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Research Article

Modified Essen Regimen for Post Exposure Rabies Prophylaxis in Cattle, a Novel Approach for Control of Rabies in Cattle

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Abstract: Objective of the study was to evaluate the success of post exposure rabies prophylaxis in cattle as a replacement of euthanasia of potentially exposed animals. Post exposure vaccination of cattle with three regimen viz. standard Essen protocol, modified Essen protocol, newly derived short interval protocol were studied with same cell culture vaccine of potency >2.5IU/ml via intramuscular route. Rabies virus neutralizing antibody level was evaluated by an approved serum neutralization assay, RFFIT, on day 0, 3, 7, 14, 28 and 90. Modified Essen regimen was found statistically superior in eliciting early immunogenicity, higher antibody level and longer protection when compared to other two schedules revealing the potential in saving potentially exposed cattle from developing fatal clinical rabies. The result of the study is extremely promising and hence could therefore make a significant contribution to the Rabies eradication campaign, success of which is vital for both animal and human welfare.

Keywords: Rabies, RFFIT, PEP, VNA, Essen regimen.

INTRODUCTION

Rabies in dairy cattle is a public and animal health issue (Yakobson, B. *et al.*, 2015). In regions where canine rabies is endemic, spill over infection in cattle is common. This species have a greater incidence of rabies as they are more prone to stray dog bite due to the open housing practices and while grazing in the field. Preventive rabies vaccination in Cattle is voluntary in many countries and is based on perception of risk hence coverage is poor (Prosperi, S. *et al.*, 1984). Reports or studies on immunogenicity in rabies vaccination, pre or post exposure, in animals other than dogs are scanty.

Currently, there are no internationally or nationally established protocols for rabies PEP of naive rabies exposed cattle. International guidelines concerning unvaccinated animals that are exposed to rabies recommend that these animals be euthanized or confined in strict quarantine for 6 months (Hanlon, C. A. *et al.*, 2002). However, it is not practical in resource poor countries due economic reasons. Social, religious and animal welfare issues also make implementation problematic in many countries. The purpose of this study was to develop a post exposure active immunization schedule for cattle to elicit early protection as a novel approach for prevention of rabies in cattle.

MATERIALS AND METHOD

Animals:

The study population consisted of three groups each with six adult cows. They ranged from 300 to 400 kg and were randomly assigned to treatment groups. They were housed separately and identified by unique tag number. Food and water were offered adlibitum.

Vaccine and Route of inoculation:

Commercial rabies cell culture animal vaccine with a potency of ≥2.5IU/ml was used in the study. Same brand and batch were used in all three groups. Vaccine was inoculated by intramuscular route on neck muscle. Inoculums of volume more than 1ML was administrated on two separate sites on both sides of neck.

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Experimental protocol:
Animals of **Group 1 (Standard Essen Regimen)** were administrated 1ML vaccine on day 0, 3, 7, 14 & 28.
Group 2 (Modified Essen Regimen) was administrated vaccine at the dose of 3ML, 3ML, 2ML, 1ML and 1ML on days 0, 3, 7, 14 and 28.
Group 3 (Short Interval Regimen) received vaccine at the dose of 1ML each on days 0, 1, 2, 3, & 4.

Blood Collection and VNA Estimation:
A blood sample (5-6ml) was collected from jugular vein of each cattle on days 0, 3, 7, 14, 28 and 90. The titer of rabies virus- neutralizing antibodies (VNA) was determined by rapid fluorescent focus inhibition test (RFFIT).

Tolerance and Safety:
All animals were daily observed for any local or systemic reaction during the study period. Temperature, feed intake, milk production and local reactions were recorded.

Statistical Analysis:
An ANOVA was used to determine overall differences between the groups. Comparison of group 2 and 3 with standard Essen regimen (group 1) was analyzed by Posthoc Duncan's Test. Values of $P < 0.05$ were considered significant.

RESULTS

Early Protection
None of the cows had detectable level of rabies VNA at the initiation of study (day 0). GMT of VNA on days 0, 3, 7, 14 28 and 90 of all three experimental groups are summarized in Table 1 and Figure 1. 67% (4/6) of the animals of group 2 (Modified Essen Regimen) were protected (VNA titer ≥0.5IU/ml) on Day 3, where as in group 3, only 50% (3/6) of animals had sufficient VNA titer and none (0/6) were protected by Standard Essen Regimen (Group 1). However there was no difference between regimens in terms of number of animals protected from day 7 onwards (Table 2 and Figure 2).

Higher antibody level (VNA titer level)
Animals of group 2 had apparently higher titer level from Day 3 to Day 90. In group 3, there was faster deduction in antibody level after Day 14 though level was protective throughout the study period. Statistical analysis revealed significant difference ($p<0.05$) between the titer levels of three groups on day 3 and 90. The analysis revealed that group 2 had significantly different titer levels than group 1 and 3 on day 3 and 90 where as no significant difference existed between group 1 and 3. Group 2 had highest titer levels among three groups on day 3 and 90. No systemic or local reactions were observed in any of the vaccinated animals.

Table 1: Rabies Virus Neutralizing Antibody Level as Evaluated by RFFIT in IU/ml

Group	Days post vaccination					
	0	3	7	14	28	90
1	0.3^{a}	0.422^{a}	3.747^{a}	17.5^{a}	36.25^{a}	8.75^{a}
2	0.267^{a}	$\mathbf{1.243^{b}}$	8.905^{a}	27.5^{a}	52.5^{a}	$\mathbf{27.5^{b}}$
3	0.27^{a}	0.638^{a}	7.185^{a}	23.75^{a}	21.25^{a}	6.562^{a}

- Mean with different superscripts within a column are significantly different.
- One way ANOVA revealed significant difference ($p<0.05$) between the titer levels of three groups on day 3 and day 90.
- Posthoc Duncan's Test revealed that group 2 had significantly different titer levels than group 1 & 3 on day 3 & 90 where as no significant difference existed between group 1 & 3.
- Group 2 had highest titer levels among three groups on day 3 & 90.

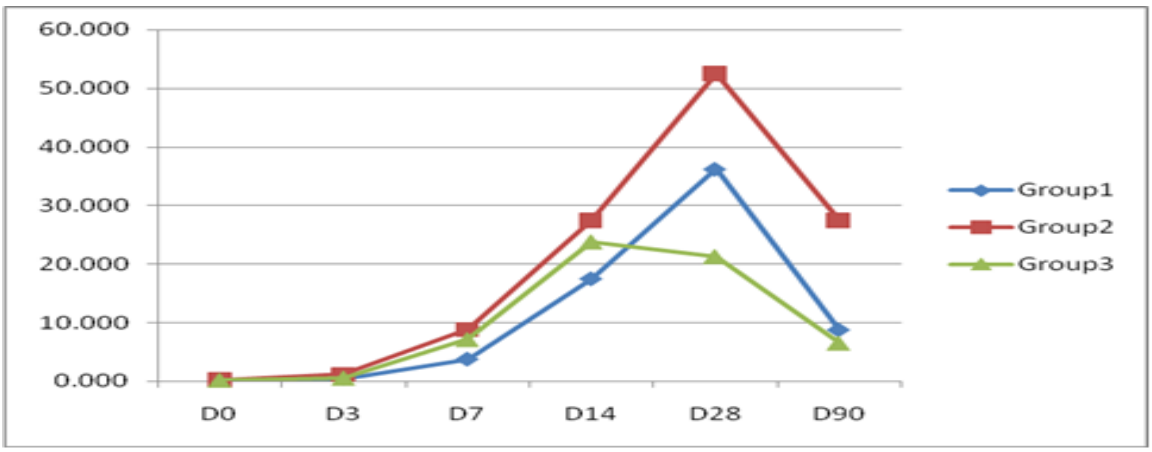

Figure 1: Rabies Virus Neutralizing Antibody Level as Evaluated By RFFIT In IU/Ml

Table 2: Percentage of Animals Protected as Evaluated by RFFIT (≥0.5 IU/ml)

Group	Days post vaccination					
	0	3	7	14	28	90
1	0	0	100	100	100	100
2	0	67	100	100	100	100
3	0	50	100	100	100	100

- None of the animals of group 1 were protected on day 3 where 66.6% of group 2 and 50% of group 3 were protected.
- All three regimens induced sufficient protection from day 7 onwards

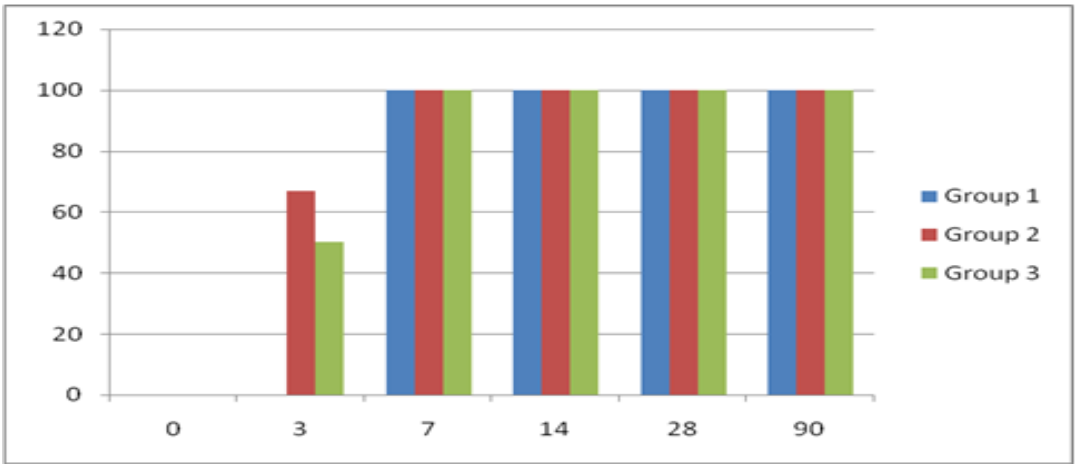

Figure 2: Percentage of Animals Protected as Evaluated by RFFIT (≥0.5 IU/ml)

DISCUSSION

Currently there are no licensed products or established protocols for rabies PEP for naïve rabies exposed animals, including domestic dogs (Hanlon, C. A. *et al.,* 2002). Nonetheless, the knowledge and biological for potential PEP for animals exist. In practice, failure rate was found high (Abraham, S.S. *et al.,* 2010) when they are treated in accordance with a protocol that emulated rabies PEP in humans without immunoglobulin therapy. RIG is in critically short supply on a global basis (Hanlon, C. A. *et al.,* 2002). The limited availability and subsequent high cost limits its use for PEP in animals in developing countries. Human fatalities have been reported when RIG is needed and not given (Hemachudha, T. *et al.,* 1999). Vaccine alone can't prevent rabies, particularly in severe exposure. Although science has advanced, production of RIG has not changed substantially warranting research for alternate ways of protecting rabies exposed animals.

The findings of the study reported here reveal the potential of a novel approach for rabies PEP in cattle for rabies endemic developing countries where local social situations, animal welfare rules, economic viability and religious attitude preclude the adoption of euthanasia or 6-month quarantine. If they can be evaluated further and eventually approved, it may be prudent to apply in decreasing PEP failures and rabies death in livestock animals. Regimen 2 (Modified Essen) revealed better immunogenicity in terms of early and longer protection (day 3 and 90), and higher antibody level than the currently practiced standard Essen regimen (Group 1). It is logical to assume that higher the antibody titer longer will be the persistence of antibody level. Findings were statistically significant also. Rabies is a disease with variable and long incubation period. Hence early attainment and sustained protection is of utmost importance. The new protocol was well tolerated, safe and potent.

The data reported here are promising and merit consideration with regard to use as a replacement of euthanasia of potentially exposed animals. Several studies highlighted the need for developing an alternative for managing rabies in cattle (Yakobson, B. *et al.,* 2015; Prosperi, S. *et al.,* 1984; Abraham, S.S. *et al.,* 2010; & Basheer, A. M. *et al.,* 1997). In addition to the obvious potential clinical application of rabies PEP in exposed cattle, development of a PEP model in cattle allows for a proof-of-principle determination, which may directly benefit other animals in need of rabies PEP. The new protocol needs further validation with clinical trials for use during outbreak situations. The results warrant the development of licensed high potency vaccine for animals or new schedules for managing rabid dog bite outbreaks in livestock animals and development of national recommendations for rabies management in animals.

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