Vaccine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

A randomized trial of the effect of vaccine injection speed on acute pain in infants

Anna Taddio [a,b,*], Horace Wong [a], Ben Welkovics [a], Angelo L. Ilersich [a], Mara Cole [c], Morton Goldbach [c], Moshe Ipp [c,d]

[a] Leslie Dan Faculty of Pharmacy, University of Toronto, 144 College Street, Toronto, Ontario M5S 3M2, Canada
[b] Child Health Evaluative Sciences, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada
[c] Paediatric Associates, 90 Warren Road, Suite 103, Toronto, Ontario M4V 2S2, Canada
[d] Department of Paediatrics, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada

ARTICLE INFO

Article history:
Received 3 April 2016
Received in revised form 4 August 2016
Accepted 5 August 2016
Available online xxxx

Keywords:
Pain management
Vaccination
Infant
Speed of injection
Injection technique

ABSTRACT

Objective: This study compared the pain caused from fast vs. slow vaccine injections.
Methods: Infants aged 2–6 months receiving primary immunizations were randomized to fast (2–4 mL/s) or slow (5–10 mL/s) injections during routine 0.5 mL Diphtheria, Tetanus, acellular Pertussis, Inactivated Polio Virus, Haemophilus influenzae type b vaccine (DTaP-IPV-Hib) injections. Those aged 2 and 4 months additionally received 0.5 mL Pneumococcal Conjugate Vaccine (PCV) injections. A research assistant and parent unaware of treatment allocation and hypothesis assessed pain using validated and recommended tools, including; the Modified Behavioural Pain Scale (MBPS, range 0–10), cry duration, and Numerical Rating Scale (NRS, range 0–10). The primary outcome was infant pain score using the MBPS.
Results: Altogether, 120 were recruited; 61 were randomized to fast injections and 59 to slow injections. One hundred and ninteen infants participated. There were no differences in characteristics, including; age ($p = 0.994$) and sex ($p = 0.540$). The mean MPBS score (standard deviation) during DTaP-IPV-Hib injection was lower in the fast injection group: 6.4 (2.7) vs. 7.4 (2.5), respectively; $p = 0.046$. Regression analysis demonstrated a positive correlation between injection speed and pain. There were no other differences between groups.
Conclusion: Fast injection reduced injection-induced pain in infants receiving DTaP-IPV-Hib but not PCV vaccine. Fast injections are recommended when administering vaccines because of the potential for a reduction in pain, feasibility and practicality.
Trial registration: NCT02504398

1. Introduction

Vaccinations are the most common painful medical procedure in infancy. Sub-optimal management of pain during infant vaccinations can lead to negative short-term and long-term effects, including; distress for infants and onlookers, dissatisfaction with the vaccination experience, and future vaccine non-compliance [1]. In its first position statement on this topic published in September of 2015, the World Health Organization stated that pain mitigation should be considered part of good immunization practice [2].

At present, vaccines are commonly administered by intramuscular injection. Evidence-based recommendations exist regarding how to perform intramuscular injections with respect to needle length and angle of injection; however, there is little evidence to guide recommendations regarding the speed of injection [3,4]. Historically, slow injection has been advocated to prevent sudden distension of tissues which may induce acute pain due to activation of nociceptors sensitive to pressure [5], but this practice is not supported by research evidence. In the only two studies we identified on this topic, either no difference in pain was observed between slow and fast injections, or fast injections were associated with less pain [6,7]. Limitations including a small number of subjects and the possibility of confounding due to the vaccine used or the injection technique (i.e., coupling injection speed with aspiration) in these studies prevents definite conclusions from being made about the impact of injection speed on pain.

It is possible that pain may actually be increased from slow intramuscular vaccine injections due to added tissue trauma associated with the longer needle dwelling time which may cause continued pressure as well as lateral movement (wiggling) of the

* Corresponding author at: Leslie Dan Faculty of Pharmacy, 144 College Street, Toronto, Ontario M5S 3M2, Canada.
E-mail address: anna.taddio@utoronto.ca (A. Taddio).

http://dx.doi.org/10.1016/j.vaccine.2016.08.023
0264-410X/

needle. Given the frequency of intramuscular administration of vaccine injections and the prevalence of acute pain as an adverse event following immunization, more investigation of the specific effects of injection speed is warranted in order to guide best practices. The objective of this study was to investigate the effect of speed of injection on vaccination pain in infants. The research question was: Does pain response differ between slow and fast intramuscular injection in 2–6 month old infants undergoing vaccination?

2. Materials and methods

2.1. Population and setting

We conducted a randomized controlled trial in an outpatient paediatric clinic (Paediatric Associates) in Toronto, Canada. Infants were eligible if they were receiving their routine primary 2, 4, or 6 month vaccinations. For 2 and 4 month old infants, this included oral rotavirus vaccine (Rotarix™) and the following two injectable vaccines: Diphtheria, Tetanus, acellular Pertussis, Inactivated Polio Virus, Haemophilus influenzae type b vaccine (DTaP-IPV-Hib; Pediacel™) and Pneumococcal Conjugate 13-valent Vaccine (PCV; Prevnar™). Six month old infants received DTaP-IPV-Hib only. We excluded infants with: impaired neurological development; history of seizures; administration of sedatives or narcotics in the preceding 24 h; and prior participation in the trial.

2.2. Consenting process

Parents were informed that a study was underway investigating the effect of two different clinician-led injection techniques on infant vaccination pain. They were not told the nature of the differences between the techniques (i.e., fast vs. slow rate of injection) in order to minimize bias that could occur due to knowledge of treatment allocation; hence, partial disclosure was used. At the end of the procedure, parents were debriefed and consent re-affirmed. Research involving partial disclosure is acceptable under certain situations (http://www.pre.ethics.gc.ca/pdf/eng/tcps2-2014/TCPS_2_FINAL_Web.pdf). The study was approved by the University of Toronto's Health Sciences Research Ethics Board.

2.3. Randomization and allocation concealment

A separate randomization sequence was created for 3 strata of infants (2, 4, and 6 months) off-site by an individual not involved in the study using a computer random number generator. Infants in each stratum were randomly allocated in a 1:1 ratio to rapid or slow injections in block sizes of 6. Treatment allocation was concealed using sequentially numbered opaque sealed envelopes (SNOSE). The clinician performing the injection was unaware of treatment allocation until the time of vaccination.

2.4. Study procedures

Rapid and slow injections were administered at a rate of 2–4 mL/s and 5–10 mL/s, respectively, which is similar to prior studies [6,7]. Infants randomized to each group received the allocated speed of injection for all scheduled vaccinations (i.e., DTaP-IPV-Hib and PCV for 2 and 4 month old infants and DTaP-IPV-Hib for 6 month old infants).

Altogether, 3 clinicians were involved in administering vaccinations, with an equal number of participating infants (i.e., 1/3) being vaccinated by each of them. They were trained to administer slow and fast injections and practiced prior to study initiation. DTaP-IPV-Hib was administered in the left anterolateral aspect of the thigh and PCV was administered in the right. A volume of 0.5 ml of each vaccine was given using a 25 gauge 22 mm needle. After each injection, the needle was withdrawn quickly, and the clinician applied a cotton ball or Band aid on the injection site, as per usual practice.

Infants benefited from the following standardized pain-reducing measures during vaccination [4]: intramuscular injection without prior aspiration; DTaP-IPV-Hib administration prior to PCV; and holding rather than lying supine. In addition, in 2 and 4-month old infants, oral rotavirus vaccine preceded injection of DTaP-IPV-Hib and PCV [4]. In 6 month old infants, exogenous oral sucrose 24% solution (Tootsweet™, Equinox Specialty Products Inc.) was given prior to administration of DTaP-IPV-Hib [4]. Oral rotavirus contains high concentrations of sucrose; hence, exogenous sucrose was not warranted for younger infants [8]. Prior to the study, parents were informed of and could implement additional pain-mitigation strategies at their own discretion, including; breastfeeding, bottle-feeding, pacifiers and topical anesthetics [4].

2.5. Study outcomes

Infants were videotaped during vaccination by a research assistant using a handheld video camera. Parents rated infant pain in real time using an 11-point Numerical Rating Scale (NRS), where 0 = no pain, and 10 = worst possible pain. Pain was assessed later from videotapes by a research assistant unaware of treatment allocation and hypothesis using validated tools, including: the Modified Behavioural Pain Scale (MBPS) [9] and cry duration. The MBPS assesses infant behaviour in 3 domains: facial expression (from positive expression to grimacing), vocalizations (no crying to full-lunged cry) and body movements (usual movements to thrashing or rigidity). A total score is derived by summing the domain scores and ranges from 0 to 10. The MBPS was scored for the baseline phase (15 s) preceding vaccine injection and post-injection(s) (15 s). Reliability was assessed by recoding of the videos by the same research assistant and calculating the intra-class correlation coefficient (ICC = 0.99). The NRS and MBPS are recommended as the primary methods of infant vaccination pain assessment for parents and researchers, respectively [4,10]. Crying was also assessed in seconds in the first minute following each injection. Crying was defined as audible vocalization in the presence of facial grimacing. Intervention fidelity was assessed by calculating speed of injection from videotapes, whereby a pragmatic cut-off value of below and above 2.5 s was used to classify injections as either fast or slow, respectively.

Parents rated satisfaction with pain control after one or both injections, as applicable, using a 0–10 NRS whereby increasing score denoted higher satisfaction. Adverse events such as injection in the incorrect anatomical site and excessive bleeding were also recorded for all injections.

2.6. Sample size calculation and statistical analysis

Using estimates from a previous study and a two-sample *t*-test as the test statistic, a sample size of 57 per group was needed to show a difference of ≈1 point in the MBPS between the 2 groups. Power was set at 80% power and two-sided alpha level was set at 0.05 [11]. We included 60/group (total, 120) to account for drop-outs and missing data due to equipment malfunction.

The primary outcome analysis compared post-injection MBPS scores between groups in all participating infants during the first injection (i.e., DTaP-IPV-Hib). Secondary outcomes included: MPBS scores during the second injection (i.e., PCV) in 2 and 4 month old infants only; NRS, cry duration and side effects during injection(s); and overall parent satisfaction with pain management. All outcomes and demographics were compared between groups using

Please cite this article in press as: Taddio A et al. A randomized trial of the effect of vaccine injection speed on acute pain in infants. Vaccine (2016), http://dx.doi.org/10.1016/j.vaccine.2016.08.023