ORIGINAL ARTICLE

Vaccine-related pain: randomised controlled trial of two injection techniques

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Videos showing children being injected can be viewed as supplementary files at http://adc.bmj.com/supplemental

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Objective: To compare acute pain response during immunisation in infants using a slow standard of care injection technique versus a rapid pragmatic technique.
Design: Randomised controlled trial.
Setting: Single-centre, urban paediatric primary care practice.
Subjects: Healthy infants 4–6 months of age receiving their routine DPTaP-Hib immunisation.
Interventions: Standard of care group: slow aspiration prior to injection, slow injection and slow withdrawal. Pragmatic group: no aspiration, rapid injection and rapid withdrawal.
Main outcome measures: Immediate infant pain measured by the Modified Behavior Pain Scale (MBPS), crying and parent/paediatrician visual analogue scale (VAS).
Results: 113 infants participated; there were no observed differences in age, birth order or prior analgesic use. Mean MBPS scores (95% confidence interval (CI)) were higher ($p<0.001$) for the standard group compared to the pragmatic group, 5.6 (5 to 6.3) vs 3.3 (2.6 to 3.9). The standard group was more likely to cry, 47/57 (82%) vs 24/56 (43%), to cry longer, median (interquartile range (IQR)) 14.7 s (8.7–35.6) vs 0 s (0–11.30), and to take longer to have the vaccine injected, median (IQR) 8.8 s (7.9–10.3) vs 0.9 s (0.8–1.1), $p<0.001$ for all comparisons. The median (IQR) VAS scores by parents and paediatricians were higher for the standard group: VAS parent, 3.5 (1.6–5.5) vs 1.9 (0.1–3.1) and VAS paediatrician, 2.8 (2.0–5.1) vs 1.4 (0.2–2.4). There were no adverse events.
Conclusion: Immunisation using a pragmatic rapid injection technique is less painful than a slow standard of care technique and should be recommended for routine intramuscular immunisations.

Immunisations are among the most aversive medical procedures for healthy infants and children and one of the commonest causes of childhood iatrogenic pain.[1–3] A review of the medical and nursing literature and research-based protocols for intramuscular injection indicates a paucity of scientific data on the optimal method for intramuscular immunisation and current recommendations have been based almost exclusively on nursing expert opinion rather than randomised trials.[4–10] These guidelines include a number of recommended combined steps which constitute a ''standard'' technique and include the following: slow advancement of the needle into the muscle,[6] slow aspiration prior to injection (the most important step, based on safety considerations, to ensure a blood vessel has not been penetrated),[7] slow injection time in order not to damage local tissues by the physical force of rapid injection (which may be painful),[8 9] and slow withdrawal of the needle after injection.[10] This standard technique may take 10–20 s and may increase immediate pain responses. The aspiration component of this recommended technique may also not accomplish the safety objective for which it was designed, because in practice most vaccinators are ''pragmatic'' and perform the procedure too quickly for it to be effective.[11]

Although experts have advocated using aspiration for many years, there is no scientific evidence to support its need[12] and the published guidelines have not been consistent.[4 5 13 14] Despite the lack of data to support aspiration, 75% of paediatricians and nurses still continue to do it.[11]

It was the objective of this study to compare the effect of two methods of vaccine administration on infant pain response using validated tools.[15] Subjects were randomised to aspiration, with slow injection and slow withdrawal (standard) versus no aspiration, with rapid injection and rapid withdrawal (pragmatic).

METHODS

This was a single-centre, randomised controlled trial conducted between August 2004 and May 2005 in an urban primary care paediatric practice in Toronto, Canada. Healthy infants 4–6 months of age, receiving their second and third routine primary DPTaP-Hib vaccine (Sanofi Pasteur, Ontario, Canada) were enrolled in the study after parents gave their written consent for participation. Ethical approval was obtained from the Research Ethics Board, The Hospital for Sick Children, Toronto, Canada.

Subjects were excluded if they had any chronic illness, a history of allergy to DPTaP-Hib or any of its components, acute febrile illness or if a topical anaesthetic was used. The use of oral analgesics (eg, paracetamol, ibuprofen) was not an exclusion factor and was recorded.

Subjects were randomly allocated to intramuscular injection with DPTaP-Hib vaccine using either the standard technique or the pragmatic technique. An individual blind to the intervention and outcome assessment, using random computer-generated numbers, prepared a randomisation schedule for injection technique allocation (standard or pragmatic). Injection allocation was placed in numbered and sealed opaque

Abbreviations: DPTaP-Hib, diphtheria-polio-tetanus-acellular pertussis-*Haemophilus influenzae* group b; IQR, interquartile range; MBPS, Modified Behavioral Pain Scale; VAS, visual analogue scale

envelopes available only to the two paediatricians delivering the interventions (MI, MG). Subjects were consecutively assigned a study number on recruitment that was linked to the number on the randomisation envelopes. Each paediatrician used both standard and pragmatic techniques.

Several lots of DPTaP-Hib were used. Vaccines were supplied as a lyophilised powder (DPTaP) and diluent (Hib) and stored at 2℃ to 8℃. The entire volume of the Hib diluent (0.5 ml) was used to reconstitute the vaccine, and the entire volume administered intramuscularly with a 25 gauge, 22 mm (7/8 inch) needle.[12] The immunisation procedure was standardised[12] and administered by one of the two participating paediatricians (MI or MG). Subjects were held during the procedure.[16] Immediately before the injection, the antero-lateral thigh muscle was wiped with a wet alcohol swab and then dried with a cotton swab. The muscle was compressed with the free hand during the injection procedure.[12]

For the standard technique, published guidelines were followed: the needle was inserted at 90 degrees with steady pressure and aspiration was performed for 5–10 s. The vaccine was slowly injected over 5–10 s and the needle was then slowly withdrawn.[10] For the pragmatic technique (for which there are no published guidelines), the needle was inserted at 90 degrees with steady pressure. No aspiration was performed[14] and the vaccine was rapidly injected over 1–2 s and the needle then rapidly withdrawn. Rubbing the immunisation site after administration was avoided in both techniques.[5]

The entire vaccine procedure was videotaped using a colour digital camera (Canon 40×) beginning 5 s before the vaccine was administered and continuing for 30 s after the immunisation was completed. Video clips from this study can be viewed as supplementary files at http://adc.bmj.com/supplemental and can also be viewed on the Quebec, Canada, Ministry of Health Government website at http://msssa4.msss.gouv.qc.ca/santpub/immunisa.nsf/liste?OpenView (click on ''Professionnels de la santé'' and look under ''Aspirer ou non avant d'injecter un vaccin'' - Vidéos).

Outcome measures

The primary outcome measure was immediate infant pain response assessed using the Modified Behavioral Pain Scale (MBPS).[15] The MBPS records infant behavioural responses to immunisation pain (facial grimacing, crying and body movements). The MBPS was scored from videotape analysis by a trained coder blind to the study design and has been used successfully in previous vaccine-related studies.[15–17] The possible scores ranged from 0 (no pain) to 10 (worst possible pain). Secondary outcome measures included infant crying time assessed from the videotapes and paediatrician and parent ratings of pain using a 10 cm visual analogue scale (VAS). A baseline pain score 5 s prior to the vaccine injection and a post-immunisation pain score within 15 s of the immunisation were measured and described the child's maximal pain response to the injection. Parents were interviewed and trained to use the VAS scale prior to the study.

Table 1 Baseline characteristics

Category	Standard, n = 57	Pragmatic, n = 56	p Value*
Age (months), median (IQR)	4 (4–6)	4 (4–6)	0.65
Male/female (% male)	22/35 (39)	36/20 (64)	0.01
Birth order, median (IQR)	2 (1–3)	2 (1–2)	0.20
Analgesic use, n (%)	11 (19)	6 (11)	0.20

Values are median (IQR) or frequency (%). IQR, interquartile range.
*Mann Whitney U test or χ^2 test, as appropriate.

A sample size of 57 subjects in each group was calculated to show a clinically important difference of 50% in pain scores between the two procedures (standard and pragmatic). The sample size calculation was made using data from a previous study using the same primary outcome[17] in which the difference in MBPS pain score (post-injection pain score minus baseline) was 2.3 in the placebo group and 1.5 in the experimental group, with a standard deviation of 1.5. Assuming an α error of 0.05 and a β error of 0.20, and a two-tailed test, the sample size calculation was 57 subjects in each group.

For continuous variables, including baseline characteristics and pain scores, the assumption of normality was tested with the Q-Q plot of the distribution of the residuals. There was no observed departure from normality for the primary outcome (MBPS), thus a t test was used to compare groups. Analysis of variance was used to assess the contribution of infant sex on pain responses, whereby group assignment and infant sex were entered as fixed factors and MBPS score was entered as the dependent variable in the model. The Mann Whitney U test was used for all other continuous variables as the Q-Q plots demonstrated departure in the distribution of residuals from normality. The χ^2 test was used for categorical variables. The significance level was $\leqslant 0.05$.

RESULTS

None of 113 parents approached refused entry of their infants into the study. Of the infants enrolled, 57 were randomised to the standard group and 56 to the pragmatic group. There were no differences between groups for age, birth order or prior analgesic use (table 1). There were more males (64%) in the pragmatic group than in the standard group (39%) ($p = 0.01$).

Immediate pain was greater for the standard versus pragmatic groups for all pain outcome measures (table 2). Infant sex had no significant effect on MBPS scores ($p = 0.91$). The median (interquartile range, IQR) duration for vaccine injection was longer for the standard group compared to the pragmatic group at 8.8 s (7.9–10.3) vs 0.9 s (0.8–1.1) ($p<0.001$). No immediate adverse events were observed in any infant.

DISCUSSION

This randomised controlled trial demonstrates that the recommended standard technique using slow aspiration and slow intramuscular injection of DPTaP-Hib vaccine is significantly more acutely painful than a pragmatic rapid injection technique without aspiration. In addition, it lengthens the procedure from 1–2 s (pragmatic) to 5–10 s (standard).

Aspiration prior to intramuscular immunisation is a widespread clinical practice that has been implemented for decades[5 8 12] yet has never been substantiated by scientific data.

Table 2 Pain measures in infants immunised with standard and pragmatic techniques

Category	Standard, n = 57	Pragmatic, n = 56	p Value*
MBPS†	5.6 (5 to 6.3)	3.3 (2.6 to 3.9)	<0.001
Cried, n (%)	47 (82)	24 (43)	<0.001
Crying duration (s)	14.7 (8.7 to 35.6)	0 (0 to 11.30)	<0.001
VAS parent†	3.5 (1.6 to 5.5)	1.9 (0.1 to 3.1)	<0.001
VAS physician†	2.8 (2.0 to 5.1)	1.4 (0.2 to 2.4)	<0.001

Values are mean (95% confidence interval) for MBPS, where scores range from 0 to 10. Values are median (IQR) for crying duration, VAS parent and VAS physician, where scores range from 0 to 10. IQR, interquartile range; MBPS, Modified Behavioural Pain Scale; VAS, visual analogue scale.
*t test, Mann Whitney U test or χ^2 test, as appropriate; †Δ (post-vaccination score minus pre-vaccination score).

What is already known on this topic

- Immunisations are among the most aversive medical procedures for healthy infants and children and one of the commonest causes of childhood iatrogenic pain.
- There are few scientific data on the optimal method for intramuscular immunisation and current recommendations have been based almost exclusively on expert nursing opinion rather than randomised trials.
- Published guidelines include a number of recommended steps which constitute a standard of care technique: aspiration prior to injection, slow injection and slow withdrawal; these recommendations have been inconsistent due to lack of evidence.

What this study adds

- This is the first randomised controlled trial to compare immediate infant pain responses to intramuscular vaccine injection using a standard of care technique (slow aspiration, slow injection and withdrawal) compared with a pragmatic technique (no aspiration, rapid injection and withdrawal).
- In this study, the standard of care slow aspiration technique was significantly more painful and took longer to administer than the pragmatic rapid technique.
- Based on this study the guidelines recommending aspiration and a slow vaccine technique for intramuscular vaccine injection should be re-examined.

In a recent survey of paediatricians and nurses in community practice who vaccinate children, we reported that 75% aspirate prior to intramuscular immunisation.[11] This continued high rate of aspiration may be due to the fact that the current published guidelines have not been consistent[4 12–14] and that the technique is still taught in nursing and medical schools.[4 5]

The guidelines to aspirate were originally recommended for reasons of safety, in order to avoid the inadvertent injection of vaccine material intravenously instead of intramuscularly, even though there are no major blood vessels that could be penetrated in the recommended immunisation sites.[14] There have never been any reported complications following inadvertent intravascular injection into the antero-lateral thigh or deltoid muscle during immunisation. The lack of reported publications might suggest that aspiration is effective. However, this is unlikely since the majority of aspirators do not follow the guidelines of slow aspiration and perform the procedure far too quickly for it to be effective (and visualise a flush back of blood).[11]

Aspiration prior to subcutaneous injection has been studied in one randomised controlled trial where no blood was aspirated in any of the enrolled subjects[18] and the procedure is no longer recommended.[5 9]

The increased pain in the standard group may be due to the combined effects of prolonged exposure to the needle and tissue irritation from needle movement. In a recent survey of vaccinators, 43% of non-aspirators reported that they thought aspiration increased pain.[11] Attempts to modify and reduce pain associated with immunisation have been studied extensively in recent years.[3] Many trials have studied pharmacological and other ways of reducing pain prior to immunisation[17 19] or post-immunisation,[20 21] but few have studied acute pain by addressing vaccine technique.[22 23] Modifying vaccine injection technique, such as not aspirating and reducing aspiration speed in order to reduce acute pain, is not only easy to implement but is also cost effective, unlike other pain-reducing modifications.[17 19] Other advantages of not aspirating include better parental vaccine compliance because of reduced pain and the administration of more injections at the same visit because of less overall injection time. The advantages of the pragmatic technique are listed on a Canadian Government website.[24]

The study had several limitations. Safety could not be ensured due to the relatively small sample size, as the number of subjects required to detect one rare major adverse event would make the study prohibitively large. The study was limited to intramuscular immunisation only and is not necessarily generalisable to aspiration prior to other intramuscular injection procedures, for example medication administration. The study design was based on published guidelines (standard of care ''slow - aspiration technique''[6] versus pragmatic real world ''rapid - without aspiration technique''[11]), making it difficult to ascertain the relative contribution of injection speed versus aspiration on the observed overall reduction in pain. The paediatrician and parent were not blind, but the videotape coder was unaware of the study objectives and infant group assignment. The paediatricians were not blinded to the groups giving rise to the potential for unintentional bias, however standardising the infant position and techniques used minimised this. The study was conducted at a single-centre site, and although only two operators were included, we expect the results are generalisable given the results of a recent survey regarding intramuscular vaccination techniques.[11] Strengths of the study include the randomised controlled design, multiple pain outcome measures and the use of several different evaluators to measure infant pain responses.

Previous studies have demonstrated that expert opinions regarding massage of the injection site, location of injection site, injection of an air bubble and changing the needle prior to injection were not substantiated when later subjected to scientific rigor.[21–23] This randomised study emphasises the need for more systematic evidence to evaluate guidelines recommended for vaccine administration techniques that go beyond expert opinion. We conclude that the guidelines for recommending aspiration prior to intramuscular injection and injection speed be re-examined.

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Contributions: MI is the guarantor for the paper. MI, AT and PP designed the study protocol. MI and MG enrolled subjects. JS, a student, entered data. AT and PP were responsible for data analysis. All authors contributed to the writing and editing of the manuscript.

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ARCHIVIST

SSRIs in pregnancy: small risk of birth defects?

Selective serotonin-reuptake inhibitors (SSRIs) were introduced as a new class of antidepressant drugs in the late 1980s. Recently, there have been reports of increased risk of birth defects associated the use of some SSRIs in early pregnancy, but now two reports in one issue of the *New England Journal of Medicine* suggest that the risk is small (Carol Louik and colleagues. *New England Journal of Medicine* 2007;**356**:2675–83; Sura Alwan and colleagues. Ibid: 2684–92; see also Editorial, ibid: 2732–3).

The Slone Epidemiology Center Birth Defects Study began in 1976 and includes areas around Boston, Philadelphia, Toronto, San Diego and part of New York State. The analysis included 9849 infants with birth defects and 5860 infants without birth defects born between 1993 and 2004. The use of SSRIs overall in the first trimester was not associated with significantly increased risks of defects previously associated with SSRI use (craniosynostosis, omphalocoel or heart defects). Among individual SSRIs there were significant associations between use of sertraline and risk of omphalocoel or septal defect, and use of paroxetine and risk of right ventricular outflow tract obstruction defects. The absolute risks, however, were small.

The National Birth Defects Prevention Study includes data for 9622 infants with birth defects and 4092 control infants born between 1997 and 2002 in eight US states. There were no significant associations between overall SSRI use and congenital heart defects or most other defects. There were statistically significant associations between SSRI use and anencephaly, craniosynostosis and omphalocoel, but again the absolute risks were small.

Some SSRIs may increase the risk of some birth defects if taken in early pregnancy, but the absolute risks are small.