Randomized trial of novel tetracaine patch to provide local anaesthesia in neonates undergoing venepuncture

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Background. Procedures such as venepuncture or heel prick are painful and may cause considerable stress to newborn infants. Topical local anaesthetics are effective for venepuncture but need to be applied for at least 60 min and the delivered dose will vary. We assessed a novel tetracaine-based self-adhesive patch in providing controlled local anaesthesia before venepuncture.

Methods. A placebo-controlled, double-blind trial was conducted using a tetracaine patch formulated from hydroxypropylcellulose discs (0.283 cm²) containing tetracaine (1 mg cm⁻²) surrounded by a low tack pressure-sensitive adhesive backing layer. Thirty-two newborn infants of gestation 32–42 weeks (median 36 weeks), aged 3–18 days (median 6 days) were randomized to receive a tetracaine-containing patch or a placebo device applied to the dorsum of the hand 30 min before venepuncture to obtain blood samples. Pain was assessed in response to needle insertion using a validated adaptation of the neonatal facial coding score (NFCS) and the presence of crying.

Results. Of 15 tetracaine-treated neonates, 14 (93%) presented little or no pain in response to the procedure compared with six of 17 (35%) who had the placebo patch applied (P=0.01).

Conclusions. The tetracaine patch produced effective pain relief during the venepuncture procedure in both term and pre-term infants. There were no adverse effects, either local or systemic.

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The efficacy of tetracaine gel as a percutaneous local anaesthetic is well known. 9, 10 This efficacy is based on the unique tetracaine phase change system, in which solid tetracaine base undergoes a phase change in the presence of water at skin temperature, forming a penetrative lipophilic oil. 13 Thus, tetracaine must be formulated in an aqueous carrier, or in a polymeric matrix to which water may be added before use. The latter system may be formulated as a skin patch. Previous patch designs have additionally used such hydrophilic polymeric carriers as skin bioadhesives to attach the patch. 14

EMLA cream and Ametop gel are semi-solid formulations that are relatively simple to manufacture and use but they can be inconvenient in certain situations. In neonates, the formulations need to be applied for some time before the painful invasive procedure. The site then requires occlusion with the use of some form of adhesive dressing with a high degree of tack or a large surface area to ensure that the semi-solid formulation remains at the required site. On removal of the adhesive film, the skin can be damaged because of the delicate nature of the epidermis in neonates, especially those who are pre-term. A further disadvantage posed by a semi-solid formulation is the inability to determine the dose of drug delivered, given that the quantitative uptake of tetracaine by intact skin is well established. 15 The amount of product applied is judged by the clinician and the area covered by an application varies between doses. The combination of these two factors leads to a variation in total dose of drug permeating through the skin.

For these reasons we developed a topical anaesthetic patch using tetracaine as the active ingredient and studied it in neonates undergoing venepuncture. The new patch system incorporates a hydrophilic polymeric carrier in order to facilitate the tetracaine phase change system but provides a more secure means of skin attachment via a surrounding pressure-sensitive adhesive, giving an overall design that is similar to an island dressing.

### Methods

#### Patients

A randomized double-blind placebo-controlled trial was conducted in the Regional Neonatal Unit and postnatal wards of the Royal Maternity Hospital, Belfast. A placebo patch was also considered essential to allow for any disturbances as a result of patch application or removal. Thirty-two newborn infants, both pre-term and term (median 36 weeks’ gestation; range 32–42 weeks) were enrolled at 3–18 (median 6) days of age. The study was approved by the Research Ethics Committee of Queen’s University Belfast. Written informed parental consent was obtained before inclusion in the study and exemption from the restrictions of product licenses for the patch device was obtained from the Medicines Control Agency, London.

All infants having venepuncture procedures for serum bilirubin measurement and Guthrie tests in the Regional Neonatal Unit or postnatal wards were eligible for the study. Infants with congenital malformations, abnormal neurological state, those who needed assisted ventilation and those having analgesia or sedation as part of their routine management were excluded. Testing was conducted in a quiet room near the nursery with the infants in their cots. The use of a soother was not permitted. The area around the vein located on the dorsum of the hand was swabbed with an alcohol wipe and allowed to dry before application of the patch. Each infant in the study received either the tetracaine or an identical placebo patch. A patch was randomly chosen from a pre-packed box of 36, equally divided between placebo and active devices. The release liner backing was removed and the disc at the centre of the patch system was moistened with sterile water and applied to the chosen area. The patch was left in place for 30 min before venepuncture. This time was chosen based on a previous statistical analysis of the influence of application time on percutaneous local anaesthesia with tetracaine gel in children. 10

Venepuncture was carried out by a trained neonatal nurse practitioner (NMS) experienced in performing this procedure. Pain was assessed in response to needle insertion using a validated adaptation of the neonatal facial coding score (NFCS) and the presence of crying. 11 This method scores each of a number of facial characteristics as being present (scoring one point) or absent (no score). These facial characteristics are brow bulge, eye squeeze, naso-labial furrow, open lips, and cry. 3

Following the application period, the patch was removed and the infant left to settle for 5 min. A Panasonic® camcorder (Panasonic UK Ltd, Bracknell, UK) was used to record the procedure both in audio and visually. The period of time starting 20 s before the procedure and 20 s following the procedure was recorded. The moment when the skin was pierced during the venepuncture procedure was identified orally by the nurse performing the procedure. The video footage was transferred to a computer using Adobe Premiere (Adobe Systems UK, Middlesex, UK).

This enabled the overlaying of information onto the infant footage. A time code was overlaid onto the footage to enable

<table>
<thead>
<tr>
<th>Study group characteristics. No significant differences. *Median (range); **number (%)</th>
<th>Tetracaine (n=15)</th>
<th>Placebo (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestation (week)*</td>
<td>35 (32–42)</td>
<td>37 (34–41)</td>
</tr>
<tr>
<td>Birth weight (kp)*</td>
<td>2.07 (1.29–3.84)</td>
<td>2.53 (1.57–3.87)</td>
</tr>
<tr>
<td>Postnatal age (days)*</td>
<td>6 (3–18)</td>
<td>6 (5–10)</td>
</tr>
<tr>
<td>Pre-term**</td>
<td>8 (53)</td>
<td>8 (47)</td>
</tr>
<tr>
<td>Males**</td>
<td>6 (40)</td>
<td>4 (23)</td>
</tr>
<tr>
<td>Reason for venepuncture:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum bilirubin**</td>
<td>2 (13)</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Guthrie test**</td>
<td>13 (87)</td>
<td>14 (82)</td>
</tr>
</tbody>
</table>
accurate determination of time before and following the venepuncture. The footage was transferred to both compact disc and VHS format.

At a later time the video footage was viewed and scored by two other nurses trained in the NFCS method. A total score was obtained from scoring each second of footage starting 5 s before the procedure and ending 5 s after. This gave a maximum score of 25 for each 5-s period. A cumulative score of 10 or less in the 5 s following the procedure was defined as indicating clinically effective anaesthesia.11

**Patch formulation**

Formulation and design of the patch device involved several stages: formulation of a gel containing the active ingredient, casting of the gel to form a thin film, formulation of a suitable dilution of acrylic adhesive and casting of that adhesive. Following the casting of the two separate films the patch was constructed.

Hydroxypropyl cellulose (1.5 g) was mixed with water (28.5 g) to form a clear 5% gel. With gentle stirring, the gel was then warmed to a temperature of 32°C. When this temperature was reached, the required amount of tetracaine base USP was introduced. The amount of tetracaine base was calculated to enable the drug loading to be estimated for the final dry film, in terms of mg cm⁻². Tetracaine base (120 mg) was added to every 30 g of gel. At 32°C the added tetracaine base melted to form an oil. The gel was then homogenized with vigorous stirring and cooling, using a cold water jacket. The oil droplets within the gel solidified to form a very fine dispersion of solid particles within the vehicle.

The tetracaine gel dispersion (25 g) was poured slowly into a template (100×100 mm) and spread evenly over the levelled release liner surface. The films were allowed to dry with the aid of a cool-air convection current by positioning the templates within a fume cupboard. After 24 h the films were completely dry. The formulation was designed to produce a dry film with a drug loading of 1 mg cm⁻².

Duro-Tak 87-2074 (National Starch and Chemical, The Netherlands) as a 12.5% dilution was used as the base for the adhesive backing film. The main reasons for choosing the adhesive were its rating of ‘minimally-irritating’ in dermal irritation scoring, low tack and high cohesive strength, as a result of its cross-linking within the polymer.

Discs of uniform area (0.283 cm²) were cut from the dried tetracaine film, which because of the formulation method, was calculated to contain 0.283 mg of tetracaine base. The discs were positioned onto the pressure-sensitive adhesive film. Release liner was applied onto the adhesive film to sandwich the tetracaine discs between the adhesive film and the release liner. Patches of 16 mm diameter were cut with the 6 mm disc of tetracaine film at the centre.

**Sample size and statistical analysis**

Based on the findings of a previous randomized controlled trial, a sample size of 34 (power 80%; \( P=0.05 \)) was estimated as necessary to show an increase of local anaesthetic action from 17 to 55%.

The coefficient of reliability between the assessors for the NFCS was assessed using the reliability formula. Differences in patient characteristics between the groups was assessed using Fisher’s exact, \( \chi^2 \) and Student’s \( t \)-tests. Differences in NFCS scores between groups was assessed using the Mann–Whitney \( U \)-test.

**Results**

The planned sample size was 34, but two sets of parents withdrew their consent after randomization and these infants, both in the tetracaine group, were withdrawn from the study. The patient characteristics of the 32 infants are shown in Table 1. No significant differences were found between the groups. Venepuncture was successfully performed in all cases.

The coefficients of reliability between assessors for the NFCS scores were 0.87, 0.85, 0.94, 0.87, and 1.0 for brow bulge, eye squeeze, deepened naso-labial folds, open mouth, and cry, respectively. The degree of agreement between the assessors in their scoring of the video footage was found to be excellent for all five features coded for.

There was no significant difference in the median cumulative NFCS scores between the two groups scored during the 5 s immediately before the venepuncture (both active and placebo were zero). The median cumulative NFCS score over the 5 s immediately following the venepuncture was 0 in the active patch group compared...
with 12.5 in the placebo group (Fig. 1; \(P=0.0002\)). Fourteen of 15 (93%) tetracaine-treated neonates presented little or no pain in response to the procedure compared with six of 17 (35%) in the placebo group \(P=0.01\), fulfilling the definition of clinically effective local anaesthesia.\(^{12}\)

The patch device displayed excellent adherence to the site of application, remaining fixed securely to the site for the required duration of up to 2 h. The patch peeled off without leaving an adhesive residue or causing additional trauma to the puncture site. No local skin reactions were witnessed after application of either the placebo or active patch device.

**Discussion**

Pain expression in neonates has been extensively documented in the past with various methodological approaches being used in an attempt to evaluate the obvious distress observed following a painful invasive procedure, such as venepuncture used to obtain blood samples. Facial response has been regarded as being the most convincing method of pain assessment,\(^{17}\) with careful documentation of facial grimaces providing a rich source of information about the neonatal reaction to noxious events.\(^{18}\) The NFCS provides detailed anatomically based and objective descriptions of the newborn’s reactions to acute painful stimuli.\(^{3}\)

A validated adaptation of the NFCS was used to assess the effectiveness of the tetracaine patch device.\(^{11}\) The evaluation was performed by viewing recorded video footage of the infant’s face before, during, and following the blood sampling procedure.

Video analysis facilitated the most objective evaluation of behaviour as it is not known whether inter-observer reliability would be as accurate with the use of real-time evaluation techniques. The video footage obtained was clear and allowed the assessors to easily ascertain the various facial expressions being coded for.

This study has shown that a significant anaesthetic effect is produced by the patch device as seen by the marked effect on the behavioural response of both term and pre-term infants to venepuncture. One infant treated with a tetracaine patch before venepuncture displayed a painful reaction to the procedure with a cumulative NFCS score of 13 over the 5 s following the puncture. This was a term male infant of 3.5 kg before venepuncture. Fourteen out of 15 infants treated with the tetracaine patch before venepuncture had a score of less than 10 over the 5 s following the puncture. Twelve infants had a score of zero. In one infant there appeared to be no anaesthetic effect. The reasons for this could involve genetic differences or an alternative source of distress for this particular infant.

The aim of this research was to evaluate a new percutaneous local anaesthetic patch device incorporating tetracaine as the active agent. The advantage of this approach was that specific amounts of the drug were delivered to a specific area of skin, this is difficult to achieve by using a conventional gel covered by an occlusive dressing. An additional important consideration is the degree of patch adhesion. Many conventional pressure-sensitive adhesive tapes used on delicate skin can cause damage upon removal. Hence a further aspect of this research was to modify medical approved adhesives to overcome this problem. In this study the adhesive properties of the patch caused no trauma to the skin at the site of application.

Although our sample size was relatively small it was calculated to be sufficient to test the effectiveness of our local anaesthetic patches based upon a previous study.\(^{11}\) Furthermore, our study was designed to be truly double-blind by using videotape to assess pain using a previously validated scoring system. The present study has shown that tetracaine patches before blood sampling by venepuncture are effective and that they may have a place in clinical practice in neonatal units and post-natal wards. Further studies of the effectiveness of tetracaine patches for local anaesthesia during heel stabs are needed, in addition to investigating shorter application periods before venepuncture.

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