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% vs 20% (40 bar and small particles v sham), and 80% vs 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.

METHODS

After local ethical approval and informed parental consent, 132 white children (aged 4–12 years of age) due to undergo day case dental surgery under general anaesthesia were recruited for this randomised, prospective, placebo (sham) controlled trial. The children were randomly allocated to one of two application sites for intravenous access: the back of the hand (BH) or the antecubital fossa (ACF). The DPL delivery system comprises a stainless steel gas cylinder filled with helium under pressure, a stainless steel rupture chamber, a drug cassette, a supersonic nozzle, and a silencer (fig 1). Actuation releases a small volume of compressed helium, penetrates the outer skin layers, and safe in a clinical situation.

Effective skin analgesia has revolutionised paediatric practice, allowing painless venepuncture and intravenous cannulation. The first of these agents, EMLA (a eutectic mixture of lignocaine and prilocaine), has been shown to provide reliable anaesthesia for venepuncture if applied on the skin for 60 to 90 minutes, but the time to achieve effective analgesia has remained a limitation. Topical amethocaine (Ametop) has a more rapid onset of anaesthesia, and is more effective than EMLA when using the recommended application times of 45 minutes for Ametop and 60 minutes for EMLA. However, an onset time of 45 minutes remains a practical barrier to the provision of pain free venous cannulation in all children. One solution is to provide topical cream for the parents to apply before arrival in hospital, but this is not always feasible. New developments in delivery of drugs directly into the skin may offer a solution. Pressurised helium gas can be used to accelerate particles to velocities sufficient to penetrate the outer skin layers. Preliminary studies on adult volunteers using this principle (dermal Powderject lignocaine, DPL), found that effective topical anaesthesia can be achieved within three minutes after administration and that this technique could provide surface anaesthesia for venepuncture. Therefore, we wished to determine if a prototype device could provide effective skin analgesia for venepuncture in unpremedicated children, and if the technique was feasible, pain free, and safe in a clinical situation.

Figure 1  Schematic diagram of Powderject device.

Abbreviations: ACF, antecubital fossa; BH, back of hand; DPL, dermal Powderject lignocaine

Schematic diagram of Powderject device.
assessment pain scales, the Oucher. Pain and discomfort were evaluated using two self
children were evaluated for pain responses immediately after
activation pressures and small lignocaine particle size at each
application site was evaluated immediately before and after
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
application of DPL and again following intravenous cannula-
lation. Pain and discomfort were evaluated using two self
assessment pain scales, the Oucher and the Faces scales. The
Oucher includes six photographs of a child with varying
degrees of pain and a corresponding numerical visual
analogue scale, with the child using either the visual or
numerical score depending on their cognitive abilities. The
Faces consists of six faces representing no pain to maximum
pain possible. For the purposes of this study, acceptable anaes-
thesia on the Oucher scale was predefined as a pain score of 0
or less on the numerical scale or the lowest two corresponding
pictures on the photographic scale. In addition, a blinded
nurse assessment of the child’s pain was made using a four
point scale (0 = no pain, 1 = mild pain, 2 = moderate pain, 3
= severe pain).

Evaluation of the skin effects from DPL activation as
increasing pressure and lignocaine particle sizes were used
was necessary to determine the safety of the device. The
application site was evaluated immediately before and after
application of DPL for 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 in depth). A Draize score of 0 to 2 was con-
sidered 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 appli-
cation 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 hydrochlor-
ide or the sham device with an allocation ratio of 2:1, result-
ing 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 statisti-
cally 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, gen-
der, and weight (table 2).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Group allocation of activation pressure and lignocaine particle size for DPL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study group</td>
<td>Activation pressure (bar)</td>
</tr>
<tr>
<td>A</td>
<td>30</td>
</tr>
<tr>
<td>B</td>
<td>30</td>
</tr>
<tr>
<td>C</td>
<td>40</td>
</tr>
<tr>
<td>D</td>
<td>40</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Ages, weights, and sex differences for the four study groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>DPL</td>
</tr>
<tr>
<td>Back of hand</td>
<td></td>
</tr>
<tr>
<td>Total (n)</td>
<td>10</td>
</tr>
<tr>
<td>(M/F)</td>
<td>(4/6)</td>
</tr>
<tr>
<td>Age (y), mean (SD)</td>
<td>9.3 (1.6)</td>
</tr>
<tr>
<td>Weight (kg), mean (SD)</td>
<td>23.7 (4.7)</td>
</tr>
</tbody>
</table>

Antecubital fossa |
| Total (n) | 11 | 5 | 10 | 6 | 10 | 5 | 10 | 5 |
| (M/F)     | (5/6) | (4/1) | (4/2) | (6/4) | (3/2) | (3/2) | (3/2) | (3/2) |
| Age (y), mean (SD) | 8.8 (2.0) | 9.4 (2.9) | 7.6 (1.7) | 7.8 (2.1) | 8.4 (2.5) | 8.6 (1.5) | 8.0 (2.2) | 7.8 (1.3) |
| Weight (kg), mean (SD) | 33 (9.8) | 36.3 (19.4) | 26.9 (5.4) | 30.8 (15.7) | 27.4 (8.4) | 28.9 (4.9) | 26.4 (5.7) | 27.3 (2.3) |
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 was not statistically significant.

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/lower 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.

**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.

**Table 3** Intensity of pain as measured by the Faces pain scale after cannulation at the antecubital fossa for DPL versus placebo

<table>
<thead>
<tr>
<th>Study group</th>
<th>Lignocaine</th>
<th>Sham</th>
<th>Differences between treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2 (0–4)</td>
<td>1 [0–6]</td>
<td>0 [−2 to 2], p &lt; 0.05</td>
</tr>
<tr>
<td>B</td>
<td>0.5 (0–3)</td>
<td>1.5 [1–6]</td>
<td>−1 [−4 to 0], p = 0.048</td>
</tr>
<tr>
<td>C</td>
<td>1 (0–3)</td>
<td>2 [1–4]</td>
<td>−1 [−2 to 0], p = 0.12</td>
</tr>
<tr>
<td>D</td>
<td>0 (0–6)</td>
<td>3 [1–6]</td>
<td>−2.5 [−5 to 0], p = 0.019</td>
</tr>
</tbody>
</table>

**Figure 2** Percentage of patients with acceptable anaesthesia at the antecubital fossa, 3 minutes after application of DPL or placebo using self reported measures of pain from the Oucher pain scale.

**Figure 3** Percentage of patients pain free on cannulation at the antecubital fossa 3 minutes after application of DPL or placebo using the nurse’s blinded pain assessment.

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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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