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Immunogenic response in obese patients undergoing rabies post-exposure prophylaxis with combined equine rabies immunoglobulin and rabies vaccination

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ABSTRACT

Background: Obesity is a risk factor for increased morbidity and mortality associated with many vaccine preventable infectious diseases such as influenza. Moreover, higher volume of passive rabies immunoglobulin (RIG) due to weight based dosing might suppress vaccine-induced immune responses in obese patients. This study aimed to evaluate the effect of obesity on humoral immune responses to combined equine RIG and rabies vaccine treatment among patients with WHO category III exposure to a rabies suspected animal.

Methods: A single centre, prospective, open-labelled study among WHO category III rabies exposed patients was conducted to compare serum rabies virus neutralizing antibody (RVNA) responses measured by rapid fluorescent focus inhibition test between obese (body mass index, BMI > 30 kg/m^2) and control (BMI < 25 kg/m^2) patients after combined immunization with equine rabies immunoglobulin and purified chick-embryo cell rabies vaccine for post exposure prophylaxis treatment.

Results: Post-vaccination geometric mean titer (GMT) of RVNA concentrations between two groups at day 7 were 0.33 (95% CI: 0.23, 0.46) *vs* 0.39 (95% CI: 0.27, 0.55), 4.61 (95% CI: 3.20, 6.63) *vs* 3.78 (95% CI: 2.77, 5.16) at day 14, and 7.45 (95% CI: 5.86, 9.49) *vs* 5.93 (95%CI: 4.46–7.90) at day 28 for obese and control patients, respectively. There was no statistically significant difference of RVNA GMT between two groups. Seroconversion to at least adequate concentration (RVNA titer ≥0.5 IU/mL) rates were 34% at day 7 and 100% at days 14 and 28 in both groups. There were no immediate hypersensitivity reaction and no serious adverse events observed during the study period.

Conclusions: There was no evidence of immunosuppression of antibodies' responses in obese patients. Combined ERIG and rabies virus vaccination for post exposure treatment is safe.

1. Introduction

Human rabies is a lethal infection caused by rabies virus which belongs to the family *Rhabdoviridae*, Genus *Lyssavirus*. Rabies virus transmits through the saliva of an infected animal by biting or scratching. Virus may replicate in the wound tissue before entering the nerve ending. Once inside the neuron, the virus spreads to the central nervous system by passive retrograde axonal transport and trans-synaptic movement, which results in fatal encephalomyelitis [1]. Each year, an estimated 59,000 people die from rabies and about 29 million receive post-exposure prophylaxis (PEP) after close contact with a suspected animal [2]. Post exposure prophylaxis for rabies consists of a combination of passive (human or equine rabies immune globulins) and active immunization (rabies vaccine) soon after exposure. Anti-rabies immunoglobulin therapy and thorough wound cleansing is the first line of defence against the virus, followed by the vaccine induced antibodies developed between day 7 and day 14 after immunization. World Health Organization (WHO) recommends the use of PEP in patients with Category III exposures [1,3].

Obesity is a growing health concern in many countries [4]. In addition to co-morbidities such as cardiovascular diseases and diabetes, obesity itself is an immunosuppressive condition. For example, obesity has been recognized as an independent risk factor

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for increased morbidity and mortality associated with many vaccine preventable infectious diseases such as influenza [5,6], and obesity impairs immune response through altered T cell activation and function [7]. The dosing of rabies immunoglobulin (RIG) administration is based on patient weight. Therefore, compared with normal or weight healthy patients, obese patients will receive higher total units of immunoglobulin. No studies have examined how obesity may affect the response to combined RIG and rabies vaccination in humans. Therefore, this study aimed to evaluate the effect of obesity on humoral immune responses to equine RIG and rabies vaccine among patients with WHO category III exposure to rabies suspected animals.

2. Methods

This was a single centre, prospective, open-labelled study of immune responses to rabies PEP, using a combination of equine rabies immunoglobulin (ERIG) and purified chick-embryo cell (PCEC) rabies vaccine among patients with WHO category III rabies exposure at Siriraj Hospital, Bangkok, Thailand (ClinicalTrials.gov ID: NCT03093545).

2.1. Participants

Male or female patients at least 18 years old who experienced WHO category III rabies exposure, with either BMI > 30 kg/m^2 or BMI less than 25 kg/m^2 were invited to participate in this study. All of them gave written informed consent prior to initiation of the study procedures. WHO has defined the category III of rabies exposure as single or multiple transdermal bites or scratches, licks on broken skin, contamination of mucous membrane with saliva from licks and exposure with rabid animal [1]. Patients who had eye(s) or eye lid(s) wound; had a known hypersensitivity to ERIG or its excipients; had participated in other studies or participated in other investigational drug studies; was concurrently using other investigational drugs within 4 weeks, or five times the half-life of the investigational drug; was currently pregnant or breast feeding, was receiving rabies vaccination more than 7 days for this exposure; had any history of complete pre-exposure or post-exposure regimen with at least 3 doses (including known detectable rabies virus neutralizing antibodies (RVNA) titer of more than 0.50 IU/ml); known allergy to egg or poultry meat; had any history of previous exposure to equine sera (such as anti-tetanus, snake anti-sera, ERIG, and diphtheria); had any significant illness that might harm or increase the risk to the patients; had any history of drug abuse or alcoholism; or unable to comply with the study procedures were excluded from the study.

After informed consent, skin allergy test to ERIG (VINRAB®, VINS BioProducts Limited, India) was performed using intradermal injection of 0.02 mL of 1:100 dilution of ERIG 1000 IU at a lower forearm with an equivalent intradermal injection of normal saline at the opposite forearm as a control. After 15 min of injection, the test was considered positive if >10 mm diameter of wheal with surrounding flare was seen while the control was negative, or if the control showed a small dermal reaction, but the test site showed a definite larger area of reaction than the control. The subjects who had positive skin test were excluded. All females received urine pregnancy testing, and patients with positive pregnancy test were also excluded from the study. The patients were then classified into two groups, obese (BMI > 30 kg/m^2) or control group (BMI < 25 kg/m^2).

2.2. Ethics

The study was approved by Siriraj Institutional Review Board (IRB) and conducted in compliance with the Declaration of Helsinki and ICH guidelines for good clinical practice (GCP) and the IRB regulations regarding ethical review, informed consent, and protection of rights and welfare of human subjects participating in biomedical research.

2.3. Interventions

After enrolment, 40 international units (IU) per kilogram body weight of ERIG were administered around the wound site as much as possible. The remainder were administered intramuscularly (into gluteal region). Immediate adverse events were closely observed for 1 h after ERIG administration. Five doses of 1 mL of PCEC rabies vaccine (Rabipur®, Chiron Behring Vaccines Pvt. Ltd., India) were administered into the deltoid muscle on the opposite body site of ERIG injection site; first dose simultaneously with ERIG administration, day 3, day 7, day 14 and day 28 afterwards. Adverse events were closely observed and recorded for 30 min after each PCEC rabies vaccine injection. Adverse events were also monitored and collected by phone call on day 1 and day 60. Standard vigorous local wound care was performed in all patients. The patient received other supportive treatments such as anti-tetanus, and antimicrobial treatment at the discretion of the patient's doctor.

2.4. Outcome measurement

Serum RVNA responses at baseline, day 7, day 14, and day 28 after PEP initiation were compared between the two study groups. RVNA antibody concentration was measured by rapid fluorescent focus inhibition test (RFFIT) at the National Reference Diagnosis Laboratory, Department of Medical Sciences, Ministry of Public Health, Thailand. The 2nd International Standard for anti-rabies immunoglobulin, human, Code: RAI, NIBSC, UK was used to express the RVNA concentration in IU/ml.

Adverse events were monitored after ERIG and first dose of rabies vaccine injection, on day 7, day 14, day 28, and until day 60. The events assessed by the investigators to be related to study vaccination (ERIG or PCEC) were referred to as adverse reactions (AR). All other events not assessed by the investigators to be related to study vaccination (ERIG or PCEC) were referred to as adverse events (AE). Local (or localized) AR/AE was defined as an AR/AE restricted or limited to a specific body part or region such as pain, swelling, and/or erythema at the site of study vaccine injection. Systemic AR/AE was defined as an AR/AE related to a system, or affecting the entire body or an entire organism such as fever, malaise, muscle pain, headache, and sepsis. The relationships to study vaccine were assessed by study investigators. The severity for AE/AR included mild, moderate, severe, and life-threatening scored according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

2.5. Sample size calculation

The data from a previous study reported that RVNA geometric mean concentration (GMT) at day 7 from 11 vaccinees receiving six doses of PCEC on days 0, 3, 7, 14, 28 and 90 plus human rabies immune globulin (HRIG) on day 0 was 0.18 (95%CI: 0.15–0.22) IU/ml [8]. Using G*Power version 3.0.10 of Institute for Digital Research and Education (IDRE), UCLA, USA with expected RVNA concentration of 0.18 in healthy weight patients or control and 0.135 IU/ml in obese patients, respectively (maximum acceptable decrease of RVNA concentration in obese patients was 25% reduction from the concentration in control), an alpha risk of 5% (one-sided hypothesis), a power of at least 80%, standard deviation (SD) of 0.0673 (SD = $(0.04 \times \sqrt{11}/1.96)$, where 0.04 was from the