BRIEF REPORT

A 4-Site, Single-Visit Intradermal Postexposure Prophylaxis Regimen for Previously Vaccinated Patients: Experiences with >5000 Patients

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We previously demonstrated that 4-site, intradermal, single-visit rabies booster vaccination provides immunogenicity greater than that provided by the standard 2-booster, 2-visit regimen. The regimen has been routinely used in 5116 patients since 1998 without any treatment failure. It is not only effective but also saves vaccine costs and transportation expenses and improves compliance.

Rabies is again increasing in prevalence in parts of Asia and Africa. More than 10 million people require post-exposure prophylaxis (PEP) annually worldwide [1]. Individuals with previous rabies vaccination do not need rabies immune globulin (RIG), a biological product which is often not accessible, when re-exposure occurs. Only 2 booster vaccinations with cell-culture vaccine on days 0 and day 3, administered either intramuscularly or at a reduced dose intradermally (ID), are recommended by the World Health Organization (WHO) [1, 2]. This is effective and has been proven to induce an anamnestic (accelerated) immune response [3–5]. However, it requires 2 clinic visits and is inconvenient for many rural residents in developing countries, who often have to travel considerable distances and thereby lose working time and incur transportation expenses that they can ill afford. Moreover, for tourists, travel schedules may have to be changed if they have to come back to receive a second booster vaccination 3 days after administration of the first dose. Furthermore, we experienced a drop-out rate of 3%–5% for the day 3 booster injection among our patients (unpublished data from Queen Saovabha Memorial Institute [QSMI] in Bangkok Thailand). To our knowledge, no human deaths from rabies have been reported among patients who received booster vaccination after earlier rabies vaccination.

Data from published studies indicate that a single booster vaccination with a cell-culture rabies vaccine elicits an adequate immune response in previously vaccinated patients [6–8]. Tantawichien et al [9] were the first to demonstrate that the 4-site ID booster regimen, given at both deltoids and thighs with 0.1 mL of purified vero-cell rabies vaccine (PVRV) administered on day 0 and requiring only 1 clinic visit, could induce significantly higher titers of rabies neutralizing antibody (NAb) and a more rapid immune response than the standard 2-booster intramuscular regimen administered on days 0 and 3. All subjects in the study received pre-exposure rabies vaccination 1 year earlier, had an anamnestic immune response after receiving the 4-site ID boosters, and all could maintain an NAb level above the WHO minimum level of 0.5 IU/mL [1] from day 14 through day 360 [9]. A later study confirmed the immunogenicity of the 4-site ID booster, which could induce NAb above the level of 0.5 IU/mL for up to 1 year in subjects who had previously received pre- or postexposure vaccination up to 10 years earlier [10]. The 4-site ID booster was also shown to induce an anamnestic response in previously vaccinated patients when used with purified chick embryo cell vaccine (PCECV) [10, 11] and human diploid cell vaccine (HDCV) [11].

The animal bite clinic at QSMI has been the principle rabies research, rabies control, and animal bite treatment center for the central region of Thailand. On the basis of cumulative data, since 1998, the Scientific Committee of QSMI has recommended 3 booster regimens for previously vaccinated individuals: the single-visit 4-site ID booster regimen on day 0, or the WHO-recommended 2-booster regimen on days 0 and 3 administered either intramuscularly (IM) or ID. Since then, the majority of previously vaccinated patients who had re-exposure received the 4-site ID booster regimen (58%) as PEP. The remaining individuals received the 2-visit ID booster regimen (24%) or the 2-visit IM booster regimen (18%). Focusing on the patients who were bitten by animals with laboratory-proven rabies that was confirmed by positive fluorescent antibody testing (FAT) results, most (67%) received the 4-site ID booster

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regimen. Eighteen percent received the standard IM booster regimen, and 15% received the standard ID booster regimen. We performed a retrospective study involving all patients who received the 4-site ID booster during the period 1998–2008.

Patients, materials, and methods. The out-patient records were reviewed for the period from 1998 through 2008 at QSMI, and we identified 5116 patients who received the 4-site booster vaccinations. The single-visit 4-site ID booster vaccination consists of 0.1-mL ID injections, one each at both deltoids and thighs, using PVRV or PCECV. Patients are given the option of either conventional 2-booster vaccination (ID or IM) or the single-visit 4-site ID booster vaccination.

Results. A total of 5116 previously vaccinated patients who had proven or possible exposure to rabies virus were given a single-visit, 4-site ID booster vaccination using PVRV or PCECV. There were 2453 male patients (48.1%). The risk of rabies exposure was classified using WHO categories, and 3335 patients (65.2%) had WHO category III risk (severe transdermal exposures). The median age of patients was 39 years (range, 2–83 years; interquartile range [IQR], 24–54 years). There were 9 and 214 patients who had ages of <2 years and <10 years, respectively. Most of the patients (83.3%) had received a full series of post-exposure prophylaxis (PEP) treatment previously, and the remaining patients had received prior pre-exposure vaccination. The median time since primary vaccination was 6 years (range, 1 month through 25 years; IQR, 3–10 years). Most of the biting animals were stray animals and were not available for observation or necropsy. However, 253 (4.95%) of the 5116 patients were bitten by animals with proven rabies that had positive necropsy findings and FAT results.

Discussions. The single-visit, 4-site ID booster vaccination, which consists of 4 injections of 0.1 mL each on each arm and thigh, has been shown to induce an anamnestic response superior to that induced by the IM regimen on day 0 and day 3. Moreover, the Nab response associated with the 4-site ID booster regimen appeared more rapidly, and it was also shown to be consistently high 1 year after the booster vaccination [9]. We previously reported our experience with using the 4-site ID booster regimen in a group of 1871 patients after it was approved by our scientific committee [10]. The 4-site ID booster regimen has now been used for more than a decade in >5000 patients. We prefer the 4-site method, particularly for patients who have incurred severe or multiple bites in high risk areas (eg, the face, hand, and fingers), because it provides more immunogenicity and more-rapid Nab response than does the standard regimen. However, in treating small children, the standard 2-visit booster regimen is more practical for our nurses, because it is less painful and is easier to administer to children (requiring administration at only 1 site per visit).

Rabies is a notifiable disease in Thailand. Surveillance of rabies in humans in Thailand has been intensified since 2000, when molecular diagnosis was introduced in both ante- and postmortem diagnosis [12]. There are 2 diagnostic centers for rabies in humans, one at the Ministry of Public Health (MOPH) and another at Chulalongkorn University. Patients with encephalitis, especially those with suspected rabies, a history of animal bite, and/or a history of receiving rabies PEP, must be reported to the Division of Disease Control, MOPH, and specimens collected during life and/or necropsy specimens must be submitted to a diagnostic center. In our study, as many as 253 individuals were bitten by animals with proven rabies and received the 4-site ID booster as PEP. There were no reports of human rabies deaths among patients in our series.

The 4-site ID booster regimen is not only effective against rabies but is also more convenient for the patients. It can be used safely in small children. Several studies have confirmed the WHO recommendations that tissue culture rabies vaccines elicit long-lasting immunity [4, 5, 13]. The longest period between the primary vaccination and exposure in our study was 25 years. The 4-site booster regimen can save 60%–80% of vaccine volume, when compared with the 2-dose intramuscular regimen. Although the vaccine costs associated with the 4-site ID booster (which requires 0.4 mL of vaccine) are double that of the conventional 2-dose ID regimen (which requires only 0.2 mL), the 4-site ID booster regimen induces a higher Nab titer and may reduce total PEP costs, because it can reduce the amount of lost work time and reduce transportation expenses. Furthermore, it reduces patient noncompliance. This may be a great advantage for all patients, but especially for those who are living in rural regions and for international travelers with time constraints.

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