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A prospective study on safety and clinical efficacy of rabies biologicals in paediatric patients with category III animal exposure

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Purpose: Rabies remains a significant public health concern worldwide, particularly among paediatric populations who are vulnerable to animal exposures. This prospective study aimed to assess the safety and clinical efficacy of rabies biologicals in pediatric patients following category III animal exposures.

Materials and Methods: A prospective study was undertaken enrolling 289 pediatric patients fulfilling eligibility criteria who presented with category III animal exposures at the anti-rabies clinic of Kempegowda Institute of Medical Sciences Hospital and Research Centre, Bangalore. All the subjects received rabies biologicals as per National Centre for Disease Control guidelines. The details pertaining to socio-demographic profile, biting animal, characteristics of wound, and details of post-exposure prophylaxis (PEP) provided were recorded. All the study subjects were followed up for immediate and delayed adverse events (AEs). Subsequently, all were followed up for 6 months to demonstrate the clinical efficacy of PEP.

Results: The mean age of study subjects was 9.4 years, and most of them (43%) were going to school. Dog was the predominant biting animal (96.6%) with most bites being abrasions (45%), mainly on the lower limbs (42%). Single rabies monoclonal antibody was the most commonly administered passive immunization (67%), and purified Vero cell rabies vaccine was the predominant vaccine (65%). AEs following PEP were primarily local, predominantly pain (13.2%), and there were no systemic events. All the subjects were alive and healthy at the end of 6 months following PEP.

Conclusion: This study contributes valuable insights into the safety and clinical efficacy of rabies biologicals in a pediatric cohort following category III animal exposures, supporting the continued use of these biologicals in pediatric patients.

Keywords: Rabies; Pediatric; Animal exposure; Safety; Efficacy

INTRODUCTION

Rabies remains a critical public health concern globally, given its potential for rapid transmission and fatal outcomes, demanding vigilant preventive measures. Globally, rabies continues to be a significant public health issue, leading to approximately 59,000 human fatalities every year [1]. Among those at heightened risk are pediatric populations, who are particularly vulnerable to animal exposures due to their inherent curiosity and limited ability to avoid potentially rabid animals [2].

Rabies exposures are especially hazardous in children, who accounted for 40% of rabies deaths and over 50% of rabies exposures in India from 2016–2018 [3].

Animal bites are the source of almost all human rabies cases [4], and improper wound management and lack of post-exposure prophylaxis (PEP) drives rabies mortality [5]. As per World Health Organization (WHO) guidelines, animal bite victims are classified into category I, II, or III exposures based on wound severity and rabies risk [6]. Category III denotes single or multiple transdermal bites from proven or probable rabid domestic or pet animals, requiring immediate administration of rabies biologics.

The primary strategy for preventing rabies after exposure is the administration of PEP, which involves thorough wound cleaning, rabies immunoglobulin (RIG) or monoclonal antibodies (mAbs) for passive immunization, and a complete course of anti-rabies vaccine (ARV). Rabies monoclonal antibodies (RmAbs) and immunoglobulins, such as human rabies immunoglobulin (HRIG) and equine rabies immunoglobulin (ERIG), have been extensively studied in clinical trials and are endorsed by WHO guidelines for their efficacy in neutralizing the rabies virus. For instance, Hobart-Porter et al. [7] demonstrated the safety and efficacy of HRIG in pediatric patients, emphasizing its role in effective rabies prevention for children with suspected exposures.

The development of RmAbs, such as Twinrab™, has been extensively studied in phase 3 clinical trials, demonstrating noninferiority to traditional immunoglobulins. These trials were pivotal in establishing the safety and efficacy profiles necessary for WHO endorsement and market approval [8]. Such rigorous testing forms the basis upon which newer biologics, like RmAbs, are adopted into practice, ensuring that their use is safe and effective across diverse populations. Recent advances in rabies biologics have also highlighted the benefits of mAbs over traditional immunoglobulins, such as reduced risk of hypersensitivity reactions, better production scalability, and favorable tolerability [8]. A review by Tarantola et al. [9] emphasized evaluating cost-effective, reduced-dose regimens that are effective in real-world contexts.

In India, modern cell-culture rabies vaccines like Vero cell rabies vaccine (VCRV) and purified chick embryo cell vaccine (PCECV) are recommended for PEP, along with RIG [10]. Recent developments in rabies vaccines, including VCRV, have shown significant improvements in safety and immunogenicity. Natesan et al. [11] highlighted advancements in rabies vaccines, emphasizing enhanced immunogenic responses and reduced adverse effects, particularly with cell-culture-based vaccines. The findings from this prospective randomized trial further validate the safety and efficacy of modern cell-culture vaccines in diverse populations, including those with severe exposures.

Though highly immunogenic and safe, data on the performance of these biologics specifically in pediatric populations is limited. Younger age is associated with increased risk of rabies PEP failure, often due to improper dosing or partial adherence [12,13]. Hence, there is a need for evidence on the optimal use of rabies biologics in children to strengthen PEP programs.

The current study focuses on evaluating the safety and clinical efficacy of these biologics in pediatric patients presenting with category III animal exposures in an urban Indian setting. This single-center, prospective study aims to contribute to the existing body of knowledge by providing real-world evidence of the effectiveness of RmAb, HRIG, and ERIG in a diverse pediatric population. Unlike prior clinical trials that were often conducted under controlled conditions, our study emphasizes practical implementation in an anti-rabies clinic, reflecting challenges faced in routine healthcare environments.

By evaluating the safety and clinical efficacy of rabies biologics in the context of pediatric patients with category III animal exposures, this study contributes essential insights that can guide medical practitioners in optimizing PEP protocols. Furthermore, the findings provide valuable information for parents, caregivers, and healthcare authorities, helping them make informed decisions about managing animal exposures and preventing rabies in vulnerable pediatric populations.

MATERIALS AND METHODS

Study setting and participants

This single-center, prospective study was conducted from June 2021 to May 2022 at the anti-rabies clinic of Kempegowda Institute of Medical Sciences (KIMS) Hospital and Research Centre, Bangalore. It focused on pediatric patients aged 1 month to 18 years presenting with category III animal exposures to investigate the safety and clinical efficacy of rabies biologics. The sample size was determined based on a 7% incidence of adverse events (AEs) from a recent study. Using a 95% confidence level, 5% alpha, and precision of 5%, the sample size was calculated as follows:

$$n = Z_{(\alpha/2)}^2 pq = (1.96)^2 \times 0.07 \times 0.93$$

$$\frac{\qquad}{\qquad} = \frac{\qquad}{\qquad} = 289$$

$$d^2 = (0.05)^2$$

where n was sample size, Z was level of confidence according to the standard normal distribution; for a level of

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confidence of 95%, it is 1.96, p was AE (7%), q was 1–p (93%), and d was absolute precision (5%).

Inclusion and exclusion criteria

Inclusion criteria encompassed animal bite victims who voluntarily sought PEP, were willing to provide informed consent, had documented incidents of category III animal bites or scratches, and were available for follow-up. Exclusion criteria included those who had previously started PEP, had a history of rabies prophylaxis, severe allergic reactions to rabies biologics, or contraindications to vaccine components.

Data collection

Data were collected using a structured case record form. The form contained information on age, sex, address, phone number, education, occupation, relevant past and present medical history, weight, physical examination, history of any allergy, intake of any medication, past history of any animal bites, characteristics of exposure, categorization of animal exposure, wound wash, anti-rabies vaccination, and volume of RIG/mAb administration based on the site, size, and severity of wounds, along with dates of vaccination and AEs PEP.

A detailed case history was taken from all the animal bite victims who visited the anti-rabies clinic for PEP, which included their socio-demographic profile, details of animal exposure, and any wound treatment received. Study subjects were asked about current or past medical problems, concomitant or past medication use, and history of allergy to any medicines.

A thorough clinical examination, including both general physical and systemic examination, was conducted to assess the health status of the animal bite victims. All wounds present in the study subjects were examined in detail, focusing on the site, size, and severity of exposure.

PEP provided in the anti-rabies clinic

PEP was provided to all study participants at the anti-rabies clinic in accordance with the National Centre for Disease Control, India guidelines. The PEP protocol began with a thorough wound wash using soap and running water for 10–15 minutes to effectively cleanse the site of exposure. Following this, participants received a complete course of intramuscular anti-rabies vaccination following the Essen regimen, which involved administering one dose of the vaccine on days 0, 3, 7, 14, and 28.

In addition to the anti-rabies vaccination, participants received administration of either RIG, i.e., HRIG, ERIG, or RmAb (single and cocktail) to all category III exposures as per the calculated volume according to weight on day "0." HRIG was administered at a dosage of 20 IU/kg body weight, whereas ERIG was administered at a dosage of 40 IU/kg body weight. RmAb was administered at a dosage of 3.33 IU/kg body weight for a single mAb or 40 IU/kg body weight for the mAb cocktail.

Mode of administration of RIG or mAbs

To ensure effective local neutralization of the rabies virus at the site of exposure, all wounds were thoroughly infiltrated with a calculated dose of RIG, whether it was HRIG, ERIG, or a mAb cocktail consisting of 2 antibodies. The infiltration was performed directly into and around each wound, targeting the virus wherever it might be present. The maximum feasible amount of the calculated dose was administered locally to each wound. If any portion of the dose remained after local infiltration, it was administered deep intramuscularly at a site distant from the ARV injection site to prevent interference between the treatments. In cases involving multiple wounds, the required volume for each wound's infiltration was carefully calculated, and the total volume needed was achieved through appropriate dilution to ensure comprehensive coverage.

Assessment of safety and clinical efficacy of PEP

All patients were monitored for AEs following the administration of PEP. Participants were observed for one hour to document any immediate local AEs, such as pain, erythema, pruritus, and induration, as well as systemic reactions, including malaise, dizziness, headache, nausea, and allergic reactions like urticaria, rash, and anaphylaxis. AEs were evaluated for causality and severity, categorized as mild (grade 1), moderate (grade 2), and severe (grade 3). Follow-up cards were provided to record late-onset AEs, including itching, fever, serum sickness, and arthralgia, during visits on days 3, 7, 14, 28, and 180. Each AE was recorded separately, even if reported multiple times.

The clinical efficacy of PEP was assessed over a six-month follow-up period through monthly phone calls and a final hospital visit. Survival beyond the typical rabies incubation period indicated the efficacy of the rabies vaccines and immunoglobulins or mAbs used.

Data analysis

Descriptive statistics were used to summarize demographic characteristics, exposure details, and AEs. Data analysis was conducted using MS Excel (Microsoft, Redmond, WA, USA) and IBM-SPSS statistics software version 21.0 (IBM Corp., Armonk, NY, USA) to calculate the incidence of AEs and the absence of rabies-related symptoms,

reported as percentages. The χ^2 tests were applied to assess associations between biologics exposure and AEs, focusing on relationships between different categorical variables. The overarching goal of the analysis was to verify the safety and clinical efficacy of the administered rabies biologics.

Ethical considerations

The study was conducted in full compliance with the ethical guidelines set forth by the Declaration of Helsinki and the International Council for Harmonization's Good Clinical Practice guidelines. Ethical approval was obtained from the Institutional Ethics Committee of KIMS Hospital (Ref. KIMS/IEC/D-06/2021) prior to the commencement of the study. Written informed consent was obtained from parents or legal guardians for subjects aged 2–17 years, and written informed assent was secured from subjects aged 7–17 years. Strict measures were implemented to uphold participant confidentiality, with all identifiable information securely stored and anonymized in any public disclosures.

RESULTS

A total of 289 pediatric patients with category III animal exposure participated in the study at KIMS Hospital and Research Centre, Bangalore. Age-wise, infants (1 month to 1 year) represented 0.3% of the cohort; toddlers (1 to 3 years) comprised 9.0%; preschool children (3 to 6 years) made up 20.4%; school-aged children (6 to 12 years) accounted for 42.9%; and adolescents (12 to 18 years) constituted 27.3% as depicted in **Table 1** (mean age 9.4 years).

Table 1. Demographic pattern of pediatric patients (n=289)

Parameters	Frequency (%)
Age-group	
Infant (1 month to 1 year)	1 (0.3)
Toddler (1 to 3 years)	26 (9.0)
Preschool (3 to 6 years)	59 (20.4)
School age child (6 to 12 years)	124 (42.9)
Adolescent (12 to 18 years)	79 (27.3)
Sex	
Male	205 (70.9)
Female	84 (29.1)
Place of residence	
Rural	73 (25.3)
Urban	216 (74.7)
Socio-economic status	
Upper class	26 (9.0)
Upper middle class	38 (13.1)
Middle class	196 (67.8)
Lower middle class	29 (10.0)

In terms of sex, males were significantly more prevalent, making up 70.9%, with females accounting for the remaining 29.1%. Evaluating the place of residence, a substantial 74.7% of the patients hailed from urban areas, in contrast to 25.3% from rural locales. When analyzing socio-economic status, the middle class emerged as the predominant group, encompassing 67.8% of the participants. They were followed by the upper middle class at 13.1%, the lower middle class at 10.0%, and the upper class at 9.0% (**Table 1**).

Regarding the nature of the biting animals, stray dogs led the count with 48.8%, closely followed by pet dogs at 47.8%. Cat bites were rarer, accounting for 2.8%, and monkey bites were the least frequent, making up 0.7%. In terms of the bite's circumstances, a significant 72.7% were unprovoked, contrasting with the 27.3% that were provoked. Examining the type of wounds, abrasions were most prevalent at 44.6%, followed by lacerations (19.4%), punctures (17.0%), and multiple types of wounds (19.0%). The site of exposure varied, with the lower limb being the most affected at 42.2%, then the upper limb (35.3%), head & neck (12.1%), trunk (4.2%), multiple sites (5.5%), and, rarely, the genitals (0.7%) as shown in **Table 2**.

Treatment-wise, 65.1% of cases employed purified VCRV (PVRV), while PCECV was administered in the remaining 34.9%. In the choice of RIG, the single RmAb was dominant, used in 67.1% of instances. The cocktail RmAb was the choice in 19.4% of the cases, while other RIG types collectively represented 13.5% as depicted in **Table 3**.

Table 2. Details of exposure among study subjects (n=289)

Variable	Frequency
Biting animal	
Dog stray	141 (48.8)
Pet	138 (47.8)
Cat	8 (2.8)
Monkey	2 (0.7)
Circumstance of bite	
Provoked	79 (27.3)
unprovoked	210 (72.7)
Type of wound	
Abrasion	129 (44.6)
Laceration	56 (19.4)
Puncture	49 (17.0)
Multiple types	55 (19.0)
Site of exposure	
Head & neck	35 (12.1)
Trunk	12 (4.2)
Upper limb	102 (35.3)
Lower limb	122 (42.2)
Genitals	2 (0.7)
Multiple sites	16 (5.5)

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Table 3. Details of rabies immune biologics (n=289)

Variables	Frequency (%)
Type of anti-rabies antibodies	
HRIG	10 (3.5)
Single RmAb	194 (67.1)
Cocktail RmAb	56 (19.4)
ERIG	29 (10.0)
Type of ARV	
PVRV	188 (65.1)
PCECV	101 (34.9)
Site of infiltration	
Local	268 (92.7)
Local & systemic	21 (7.3)
Type of adverse drug event	
Pain	38 (13.1)
Erythema	22 (7.6)
Itching	18 (6.2)
Swelling	17 (5.9)
Bodyache	15 (5.2)
Fever	10 (3.5)
Malaise	5 (1.7)

HRIG, human rabies immunoglobulin; RmAb, rabies monoclonal antibody; ERIG, equine rabies immunoglobulin; ARV, anti-rabies vaccine; PVRV, purified Vero cell rabies vaccine; PCECV, purified chick embryo cell vaccine.

Adverse reactions to RIG were relatively uncommon but did manifest in some patients. The most frequently reported reactions included local pain in 13.1%, erythema in 7.6%, and itching in 6.2% (**Table 3**).

The association tables reveal that while AE occurrence varies by age group, vaccine type, reaction type, and area, the differences are not statistically significant. Specifically, 45.3% of PVRV recipients and 39.2% of PCECV recipients reported AEs. Those with both local and systemic reactions reported slightly more AEs (44.4%) than those with only local reactions (43.2%). In terms of area, 45.8% from urban and 35.6% from rural reported events (**Table 4**).

DISCUSSION

Rabies remains a significant global health concern, particularly affecting vulnerable populations such as children. PEP is crucial in managing potential rabies exposure in pediatric cases, which present unique challenges. This study, conducted at KIMS Hospital and Research Centre, Bangalore, provides insights into the management of category III animal exposures in an urban Indian context, emphasizing trends in demographics, exposure characteristics, and PEP outcomes.

The age distribution observed in our study, with preschool (3 to 6 years) and school-aged children (6 to 12 years) constituting the majority of cases, is consistent with findings from Hobart-Porter et al. [7], who noted that a large proportion of pediatric rabies exposures occur in younger children due to increased curiosity and reduced awareness of the risks posed by animals.

Pediatric populations face unique challenges compared to adults, including lower awareness of animal behavior and a higher risk of severe bite sites, such as the face or head. These differences highlight the need for rapid and tailored PEP interventions for children, highlighting the importance of targeted public health strategies for pediatric rabies prevention.

Our study showed a significant representation from middle-class families (68%), consistent with the Lublin province

Table 4. Characteristics of study participants and associated AEs

AEs	Present	Absent	χ^2	df	p-value
Age group			2.733	4	0.603
Infant (1 month to 1 year)	1	0			
Toddler (1 to 3 years)	9	17			
Preschool (3 to 6 years)	26	33			
School age child (6 to 12 years)	57	67			
Adolescent (12 to 18 years)	32	47			
Type of vaccine			0.0064	1	0.93
PVRV	24	164			
PCECV	14	87			
Site of infiltration			-	-	-
Local	117	154			
Both local & systemic	8	10			
Area			1.92	1	0.166
Rural	26	47			
Urban	99	117			

AE, adverse event; df, degrees of freedom; PVRV, purified Vero cell rabies vaccine; PCECV, purified chick embryo cell vaccine.

study in Poland and the National Institute of Epidemiology Rabies Survey, both of which noted higher reporting rates among middle and upper-middle classes due to better healthcare access [14,15].

A slight male predominance (71%) was noted in our study, which aligns with findings from Ngugi et al. [16] in Kenya and Krzowska-Firych et al. [14] in Poland, both of whom reported a higher incidence of animal bites among male children. This may be attributed to the increased likelihood of boys engaging in outdoor play and activities that put them at higher risk for animal interactions. Ngugi et al. [16] further emphasized that male children were more likely to sustain severe bites, such as those to the head or face, necessitating prompt and comprehensive PEP.

Our study found that the predominant biting animal was the stray dog (48.8%), followed closely by pet dogs (47.8%). These findings are comparable to those reported by Ngugi et al. [16], where free-roaming dogs were responsible for the majority of bites. Furthermore, Thangaraj et al. [15] and Reddy et al. [17] emphasized the need for robust stray dog control measures, such as vaccination and neutering programs, to mitigate rabies risk. In a study on the molecular epidemiology of rabies virus, Reddy et al. [17] found that the majority of rabies cases were associated with stray dogs, underscoring the importance of effective population control to reduce the risk of rabies transmission.

Regarding PEP administration, our study showed that the single RmAb was used in 67% of cases, while HRIG was used in 3%. Similar trends were observed in studies by Ravish et al. [18], who demonstrated the safety and efficacy of RmAb for PEP across different age groups, including pediatric patients. Additionally, Hobart-Porter et al. [7] found HRIG to be safe in pediatric populations, with no serious AEs recorded, which supports its use despite its higher cost and limited availability in many regions. The use of mAbs is increasingly seen as a practical and effective alternative to HRIG, particularly in resource-constrained settings where affordability and availability are critical factors.

Our study reported adverse reactions such as pain at the injection site (13.1%) and erythema (7.6%), which were comparable to other studies. For instance, Ravish et al. [19] reported an AE rate of 11.4%, with most reactions being mild and self-limiting. The findings from Hobart-Porter et al. [7] similarly indicated that the AEs following HRIG and PEP administration were generally mild and manageable. Additionally, in a study from Kenya, Ngugi et al. [16] found that the adverse effects associated with PEP were well-tolerated, further supporting the safety of rabies biologics in pediatric patients.

A recent study conducted by Haradanahalli et al. [20], evaluated the safety and immunogenicity of the 4-dose Essen intramuscular regimen for rabies PEP. Their findings indicated that both the 4- and 5-dose regimens were effective in inducing protective antibody titers, with no significant difference in the incidence of AEs. This aligns with our observations, where the use of RmAbs and HRIG in combination with vaccines effectively prevented rabies in all pediatric patients. The study by Haradanahalli et al. [20] supports the potential for reduced-dose regimens to achieve comparable protection while increasing compliance and reducing the cost of PEP administration, especially in resource-limited settings.

A comparison with the post-marketing surveillance (PMS) study of TwinRab™, the novel cocktail of RmAbs, further emphasizes the efficacy and safety of mAb for PEP [21]. The PMS study conducted at Byramjee Jeejeebhoy Government Medical College in Pune demonstrated the favorable safety and efficacy of TwinRab™, supporting the effectiveness of mAb-based PEP. Similar findings were reported in a post-marketing surveillance study of TwinRab™, which demonstrated a favorable safety and efficacy profile for mAbs, aligning well with our results.

The comparison with the PMS study also highlights the growing trend towards mAbs as a preferred alternative to traditional RIGs. TwinRab™ demonstrated several advantages, including reduced risk of hypersensitivity reactions, easier production scalability, and favorable tolerability among patients and healthcare providers [21]. In our study, the use of RmAb instead of HRIG in most cases reflects a similar shift towards mAb therapy, which is endorsed by the WHO due to its standardized quality and lower risk of AEs.[22]

These findings contribute to the WHO's 'Zero by 30' initiative, which aims to eliminate human deaths due to dog-mediated rabies by 2030. By demonstrating the real-world safety and efficacy of mAbs as an alternative to traditional immunoglobulins, our study supports the WHO's vision of making effective PEP accessible in resource-constrained settings. This alignment with WHO's global mission highlights the relevance of our study in contributing to the goal of eliminating rabies as a public health threat.

While several studies, such as Tambe et al. [21], and Hobart-Porter et al. [7], have evaluated PEP efficacy in different contexts, our study adds value by specifically focusing on a diverse pediatric population in an urban Indian setting. The use of RmAbs as a predominant PEP method, particularly the practical use of TwinRab™ in real-world scenarios, contributes to understanding the evolving approach towards more accessible and scalable prophylaxis solutions in rabies management.

Unlike previous controlled trials, this single-center, real-world study captures the challenges faced in routine

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healthcare settings, providing practical insights into the management of pediatric category III animal exposures in an urban Indian context. These findings highlight the real-world effectiveness of PEP protocols, emphasizing barriers and facilitators that healthcare practitioners may encounter in typical clinical environments. This focus on implementation under real-world conditions sets our work apart, making it a valuable addition to the body of knowledge on rabies management in pediatric patients.

While our study provides valuable insights into the safety and clinical efficacy of rabies biologicals in a pediatric population, it is important to acknowledge certain limitations. One of the key limitations of our study is the absence of confirmation of rabies infection in the patients or the animals involved in these incidents. Due to ethical considerations and standard clinical protocols, PEP was administered immediately without waiting for confirmation of rabies infection. This makes it challenging to determine whether the absence of rabies cases in the participants was due to the efficacy of the intervention or simply the absence of rabies infection. Future studies might include comparisons with regional data on rabies cases following non-PEP treatment to better ascertain the clinical efficacy of the prophylaxis used.

In conclusion, this study provides an important snapshot of the current scenario of category III animal exposures in pediatric patients in Bangalore. The findings underscore the necessity of targeted public health interventions, such as increasing awareness among children and communities regarding animal interactions, effective stray animal control, and ensuring timely PEP administration. Comparative analysis with similar studies reveals that our findings are consistent with global trends, contributing valuable evidence to the ongoing efforts to eliminate rabies as a public health threat. The results also highlight the importance of improving healthcare accessibility, particularly for vulnerable populations, to achieve the goal of eliminating dog-mediated rabies by 2030.

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No potential conflict of interest relevant to this article was reported.

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