**METHODOLOGY**

Rapid skin anaesthesia using high velocity lignocaine particles: a prospective placebo controlled trial

A R Wolf, P A Stoddart, P J Murphy, M Sasada

**Background:** Local anaesthetic creams (EMLA and Ametop) are used widely to provide pain free intravenous cannulation. However, they take a minimum of 45 minutes to become effective.

**Aims:** To evaluate a prototype device, dermal Powderject lidocaine (DPL), that delivers high velocity lignocaine particles into the skin.

**Methods:** A total of 132 children (aged 4–12 years) were randomised to receive either a sham delivery or a delivery of DPL on the skin at the antecubital fossa, or back of hand. Pain of intravenous cannulation was assessed four minutes later using self reporting behaviours and blinded observation with standard pain assessment tools. The trial was designed to measure both efficacy of skin anaesthesia and potential skin damage with increasing driving pressure of the device (30 or 40 bar), and different lignocaine particle sizes (<38 µm or 38–53 µm) in a block randomised fashion.

**Results:** A total of 128 patients were evaluable. There was a trend towards improved anaesthesia at higher device pressure at the antecubital fossa with both self reporting and blinded observation. Acceptable analgesia was achieved in 90% of patients for high pressure at both particle sizes compared to 60% and 40% for the sham device using self reporting measures. The observed differences using the blinded observer were similar: 90% v 20% (40 bar and small particles v sham), and 80% v 40% (40 bar and large particles v sham). At the back of hand the differences between active and sham devices were not significant. The device was well tolerated and not associated with pain on deployment. One patient had mild petechiae and oedema after deployment (Draize score of 3).

**Conclusions:** This prototype device appears to provide significant skin anaesthesia at the antecubital fossa, but not at the back of hand. The device is not painful to use and causes only minor short term skin changes.
which ruptures the membranes of the cassette and accelerates the powdered lignocaine (3 mg) to high velocities.

In this study we wished to evaluate the relative efficacy of varying both the driving pressure of the helium gas (activation pressure), and the lignocaine particle size. The activation pressures chosen for study were 30 and 40 bar, and the two ranges of lignocaine particle sizes chosen for investigation were <38 µm and 38–53 µm. Higher activation pressures and particle sizes were considered likely to be more effective but potentially damaging to the skin. Therefore, patients were block randomised into four groups starting with low activation pressures and small lignocaine particle size at each of the two application sites (BH or ACF) and progressing to the higher activation pressures and particle sizes (table 1). Five patients in each group were allocated blindly to receive an identical sham device containing helium gas but with an empty drug cassette.

Three minutes after the device was deployed, venous cannulation was performed using a 22 gauge cannula. All children were evaluated for pain responses immediately after cannulation was performed using a 22 gauge cannula. All treatment groups were well matched for age, gender, and weight (table 2).

Evaluation of the skin effects from DPL activation as erythema and oedema using the Draize scale. This is a numeric scale describing skin trauma varying from 0 (no effect) to 4 (severe erythema and oedema greater than 1 mm depth). A Draize score of 0 to 2 was considered acceptable. Any bleeding at the application site was also recorded. These observations were repeated at 30 and 60 minutes after venous cannulation. Photographs of each application were made at the same time as the nurse observations and were independently monitored. It was predetermined as part of the study design that if any patient was given a Draize score of 4, the study would immediately be terminated.

Statistics
A two group χ² test with a 0.05 two sided significance level has 80% power to detect a difference in the proportion of patients with acceptable anaesthesia between the sham device (expected to be 20%) and the active device containing lignocaine hydrochloride (expected to be 90%). This results in an odds ratio of 36, when the sample sizes are five sham and 10 active, respectively (a total sample size of 15). Therefore 15 patients within each activation condition and body site (BH or ACF) were randomised to receive either lignocaine hydrochloride or the sham device with an allocation ratio of 2:1, resulting in 10 patients randomised to lignocaine and five patients to the sham device.

The Faces pain scale was analysed using analysis of variance. Using the error variance from this, pairwise comparisons between the active and sham devices were conducted using the Student’s t distribution, and estimates of the differences in the adjusted means were calculated. The proportion of patients with acceptable anaesthesia on the Oucher scale was analysed separately for activation condition and site of administration (BH or ACF) using logistic regression. Pairwise comparisons between the active and sham devices were conducted using the Wald statistic and estimates of the odds ratio and 95% confidence interval were calculated. The proportion of patients assessed by the nurse as having no pain immediately post-cannulation was analysed post hoc using logistic regression and the significance level of the treatment effect investigated using the Wald statistic. A significance level of less than 0.05 was considered to be statistically significant.

RESULTS
A total of 132 patients were recruited for study of which 128 received the study treatment, the remaining four patients being unable to enter the study after consent because of non-compliance. Three further patients were unable to complete the trial as per protocol because of lack of compliance after application of DPL. This left a total of 125 patients for final analysis. All treatment groups were well matched for age, gender, and weight (table 2).

<table>
<thead>
<tr>
<th>Study group</th>
<th>Activation pressure (bar)</th>
<th>Lignocaine particle size (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>30</td>
<td>&lt;38</td>
</tr>
<tr>
<td>B</td>
<td>30</td>
<td>38–53</td>
</tr>
<tr>
<td>C</td>
<td>40</td>
<td>&lt;38</td>
</tr>
<tr>
<td>D</td>
<td>40</td>
<td>38–53</td>
</tr>
</tbody>
</table>

Patients randomised to sham treatment within the study group received the same activation pressure but did not have lignocaine.

### Table 1

**Group allocation of activation pressure and lignocaine particle size for DPL**

<table>
<thead>
<tr>
<th>Study group</th>
<th>Activation pressure (bar)</th>
<th>Lignocaine particle size (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>30</td>
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<td>B</td>
<td>30</td>
<td>38–53</td>
</tr>
<tr>
<td>C</td>
<td>40</td>
<td>&lt;38</td>
</tr>
<tr>
<td>D</td>
<td>40</td>
<td>38–53</td>
</tr>
</tbody>
</table>

### Table 2

**Ages, weights, and sex differences for the four study groups**

<table>
<thead>
<tr>
<th></th>
<th>A (DPL)</th>
<th>B (Sham)</th>
<th>C (DPL)</th>
<th>D (Sham)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back of hand (M/F)</td>
<td>(4/6)</td>
<td>(2/3)</td>
<td>(5/5)</td>
<td>(2/3)</td>
</tr>
<tr>
<td>Age (y), mean (SD)</td>
<td>9.3 (1.6)</td>
<td>7.4 (0.5)</td>
<td>8.9 (2.2)</td>
<td>7.2 (2.2)</td>
</tr>
<tr>
<td>Weight (kg), mean (SD)</td>
<td>23.7 (4.7)</td>
<td>23.7 (4.7)</td>
<td>31.2 (10.3)</td>
<td>23.7 (4.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>A (DPL)</th>
<th>B (Sham)</th>
<th>C (DPL)</th>
<th>D (Sham)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antecubital fossa (M/F)</td>
<td>(5/4)</td>
<td>(4/1)</td>
<td>(6/4)</td>
<td>(3/2)</td>
</tr>
<tr>
<td>Age (y), mean (SD)</td>
<td>8.8 (2.0)</td>
<td>9.4 (2.9)</td>
<td>7.6 (1.7)</td>
<td>7.8 (2.1)</td>
</tr>
<tr>
<td>Weight (kg), mean (SD)</td>
<td>33 (9.8)</td>
<td>36.3 (19.4)</td>
<td>26.9 (5.4)</td>
<td>30.8 (15.7)</td>
</tr>
</tbody>
</table>
Rapid skin anaesthesia using high velocity lignocaine particles

At the ACF site, there was a trend towards a higher percentage of acceptable pain scores after intravenous cannulation in the active compared to the sham treatments at higher activation pressures and lignocaine particle sizes at the ACF (fig 2), but this just failed to reach statistical significance (p = 0.06 with 40 bar activation pressure and 38–53 μm lignocaine particles). However, a comparison of pain intensity between the active and sham groups at the ACF using the Faces pain scale reached a significance level of 0.048 in group B and 0.019 in group D (table 3). Assessment of pain on cannulation by the blinded study nurse again showed significantly higher pain free cannulation (p < 0.05) with DPL at higher pressures compared with the sham treatments (fig 3).

At the BH, there was a trend towards DPL to be better than sham when administered to the BH, but these differences were not statistically significant. The device was well tolerated when deployed on the skin. Of the 128 children (both active and sham) who were treated with the device 102 (80%) reported no pain; 21 of 85 patients in the active group (25%) and five of 43 in the sham group (12%) reported mild or moderate pain. There was no trend towards increased pain on activation in patients who were in the groups receiving higher pressures or particle sizes. One patient receiving high pressure/low particle size lignocaine in the ACF was judged to have a Draize score of 3. All other patients had a Draize score of 2 or less. One patient reported itching of the hand after receiving lignocaine.

### Table 3

<table>
<thead>
<tr>
<th>Study group</th>
<th>Lignocaine</th>
<th>Sham</th>
<th>Differences between treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Faces score, median (range)</td>
<td></td>
<td>Median (95% CI)</td>
</tr>
<tr>
<td>A</td>
<td>2 (0–4)</td>
<td>1 (0–6)</td>
<td>0 [2 to 2]</td>
</tr>
<tr>
<td>B</td>
<td>0.5 (0–3)</td>
<td>1.5 (1–6)</td>
<td>0 (4 to 0)</td>
</tr>
<tr>
<td>C</td>
<td>1 (0–3)</td>
<td>2 (1–4)</td>
<td>0 (2 to 0)</td>
</tr>
<tr>
<td>D</td>
<td>0 (0–6)</td>
<td>3 (1–6)</td>
<td>−2.5 (5 to 0)</td>
</tr>
</tbody>
</table>

### Discussion

High velocity particles are capable of penetrating the epidermis and can deliver drugs systemically. We have adapted this technique with a prototype device (DPL) to determine if lignocaine particles can be embedded in the skin to produce rapid topical analgesia in children. The results show that at the ACF it is possible to reduce or eliminate the pain of cannulation better than a sham device and that the higher pressure of 40 bar is more effective than 30 bar. It is unclear from this study whether particle size affects the onset and quality of anaesthesia.

One of the confounding issues in this study was the low incidence and intensity of pain recorded by the children undergoing venous cannulation, and by the observing study nurse. In the sham group, over 50% of patients reported minimal or no pain (Oucher scores of 0, 1, or 2) on venous cannulation at either the ACF (14 of 21) or BH (10 of 21). This made it difficult to resolve differences between treatment and study groups and had not been expected. However, all cannulations were carried out by experienced paediatric anaesthetists and this group of patients did not have previous experience of hospital visits or blood taking procedures, which could explain the low pain scores in this group of patients. Generally, the self reporting pain scores agreed well with the nurse observer. However, on several occasions children who showed significant facial expressions of pain failed to score pain on their self reported assessment, and this may have influenced the results. While the primary outcome measure in this study was chosen to be self reporting measures of pain, a recent study in a similar group of patients, concluded that observed facial expression is a more reliable measure of pain on venepuncture than self reporting techniques. This suggests that when assessing pain in this age group, while both assessments are valuable, more emphasis should be put on pain assessment from the blinded observer than from the child.

The current prototype device failed to show benefit at the BH from either patient self evaluation or from the nurse observation. The most likely explanation is that the BH site has reduced sensitivity to noxious stimuli, while the increased thickness of the skin over the back of the hand would make penetration by lignocaine more difficult. Future devices will need to evaluate increased pressure or changes in particle size to improve lignocaine penetration. However, it is already clear that as pressure and particle size increases, the skin damage in terms of petechiae and surface bleeding also increases. In this study, only one patient had a Draize score of 3, but there was a trend towards skin trauma with higher pressures and larger particle sizes.
One of the major fears of the child entering hospital is painful needle insertion. EMLA cream and Ametop cannot always be used effectively, either because they take too long to produce anaesthesia or because of failure to insert the cannula at the chosen site. The DPL prototype is effective at the ACF but further development is needed. To be widely accepted it will need to be effective at other cannulation sites without significant skin trauma. It could then become a valuable alternative to the current anaesthetic creams. The rapid onset of skin anaesthesia with DPL would allow an appropriate skin site to be selected and cannulated without delay when topical creams are ineffective, to achieve painless intravenous cannulation.

References
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