Order of Vaccine Injection and Infant Pain Response

Moshe Ipp, MBBCh; Patricia C. Parkin, MD; Naomi Lear, MD; Morton Goldbach, MD; Anna Taddio, PhD

Objective: To determine if acute pain response after administration of the diphtheria, polio, and tetanus toxoids and acellular pertussis and Haemophilus influenzae type b (DPTaP-Hib) vaccine and the pneumococcal conjugate vaccine (PCV) is affected by the order in which they are given.

Design: Single-center, double-blind, randomized clinical trial.

Setting: Outpatient pediatric clinic in Toronto, Ontario, Canada.

Participants: Healthy infants 2 to 6 months of age undergoing routine immunization.

Interventions: Infants received either their primary DPTaP-Hib vaccine or the PCV first, followed by the other vaccine.

Main Outcome Measures: The primary outcome was infant pain during vaccine injection as assessed by a validated measure, the Modified Behavioral Pain Scale (MBPS), using videotaped recordings of the procedure. In addition, parents rated pain using a 10-cm visual analog scale (VAS). Crying (yes/no) was also measured.

Results: The study was conducted between July 21, 2006, and June 21, 2007. A total of 120 infants participated: 60 received the DPTaP-Hib vaccine first and 60 received the PCV first. Infant characteristics did not differ between groups. Overall mean (SD) pain scores per infant after receiving both vaccine injections were significantly lower when DPTaP-Hib was administered first compared with when PCV was administered first (MBPS score, 7.6 [1.5] vs 8.2 [1.5], P = .037; parent VAS score, 4.2 [2.3] vs 5.6 [2.6], P = .003). When given first, the DPTaP-Hib vaccine caused significantly less pain (P < .001) than the PCV, as assessed by the MBPS, VAS, and crying.

Conclusions: Pain was reduced when the DPTaP-Hib vaccine was administered before the PCV in infants undergoing routine vaccination. We recommend that the order of vaccine injections be the DPTaP-Hib vaccine followed by the PCV.

Trial Registration: clinicaltrials.gov Identifier: NCT00390130


Vaccine injections are the most common painful iatrogenic procedures performed in childhood. Multiple injections are routinely administered during a single visit to a physician. Because some vaccines cause more pain than others, the order in which they are given may affect the overall pain experience. The objective of this study was to determine if acute pain response after administration of 2 separate vaccines was affected by the order in which they were administered.

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Methods: We conducted a randomized, double-blind study of healthy infants 2 to 6 months of age who were attending a shared pediatric community practice in Toronto, Ontario, Canada, for their routine primary series of vaccinations. We excluded infants with acute febrile illness, chronic medical conditions, and allergy to any of the vaccine components or those concurrently receiving topical local anesthetics. Use of systemic analgesia (eg, ibuprofen, acetaminophen) before the vaccination was recorded and was not an exclusionary factor.

Infants received the diphtheria and tetanus toxoids, polio, acellular pertussis, and Haemophilus influenzae type b conjugate vaccine (DPTaP-Hib) (Pentacel; Sanofi Pasteur, Toronto) and the pneumococcal conjugate vaccine (PCV) (Prevnar; Wyeth, Montreal, Quebec, Canada) at the same physician’s visit. Infants were randomized, using random computer-generated numbers, to receive either the DPTaP-Hib vaccine first or the PCV first immediately followed by the other vaccine. Concealment of randomization allocation was achieved by performing the randomization off site by one of the investigators (P.C.P.) and placing the treatment assignment for each.
Table 1. Characteristics of the DTaP-Hib Vaccine and the PCV

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PCV</th>
<th>DTaP-Hib Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color</td>
<td>Pearly white to off-white</td>
<td>Pearly white to off-white</td>
</tr>
<tr>
<td>pH</td>
<td>5.5–6.5</td>
<td>7.1</td>
</tr>
<tr>
<td>Osmolarity, mOsm/kg³</td>
<td>200–300</td>
<td>300–400</td>
</tr>
<tr>
<td>Active ingredient</td>
<td>7 Saccharides</td>
<td>DTaP-Hib antigens</td>
</tr>
<tr>
<td>Aluminum phosphate adjuvant, mg</td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Other ingredients</td>
<td>Sodium chloride</td>
<td>Formaldehyde (trace), polymixin B</td>
</tr>
</tbody>
</table>

Abbreviations: DTaP-Hib, diphtheria and tetanus toxoids, polio, andacellular pertussis and Haemophilus influenzae type b; PCV, pneumococcal conjugate vaccine.

Data are from personal e-mail communication with Elaine Wang, MD, of Sanofi Pasteur, Toronto, Ontario, Canada, on February 22, 2004, and Joya Hill, BSc, of Wyeth, Montreal, Quebec, Canada, on May 13, 2005.

RESULTS

The study was conducted between July 21, 2006, and June 21, 2007. Of 126 parents of infants approached for participation, 120 infants were eligible and all of the parents agreed to let their children participate. Sixty infants were randomized to receive the DTaP-Hib vaccine first and 60 received the PCV first (Figure). Demographic characteristics did not differ between groups (Table 2). Outcome data were available for all 120 infants using observer MBPS and crying scores and for 119 infants using parent VAS scores.

The primary analysis showed that the overall mean (SD) pain scores per infant following both vaccine in-
Infant pain response during routine intramuscular vaccine injection was affected by the order of administration of the vaccine. Infants given the less painful DPTaP-Hib vaccine first followed by the more painful PCV experienced less pain overall compared with those given the vaccines in the reverse order. In addition, pain increased from the first to the second injection, regardless of the order of vaccine injection.

Our finding of variability in pain from different vaccine formulations is consistent with previous research. The reason for these pain differences is presumed to be related to the physicochemical properties of the vaccine. The 2 vaccines used in this study have several differences (Table 1), including pH, which may account for the pain variability. In addition, our finding of an increase in pain with subsequent injections in infants exposed to repeated painful procedures is consistent with research in infants undergoing repeated heel lance and vaccine injections.

To our knowledge, the effect of varying the order in which vaccines of different degrees of painfulness are given has not previously been examined. Our data suggest that the least painful vaccine should be administered first when 2 vaccines are given at 1 physician’s visit to reduce overall pain. We hypothesize that, in the alternative, giving the more painful injection first focuses the infant’s attention on the procedure and activates central and peripheral mechanisms of pain processing that together result in amplification of the pain signal during subsequent injections administered immediately thereafter.

Minimizing the pain of vaccine injection experienced by infants and children is currently receiving considerable attention by clinicians and pain researchers. Steps to minimize vaccine-related pain reduces the pain experienced by the child and improves the immunization experience of parents and health care workers. This is important because in a recent study of pediatricians in the United States, more than 90% reported at least 1 parental vaccine refusal in the past year, most commonly as a result of pain from multiple vaccines. Reductions in pain therefore have the potential to improve compliance with the vaccination schedule, thereby preventing a resurgence of vaccine-preventable infections. Varying the order of vaccine administration to reduce pain is a strategy that is simple and effective, cost free, and easily incorporated into clinical practice. In considering meth-

### Table 2. Characteristics of the Study Infants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>DPTaP-Hib Vaccine First (n=60)</th>
<th>PCV First (n=60)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), mo</td>
<td>4.4 (1.6)</td>
<td>4.8 (1.7)</td>
<td>.26</td>
</tr>
<tr>
<td>Males</td>
<td>31 (52.0)</td>
<td>28 (47.0)</td>
<td>.58</td>
</tr>
<tr>
<td>First born</td>
<td>33 (55.0)</td>
<td>53 (57.0)</td>
<td>.84</td>
</tr>
<tr>
<td>Infants receiving oral analgesic (eg, acetaminophen)</td>
<td>9 (15.0)</td>
<td>12 (20.0)</td>
<td>.47</td>
</tr>
<tr>
<td>Infants receiving injection from Physician 1 (M.I.)</td>
<td>53 (88.0)</td>
<td>51 (85.0)</td>
<td>.59</td>
</tr>
</tbody>
</table>

Abbreviations: DPTaP-Hib, diphtheria and tetanus toxoids, polio, and acellular pertussis and *Haemophilus influenzae* type b; PCV, pneumococcal conjugate vaccine.

aData are presented as number (percentage) of infants unless otherwise indicated.

Pain was lower after the first injection was significantly lower when the DPTaP-Hib vaccine was administered first compared with when the PCV was administered first (MBPS score, 7.6 [1.5] vs 8.2 [1.5], P = .037; parent VAS score, 4.2 [2.3] vs 5.6 [2.6], P = .003) (Table 3).

Pain after the first injection was significantly lower when the DPTaP-Hib vaccine was administered first compared with when the PCV was administered first as assessed by observer MBPS (P < .001), parent VAS (P < .001), and crying (P < .001) (Table 4). Pain was lower after the second injection for observer MBPS (P = .004) but not for parent VAS (P = .94) or for crying in infants (P = .11) (Table 4). In all infants, pain increased from the first to the second injection (observer MBPS score, 7.3 [2.4] vs 8.6 [1.5], P < .001; parent VAS score, 3.9 [3.0] vs 5.9 [2.7], P < .001).

### Table 3. Mean (SD) Pain Scores After Injection of the DPTaP-Hib and the PCV Vaccines in Infants According to Order of Vaccine Administration

<table>
<thead>
<tr>
<th>Scale</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DPTaP-Hib First (n=60)</td>
</tr>
<tr>
<td>Behavioral Pain Scale</td>
<td>6.3 (2.8)</td>
</tr>
<tr>
<td>Parent (visual analog scale)</td>
<td>2.5 (2.5)</td>
</tr>
<tr>
<td>Crying (yes)</td>
<td>41 (88.3)</td>
</tr>
</tbody>
</table>

Abbreviations: DPTaP-Hib, diphtheria and tetanus toxoids, polio, and acellular pertussis and *Haemophilus influenzae* type b; PCV, pneumococcal conjugate vaccine.

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ods of reducing pain with vaccination, vaccine manufacturers must play a more integral role in attempting to produce vaccine formulations that are less painful.1

In conclusion, pain was reduced when the DPTaP-Hib vaccine was administered before the PCV in infants undergoing routine vaccination. On the basis of these results, we recommend that the order of vaccines be the DPTaP-Hib vaccine followed by the PCV.

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REFERENCES


Growing up is a dialectical process that requires things that one can push against in order to become stronger. It takes limited war against worthy opponents; a child matures by testing himself against limits set by loving adults.

—“On Being an American Parent,” from Time, Dec 13, 1967