri Lanka and is a major health problem that reportedly causes 60 - 100 deaths annually.[1] Primitive nervous tissue Semple vaccine produced in goats was replaced with tissue culture vaccines since 1995, thereby causing heavy expenditure on the government of Sri Lanka for post exposure prophylaxis.[2,3] This ever-increasing demand for tissue culture vaccine had led to the introduction of economical intradermal regimen, which became the standard practice in Sri Lanka as a cost saving measure.[4,5,6] Currently practiced post exposure intradermal regimens(2-site and 8-site) use only 40% of the vaccine required for the standard intramuscular regimen.[7,8] The 2-site intradermal regimen involves two injections (0.1ml of purified Vero cell vaccine-PVRV at each site) over the deltoids on day 0, 3 and 7 and single-site boosters on day 28 and 90.[9,7,1] This regimen should to be used with rabies immunoglobulin(RIG), following category III (major) animal bites. Of the RIGs, human RIG is prohibitively expensive compared to equine RIG and is not common to cause allergy.

In a situation where RIG is not available, 8-site intradermal regimen was recommended.[10] This regi-men involves eight sites of intradermal injections (0.1ml/site) on day 0, four sites on day 7 and single site on days 28 and 90. The evidence of the clinical efficacy of the eight-site method is found in the original research where a randomised controlled clinical trial showed no deaths in patients who were bitten by proven rabid animals (36 severe and 42 mild cases)

having received this vaccine regimen where only severe cases had received RIG.[6] In 2002 there was a severe shortage of RIG in Sri Lanka and the eight-site intradermal regimen (0.1ml of purified inactivated vero cells vaccine - VERORAB) was practiced in the Government Hospitals for category III major animal bites. We followed up these patients who received eight-site regimen and compared them with a group of patients who received the combined 2-site anti rabies vaccine regimen and RIG in 2003. The outcome of either regimen was studied two years later and presented.

Materials and Methods

We collected case records of 667 patients who had eight-site intradermal injections for category III exposures (major animal bites) in 2002 (study group 1). They had received 0.1ml of purified inactivated vero cell vaccine - VERORAB *(Aventis Pasteur),* at eight-sites intradermally on day 0, four sites on day 7 and a single site on days 30 and 90. This was compared with 670 patients who had both equine rabies immunoglobulin (Changchun Intitute of Biological Products,P.R. China) and 2-site intradermal rabies vaccine (0.1ml of purified inactivated vero cells vaccine - VERORAB *(Aventis Pasteur)* in 2003 (study group 2). The 2-site intradermal regimen involved two intradermal injections (0.1ml/site) over the deltoids on days 0, 3 and 7 and single-site boosters on days 30 and 90. In 2005, patients in both groups were investigated for development of rabies (two years after post-exposure treatment) from the human rabies surveillance report maintained at the Epidemiology Unit of the Ministry of Health, Colombo, Sri Lanka

Statistical method

Data were analyzed using the statistical software package, SPSS version 11. Initially the two sets of data were analyzed according to the patient's demographic characteristics, sites of bites on body and the type and behaviour of the animal involved. Chi square and Student's t tests were appropriately used for the analysis. Since there were no deaths identified in both sets of data no further analysis was carried out.

Results

The mean age of study group 1 was 25 (SD 18) and study group 2 was 25(SD 20) years respectively. The rest of the parameters such as gender of the patients, type of the animal and the severity of bite were similar in both groups (Table 1). However, study group 1 (eight-site) had 70.6% of stray animal bites compared to group 2 which had 71.5% domestic animal bites. Most of the bites were on hands and legs and the two groups were similar but bites on head and neck regions were observed to be higher in the study group 2 (Table 2). There were no deaths in both groups due to rabies by 2005.

Table 1 Comparison of parameters between two groups

Parameter		Group 1 (Eight site)		Group 2 (RIG)*		P value
Gender	Male	369	55.3%	356	53.1%	0.422
	Female	298	44.7%	314	46.9%	0.422
	Total	667	100%	670	100%	
Type of animal	Dog	527	79.0%	546	81.7%	0.411
	Cat	122	18.3%	105	15.7%	0.411
	Others	10	2.7%	17	2.5%	0.411
	Total	667	100%	668	100%	
Behaviour	Domestic	25	29.4%	241	71.5%	<0.001
	Stray	60	70.6%	96	28.5%	<0.001
	Total	85	100%	337	100%	
Type of bite	Bite	626	95.1%	614	92.7%	0.069
	Scratch	32	7.3%	48	7.3%	0.069
	Total	658	100%	662	100%	
Age		25.26 (Mean)		25.46 (Mean)		0.848

*Rabies immunoglobulin + 2-site rabies vaccine

Table 2 Site of the animal bite

Site	Group 1 (Eight site)		Group 2 (RIG)*	
	No	%	No	%
1. Head & neck	25	5.9	88	15.2
2. Hand	175	41.3	192	33.2
3. Arm	43	10.1	43	7.5
4. Leg	181	42.7	256	44.1
Total	424	100	579	100

Discussion

In this study we found no treatment failures in either regimens used as post-exposure prophylaxis. We used this rare opportunity to provide clinical evidence in favour of the 8-site regimen, which is already in practice. However, we were not able to confirm rabies infection in the biting animals that remains the main drawback of the study. As there are no data on the prevalence of rabies in dogs available in Sri Lanka, we are not in a position to calculate an approximate value of infected animals in the study. However, it is noteworthy that 70% of the animals were stray dogs where the patients were administered the 8-site regi-men. Stray dogs were responsible for 46% of 76 human rabies cases reported in 2003.[11] The Medical Research Institute of Sri Lanka has received 807 ani-mal heads in 2000 which represent a tip of an iceberg, and 71% of them were positive for rabies.[11] Considering the above information and a large number of animals involved in the study, we could presume that a sizable proportion of them may be infect-ed with rabies at the time of bite. Furthermore, estimation of serum neutralizing antibody titres, that we were unable to determine, would have enhanced the findings of the study.

The Thai Red Cross did a study on 100 patients severely bitten by proven rabid animals. They were given 2-site intradermal vaccine regimen and RIG and followed up. There were no deaths after one year and a randomly selected subgroup of 10 patients had shown seroconversion testifying the efficacy and safe-ty of the 2-site regimen.[9] Meanwhile, Khawplod[12] showed the 8-site regimen to give significantly higher antibody levels than the 2-site regimen from day 7 onwards using purified chick embryo cell vaccine (PCECV). However, Sriaroon used the 8-site double dose rabies vaccine that resulted in higher antibody titers than the 2-site regimens by day 14, but hardly any significant titers by days 5 and 7.[13] Hence, the administration of rabies immunoglobulin into and around the bite wounds on the first day of rabies prophylaxis combined with anti rabies tissue culture vac-cine was stressed as the best post-exposure therapy for all category III exposures. However, 8-site regimen remains as the best option when RIG is not available, which specially occurs in rabies endemic countries with limited resources. But safety of 8-site regimen in very severe bites is questionable now, as a treatment failure has already been reported. A child, bitten on the face by a proven rabid dog with severe exposure was given 8-site PCECV as RIG was not available in the hospital and had died due to rabies after 15 days in Thailand.[4]

The answer to this dilemma of post-exposure prophylaxis would be to develop an effective equine rabies immunoglobulin that is affordable even for a poorer nation. Furthermore, development of monoclonal antibody technique would be the best option for the future to overcome the shortage of this life saving biological product.

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Authorship

S A M Kularatne was the principal investigator, designed the study, and wrote the paper. MMKP SKCP, SW and UB undertook data collection. PVRK analysed the data. OW made intellectual contribution.

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