A systematic review of lidocaine-prilocaine cream (EMLA) in the treatment of acute pain in neonates
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Authors' objectives
To determine the efficacy and safety of lidocaine-prilocaine 5% cream (EMLA) as an analgesic for procedural pain treatment in neonates and provide evidence-based recommendations for clinical practice.

Searching
The following electronic databases were searched: MEDLINE (Jan 1966-Dec 1996), EMBASE (1993-1996) and Reference Update (Jan 1995-Dec 1996); using the MeSH terms/textwords: 'infant-newborn', 'pain', 'analgesic', 'anesthesia', 'EMLA', 'lidocaine-prilocaine', and 'local anesthetics'. In addition manual searches of bibliographies, personal files, scientific meeting proceedings, and recent issues of key journals were performed. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and cohort (non-randomised) studies.

Specific interventions included in the review
EMLA as used in the following procedures: circumcision, heel lancing, percutaneous venous catheter (PVC) insertion, lumbar puncture, and venous/arterial puncture. Doses of EMLA ranged from 0.5-2g, administered at time periods ranging from 30-180mins before the start of the procedure. Intervention groups were compared against placebo or no-treatment controls.

Participants included in the review
Neonates defined as up to 1 month of age. Those neonates included in the review had gestational ages at birth ranging from 26wks to full-term. One study included very low birth weight neonates.

Outcomes assessed in the review
Behavioural (e.g. cry duration, facial action, body action), physiologic (e.g. heart rate, respiratory rate, blood pressure), hormonal (examples not given), and metabolic changes (examples not given); adverse effects relating primarily to incidences of methemoglobinemia (defined as methemoglobin (MetHb) concentrations >5% requiring medical intervention). Experimental pain procedures such as the measurement of pain thresholds using von Frey hairs were excluded.

How were decisions on the relevance of primary studies made?
Two reviewers assessed the relevance of the studies and consensus was reached on each decision.

Assessment of study quality
No formal assessment of validity was undertaken.

Data extraction
Data (including procedure, study design, gestational age, dose, control treatment and outcomes) were extracted and verified by two of the reviewers. Attempts were made to obtain additional data from authors.

Methods of synthesis
How were the studies combined?
A priori, a decision was made to pool data (using a random-effects model reporting weighted mean differences (WMD)), where there were at least two studies which looked at the same procedure using the same outcome measure. Similarly, overall differences in MetHb concentrations were pooled where appropriate and the estimated overall incidences and risks reported with 95% confidence intervals (95% CI).

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review
Eleven studies (3 double-blind, placebo-controlled RCTs; 5 placebo-controlled RCTs; 1 RCT; 2 non-randomised controlled trials) including a total of 662 participants.

Circumcision (1 double-blind RCT and 2 RCTs; 138 participants): All three studies demonstrated that EMLA diminishes pain responses. Two studies were pooled to give a mean increase (WMD) in heart rate (compared to baseline values). The heart rate with EMLA varied as compared to placebo depending on the stage of the procedure from WMD=-11.67 (95% CI: -19.93, -3.42) for clamp removal to WMD=-27.21 (95% CI: -35.98, -18.45) when applying the clamp (P<0.05).

Heel lancing (1 double-blind RCT, 2 placebo controlled RCTs and non-randomised controlled study; 225 participants):
The four studies used various outcome measures to assess the level of pain (heart rate, blood pressure, crying, respiration rate, Premature Infant Pain Profile (PIPP), transcutaneous oxygen tension and carbon dioxide tension). EMLA was not shown to significantly diminish pain in any of the studies.

Venipuncture (1 double-blind RCT and 1 non-randomised controlled trial; 127 procedures):
Both studies demonstrated EMLA was effective at decreasing pain. In the RCT both heart rate and cry duration were lower in the EMLA as compared to the placebo group, however no data or significance levels were provided. In the cohort study significant changes in favour of EMLA (vs control) were observed for both heart rate and the behavioural pain score.

Arterial puncture (1 non-randomised controlled trial, 90 procedures): The study showed a higher frequency of low pain scores (41% vs 21.5%, P<0.05) for the EMLA vs the control group. Heart rate and oxygen saturation also favoured the EMLA group, however these findings were not significant (P>0.05).

Lumbar puncture (1 RCT, 49 participants):
The study showed physiologic parameters (heart rate, blood pressure, and oxygen saturation) and behavioural pain measures as compared to baseline values did not differ significantly between the EMLA and control groups. Therefore EMLA appeared to have no effect on pain. However, the nature of the behavioural pain score and the observed values were not reported.

PVC placement (1 RCT, 13 participants):
The heart rates of EMLA-treated neonates were significantly lower than controls and the respiration rate responses attenuated, but only during skin puncture. Blood pressure and oxygen saturation rates were not significantly altered. EMLA therefore appeared to have some efficacy in terms of decreasing pain.

Safety data (12 studies, >355 participants):
MetHb concentrations were compared in infants before and after administration of EMLA, or between infants exposed to EMLA and placebo, with no significant differences observed in seven studies. Data from four of the RCTs was combined and the results showed that mean MetHb concentrations did not differ between EMLA-treated and placebo-treated individuals (WMD=-0.11%, 95% CI: -0.31%, 0.10%). Overall, the studies suggested that the risk of
methemoglobinemia is low after a single dose. In full-term neonates, single doses ranging from 0.5-2g applied for 10-180min were not been reported to cause methemoglobinemia. Concentrations of lidocaine and prilocaine were considerably lower than those considered toxic (>5micrograms/ml) using these dose regimens. There was insufficient data however to comment on the safety of repeated administration of EMLA.

Authors' conclusions
EMLA diminishes pain during circumcision. It may also diminish the pain from venipuncture, arterial puncture, and percutaneous venous catheter placement; however, efficacy data for these procedures are limited. EMLA does not diminish the pain from heel lancing.

CRD commentary
This was a clearly reported review based on a well-defined question. The review methodology was clearly stated and a thorough literature search was carried out which also attempted to locate unpublished data. The validity of the studies was not formally assessed and there was no report of the level of heterogeneity between studies. Nevertheless, those randomised controlled studies that evaluated the same procedure and used the same outcome measures were pooled. In particular those studies relating to pain during circumcision were pooled and these data have been published in the form of a Cochrane review (see Other Publications of Related Interest no.1).

The authors discuss in detail a number of factors, which may possibly have influenced the findings of their review, and overall their findings would be appear to be valid taking into account the points previously mentioned.

Implications of the review for practice and research
Practice: The authors state that 'EMLA is recommended for the treatment of pain from circumcision but not heel lance'; 'there is insufficient data to recommend its use for other procedures'; 'single doses do not cause methemoglobinemia'.

Research: The authors state that 'additional research is recommended in neonates before EMLA is used routinely for procedures other than circumcision and to determine the safety of repeated administration'.

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