What are the consequences of having frequent rabies booster vaccinations?

Kanitta Suwansrinon, Maneerat Benjavongkulchai

Background: Physicians, laboratory scientists, veterinarians and public health officers who have had several potential rabies exposures, are given repeated booster injections often over years. We have experienced that these groups occasionally have a decline in Rabies Neutralizing antibodies (NAbs) when given frequent booster injections.

Objective: We compared the dynamics of NAb titers between volunteers following primary vaccination and volunteers who had received repeated booster injections after primary vaccination.

Method: We studied subjects who had a previous post-exposure rabies vaccine series and then received an intradermal booster on days 0 and 3.

Results: Subjects who had only the primary series and no prior boosters had higher geometric mean NAb titers than those who had received one or more prior boosters.

Conclusion: We present hypotheses for this phenomenon and recommend further studies to elucidate mechanisms that might have clinical implications.

Keywords: Booster vaccine injections, immune tolerance, rabies vaccination.

Physicians in canine rabies endemic countries often encounter patients who have had repeated rabies exposures and received several booster injections over months and years. Laboratory scientists, veterinarians, and public health officers are potentially exposed to rabies and are also a group that is given frequent rabies vaccine boosters. We also have experience with our regular volunteers, who donate serum for human rabies immunoglobulin production and have a decrease in their Rabies Neutralizing antibodies (NAbs) when given many booster injections. A similar unpublished observation came from our horse farm that is used to produce equine rabies immunoglobulin. The overall antibody titers of collected blood declined over time where the horses had received regular boosters and were used as serum donors [P. Khawplod, unpublished data]. This led us to wonder “how many boosters are either enough or too many”. A recent study has shown that WHO-approved pre-and post-exposure intramuscular or intradermal regimens (PREP and PEP) result in long-lasting memory cells. A normal host, given 2 booster injections after many years following primary vaccinations, will still respond with an accelerated neutralizing antibody rise and does not require either the administration of immunoglobulin or repeated doses of rabies vaccination [1, 3]. We raised the conjecture that: “Multiple boosters may be unnecessary or perhaps even result in lower NAbs?” This preliminary study was carried out to elucidate this issue and to indicate a direction for further inquiries.

Material and method

Serologic data on volunteers from the previously reported “Rabies Vaccine Call-back Project” [1] at the Queen Saovabha Memorial Institute (QSMI), Bangkok were analyzed. A baseline serum sample was then collected from each new volunteer. The volunteers then received one 0.1 mL intradermal injection of Purified Vero cell rabies vaccine (PVRV, Sanofi Pasteur Lyon, France) Lot X-0880-2, potency 9.0 IU/mL (at 5°C) on days 0 and 3. Their immune response was measured by a standard NAb assay.

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response was determined by titration of neutralizing antibody, using the rabies fluorescent focus inhibition test (RFFIT) on days 0, 5, 7 and 14. The geometric mean titer (GMT), expressed in international units per mL with 95% confidence interval, was calculated for each study group for each serum collection time-point. Differences between groups in GMT values were assessed using Student’s T-test. The studies were carried out using the SPSS program at the immunology laboratory of the Queen Saovabha Memorial Institute, Bangkok. All volunteers had received pre- or post-exposure tissue culture rabies vaccines and had provided a precise history of all previous rabies vaccinations. Those who also had received rabies immunoglobulin were eliminated from the study. The 107 remaining volunteers were divided into two groups. The first group had received only primary vaccination; the second group had also received one to four prior booster injections. The time-interval between the previous booster injection(s) and the inclusion in the study was 5-20 years with a mean of 8.79 years. The study was approved by the Ethics Committee of the Thai Red Cross Society.

Results
Statistical analysis of the results showed that there were significant differences in NABs between the two groups on days 0, 5 and 14. As expected, in Group 1 (without prior boosters), their NABs were less than that of Group 2 (with previous boosters) on days 0 and 5 ($p<0.01$). There were no differences statistically, between the two groups on Day 7. Group 1, however, had statistically significantly more NABs than Group 2 on Day 14 ($p<0.05$) (Table 1, Fig. 1). The age range of volunteers was 16-78 years with a mean of 42 years. The male/female sex ratio was 1:2.

Discussion
Neutralizing antibody titers readings after booster rabies vaccinations indicated that patients with lower baseline titers (Group 1) exhibited a robust serologic response but not before Day 14. As the number of subjects was small it was impossible to make any valid conclusions and we are not any closer to an explanation as to why some frequently used human volunteers, or horse serum donors show a decrease in antibody titers over time. One possible mechanism could be the desensitization phenomenon [6]. Immunological tolerance is less likely. These issues deserve further larger and longer studies on both humans and horses. It appears, however, those human and equine serum donors for rabies immunoglobulin should be screened periodically for the gradual reduction of their antibody response over a period of time. The current common practice to screen the pooled sera and booster of each donor blindly at every collection session may have to be either abandoned or modified.

Acknowledgement
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Table 1. The Geometric Mean Titers (GMT) and range of Rabies Neutralizing antibody (NAb) after intradermal boosters (1 site, days 0 and 3) on day 0, 5, 7 and 14 in the volunteers who had only primary vaccination (Group 1) and who had the booster(s) (Group 2).

<table>
<thead>
<tr>
<th>Group</th>
<th>Statistic analysis</th>
<th>Day 0</th>
<th>Day 5</th>
<th>Day 7</th>
<th>Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GMT (IU/mL) range</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 Primary</td>
<td></td>
<td></td>
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<tr>
<td>vaccination only</td>
<td></td>
<td>0.83</td>
<td>1.27</td>
<td>4.46</td>
<td>18.28</td>
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<tr>
<td>(N=78)</td>
<td></td>
<td>0.03-16.71</td>
<td>0.04-30.84</td>
<td>0.48-35.13</td>
<td>3.26-84.08</td>
</tr>
<tr>
<td>Group 2 Booster</td>
<td>GMT (IU/mL) range</td>
<td>3.08</td>
<td>4.37</td>
<td>7.74</td>
<td>14.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.68-11.97</td>
<td>0.77-19.15</td>
<td>2.38-30.84</td>
<td>4.00-42.04</td>
</tr>
</tbody>
</table>

There were too few cases to allow a statistical analysis of the time elapsed between the primary vaccination and the boosters.

Table 1. The Geometric Mean Titers (GMT) and range of Rabies Neutralizing antibody (NAb) after intradermal boosters (1 site, days 0 and 3) on day 0, 5, 7 and 14 in the volunteers who had only primary vaccination (Group 1) and who had the booster(s) (Group 2).
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**Fig. 1** Linear graphs of the responsiveness of Rabies Neutralizing antibody (NAb) titers on day 0, 5, 7 and 14 in groups 1 and 2, respectively, after 1 site intradermal boosters on days 0 and 3. *(Group 1 = had only primary vaccination, Group 2 = had prior booster injection(s)).*

**References**