Letter to the Editor

The Adverse Effect of the 2-1-1 Regimen for Rabies PEP in Preschool Children*

LIU Shu Qing[1], TAO Xiao Yan[1], YU Peng Cheng[1], JIN Chun Qiu[2], YU Hong Jie[3], CHEN Mei Shun[2,#], and ZHU Wu Yang[1,#]

Post-exposure prophylaxis (PEP) has proved to be the most important measure for rabies prevention and control. There is little information regarding adverse reactions to the Essen and 2-1-1 regimens in preschool children (aged 0-6). We reexamined the outcomes of 1,109 preschool children who were vaccinated using SPEEDA under the Essen regimen between January 2011 and December 2012 and 1,267 preschool children under the 2-1-1 regimen between January 2013 and December 2014. We find that, in preschool children, the febrile reaction after the first 2-dose injection in the 2-1-1 regimen was significantly higher than that induced by the first 1-dose in the Essen procedure. Thus, we recommend that the Essen regimen should still be used for rabies PEP in preschool children.

Key words: 2-1-1 regimen; Essen regimen; PEP; Preschool children

Rabies remains a serious public health problem worldwide with high mortality, leading to almost 55,000 deaths per year with Asia accounting for approximately 80% of the worldwide total[1]. China has the second highest rate of human rabies in Asia, which was among the top three causes of human death due to infectious diseases in the country. Although rabies vaccines are widely used, human rabies cases remain high in recent years[2]. Immunizations of animals with rabies virus vaccines and post-exposure prophylaxis (PEP) have proved to be the most important measures for rabies prevention and control. Appropriate PEP with reliable vaccines and a scientific regimen is thought to be most important measure to ensure patient survival in humans. In 2007, China CDC published treatment guidelines for rabies PEP of humans based on the WHO criteria. Appropriate wound care consisting of immediate and thorough washing of the wound for at least 15 min using soap and water and rabies vaccine administration are needed for category II and III contacts. The intramuscular PEP recommended by the World Health Organization comprises the Essen 5-dose regimen or the Zagreb 4-dose regimen (2-1-1 regimen)[3]. The 2-1-1 regimen has been used in other countries for many years[4-5]. The traditional Essen regimen has been formally approved and recommended in China since 1980 while the purified Vero cell rabies vaccine (SPEEDA, manufactured by Cheng Da Co., Ltd.) has been ratified by the Chinese State Food and Drug Administration using the 2-1-1 regimen in 2010. Previous studies showed that the 2-1-1 and Essen 5-dose regimens were equally safe and immunogenic. There was no significant difference between the rates of adverse reactions with the two regimens[6-7]. However, previous research mainly compared the outcomes of the two regimens in all individuals given PEP while rare studies reported adverse reactions to the Essen and 2-1-1 regimens in preschool children (aged 0-6).

Hu et al. reported that most patients with fever were aged below 5 years both in the Zagreb and Essen groups (12/15 and 8/12 for Zagreb and Essen respectively). Zagreb showed more side effects (induration, edema, tenderness, erythema) in < 5-y-old patients, especially after the first immunization[8]. To compare adverse reactions to the Essen and 2-1-1 regimens in preschool children,

doi: 10.3967/bes2017.048

*This work was supported by the China Mega-Project for Infectious Disease (2014ZX10004002-004-001); National Natural Science Foundation of China (31500152); National Key Technology R&D Program (2014BAI13B04); and National program on key research project of china (2016YFD0500400).

1. Key Laboratory of Medical Virology, Ministry of Health, National Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing 102206, China; 2. Wenling Center for Disease Control and Prevention, Wenling 317500, Zhejiang, China; 3. Division of Infectious Diseases, Key Laboratory of Surveillance and Early-warning on Infectious Disease, Chinese Center for Disease Control and Prevention, Beijing 102206, China

we reexamined the outcomes of 1,109 preschool children who visited the clinic of Wenling Centers for Disease Prevention and Control with WHO category II exposure to rabies within 24 h and vaccinated using SPEEDA under the Essen regimen between January 2011 and December 2012 and 1,267 preschool children under the 2-1-1 regimen between January 2013 and December 2014. The focus of this study was only on the adverse effect of the PEP given that PEP is aimed at saving lives. Children were excluded if they had been previously vaccinated with rabies or if presented with other clinical diseases. In addition, a face-to-face survey was also performed to collect the demographic and clinical information. Clinical symptoms were observed for 30 min after each vaccination and a telephone visit was conducted at 24 h, 48 h, and 72 h post-immunization to record any adverse reactions. Clinical data were defined according to the 'Preventive vaccine clinical trials, adverse events grading guidelines' issued by the China Food and Drug Administration. Statistical analysis was performed using the chi-squared test using the SPSS16.0 software. No patient was injected with immunoglobulin and no patient developed clinical rabies during the study period.

Preschool children in both the 2-1-1 and the Essen groups presented systemic and local symptoms, fever being the most common symptom. Among the children given the Essen regimen, 46 had adverse reactions, a reaction rate of 4.15%. 43 children had body temperatures of less than 38.5 °C and 2 children greater than 38.5 °C. One child over 40 had local swelling in the injected sites. All the adverse reactions occurred on the day after the first 1-dose. Of the 1,267 preschool children who received the 2-1-1 regimen, 142 had adverse reactions, a reaction rate of 11.21%. 122 children had body temperatures under 38.5 °C and 18 children above 38.5 °C. 2 children had local swelling in the injected sites, all of whom developed fever and local swelling on the day following the first 2-dose. The adverse reaction rate differed significantly between the two regimens ($\chi^2 = 32.70$, $P < 0.005$). Several preschool children developed local symptoms after immunization including pain, local swelling, pruritus, induration, and erythema but were not significant between the two regimens. Although no significant differences between the 2 groups were found for all side effects, the 2-1-1 regimen showed more adverse reactions, especially after the first 2-dose immunization. All children with fever recovered and other local symptoms regressed spontaneously within 48-72 h without treatment. The severity of all adverse effects belonged to class I and II according to the 'Preventive vaccine clinical trials, adverse events grading guidelines' issued by the China Food and Drug Administration.

Compared with the Essen regimen, the advantages of the 2-1-1 regimen include 1 less dose of the rabies vaccine, 2 fewer treatments, and the earlier seroconversion[6-9]. To our knowledge, there are rare reports comparing the adverse reaction rates for the Essen and 2-1-1 regimens in preschool children. Thus, we reexamined the outcomes of 1,109 preschool children using the Essen regimen between January 2011 and December 2012, and 1,267 preschool children under the 2-1-1 regimen between January 2013 and December 2014. In preschool children, the fever reaction after the first 2-dose immunization in the 2-1-1 regimen was significantly higher than that induced by the first 1-dose in the Essen procedure, perhaps because of the low immune tolerance, high metabolic rate, and poor temperature regulation of preschool-aged children.

Considering its lesser effect on study, work, and economic factors, the lower incidence of fever, reduced anxiety for parents and increased safety of the rabies vaccine, we recommend that the Essen regimen should still be used for rabies PEP in preschool children.

We wish to express our gratitude to all medical staff from Wenling Center for Disease Control and Prevention for their assistance in the collection of the demographic and clinical information.

Competing Interests Authors have no competing interests.

Ethical Approval The protocol of this study was approved by the Institutional Review Board of Wenling Centers for Disease Prevention and Control and written informed consent was obtained from all participants, or their parents or legal guardians in the case of children up to 18 years of age. All the materials and methods used in this study were approved by the Chinese State Food and Drug Administration (Approval No: 2008B0914, 2010B00516, 2008S00001) and have been used in many countries in the world, including in China[3]. Thus no clinical trial registration is needed for this study. In addition, we performed a clinical observation, not a clinical trial, to collect the clinical data, which won't affect the vaccination policy for SPEEDA and 2 regimens in China, but provides a reference for the clinical doctors and patients when choosing a regimen. The severity of all adverse

effects belonged to class I and II according to the 'Preventive vaccine clinical trials, adverse events grading guidelines' issued by the China Food and Drug Administration.

#Correspondence should be addressed to ZHU Wu Yang, Tel: 86-10-58900895, E-mail: zhuwuyang1971@sina.com; CHEN Mei Shun, Tel: 13906865445, E-mail: 13906865445@163.com

Biographical note of the first author: LIU Shu Qing, female, born in 1986, PHD, Research Assistant, majoring in pathogen biology.

Recepted: December 2, 2016;
Accepted: April 25, 2017

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