Published in final edited form as:
J Pediatr Urol. 2013 February ; 9(1): e86–e90. doi:10.1016/j.jpurol.2012.09.013.

Loss of Anatomical Landmarks with Eutectic Mixture of Local Anesthetic Cream for Neonatal Male Circumcision

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Abstract

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Conflict of interest statement
None of the authors has any financial or personal relationships with other people or organisations that could inappropriately influence his or her work.

Ethical Approval
The study was approved by the Botswana Ministry of Health's Health Research and Development Committee and by Partners Institutional Review Board (Brigham and Women's Hospital). Written informed consent was obtained from the mothers for the procedure and for the photos.

The larger trial is registered at www.clinicaltrials.gov as NCT00971958.

We report two cases of newborns who developed marked local edema after application of a eutectic mixture of local anesthetic (EMLA) topical anesthetic cream for neonatal male circumcision (NMC). Although local edema and erythema are known potential side effects of EMLA cream, a common anesthetic used for NMC, the loss of landmarks precluding safe NMC has not previously been reported, and is described here. Although we cannot recommend an alternate local anesthetic for neonates with this reaction to EMLA, based on a review of the published data we think that serious systemic adverse events related to EMLA are extremely rare.

Keywords

Male circumcision; neonatal; EMLA; Eutectic Mixture of Local Anesthetic; adverse events; edema

Background

Local anesthesia is routinely used during NMC. Methods of pain control studied for NMC include injected lidocaine for dorsal penile nerve block (DPNB) or ring block, topical lidocaine, topical EMLA (2.5% lidocaine and 2.5% prilocaine) cream, acetaminophen and sucrose/dextrose pacifiers. Many practitioners advocate a combination of interventions, such as injectable anesthesia together with sucrose pacifiers[1]. While mild to moderate blanching, erythema and edema[2–4] are known potential side effects of EMLA cream, we do not know of cases in which the topically applied anesthesia resulted in loss of landmarks necessary for safe NMC.

Although clinical trials have concluded that DPNB is more effective for pain control than topical anesthetic creams during NMC[1], the latter have some practical advantages. Topical anesthetic creams avoid pain of the injection, avoid potential complications from inadvertent intravascular injection, including overdose[5], and eliminate potential nosocomial infections, such as methicillin-resistant Staphylococcus aureus, that have been reported with multiuse vials of injectable anesthetics[6]. They do not require new needles and syringes and reduce the need for sharps disposal, important in resource-limited settings[7]. Additionally, they can be applied safely by non-physician providers, a vital issue for settings where physicians' time is limited[8, 9].

Male circumcision has been demonstrated to reduce heterosexual acquisition of HIV in men by about 60% [10–12] and to reduce significantly the acquisition of human papilloma virus and herpes simplex virus[13]. The World Health Organization (WHO) recommends "that male circumcision should be recognized as an efficacious intervention for HIV risk reduction"[14]. WHO further states that, "Since neonatal circumcision is a less complicated and risky procedure than circumcision performed in young boys, adolescents or adults … countries should consider how to promote neonatal circumcision in a safe, culturally acceptable and sustainable manner"[14]. NMC is not, however, currently a routine practice in southern Africa. In keeping with the WHO guidelines, we are conducting a pilot study of the safety, feasibility and uptake of NMC in Botswana and, for the reasons noted above, we selected EMLA cream as the anesthetic of choice.

Cases Reports

Case 1

Infant 1 was born at estimated 39 weeks gestation, weighing 2.73 kg. On day 2 of life, his family requested circumcision. Initial examination of the infant by the nurse midwife revealed normal external male genitalia. As per protocol, approximately 1 gram of EMLA

cream was applied to the penis and covered with an occlusive dressing. Approximately 2 hours later he was brought to the study physician for circumcision. On examination at that time the foreskin was edematous and no corona was discernable (Figures 1a and 1b). EMLA cream was removed and the newborn was not circumcised. He had no other local or systemic signs of reaction to the medication. He was discharged home in good condition. He was examined 96 hours later and found to have normal uncircumcised external male genitalia (Figure 1c).

Case 2

Infant 2 was born at estimated 41 weeks gestation, weighing 3.32 kg. On day 2 of life, his family requested circumcision. Initial examination of the infant by the nurse midwife revealed normal external male genitalia. Approximately 1 gram of EMLA cream was applied to the penis and covered with an occlusive dressing. Approximately 2 hours later he was brought to the study physician for circumcision. On examination at that time the foreskin was markedly edematous and no corona was discernable (Figure 2a). EMLA cream was removed and the newborn was not circumcised. He had no other local or systemic signs of reaction to the medication. He was examined 24 hours later and found to have normal uncircumcised external male genitalia (Figure 2b).

The same tube of EMLA was used for the two infants and also for several other infants who did not experience any discernable reaction. In more than 450 NMCs performed at our site these are the only two such reactions we have seen. The typical reaction we have seen in our practice is mild edema of the distal foreskin (Figure 3).

Discussion

Transient local reactions to EMLA cream are not uncommon[2–4, 9, 15]. One series reported erythema and mild blistering of the foreskin; this is the only published report we found (using PubMed keyword search “EMLA” and “circumcision”) in which EMLA cream precluded NMC[16]. We report here for the first time loss of anatomical landmarks secondary to marked local edema after the application of EMLA cream that precluded NMC. No other local or systemic adverse events were noted in these cases.

Previous clinical trials with EMLA cream for NMC have used doses ranging from 0.5 grams – 5.0 grams left under an occlusive dressing from 30 – 120 minutes or more[9, 17–19]. Although longer application time (2–3 hours) results in maximal anesthetic effect[20], this must be weighed against the concern for local side effects and for systemic absorption of the anesthetic agents which increases with size of the application area, amount of cream applied and duration of application. The development of a local reaction to EMLA cream does not in itself indicate an increased risk for systemic toxicity.

The most common concern for systemic toxicity is methemoglobinemia, which has been reported after the use of some local anesthetic agents, such as injected prilocaine[21]. Methemoglobinemia is the oxidation of the iron moiety within the hemoglobin molecule that results in effective tissue hypoxia. This rare complication is of special concern in neonates, as they have a relative deficiency of the enzyme required to reduce methemoglobin (mtHB). Immature skin barrier and relatively high ratio of surface area to body weight are additional risk factors placing neonates at greater risk for systemic toxicity from mtHB-inducing agents. The manufacturer of EMLA cream, AstraZeneca, warns: “EMLA Cream should not be used in neonates with a gestational age less than 37 weeks nor in infants under the age of twelve months who are receiving treatment with [other] methemoglobin-inducing agents”. Of note: neither infant in this series had received any other potentially mtHB-inducing

agents. The manufacturer also recommends that for children 0–3 months or < 5 kg, the dose not exceed 1 gram applied to more than 10 cm2 and application no more than 1 hour[20].

Nonetheless, in published studies of EMLA cream for NMC in which serum levels of mtHB were measured, no infant was found to have toxic levels. One study found no difference in percentage of mtHB concentration in blood between infants who received EMLA cream (1 gram for 60–80 min) and those who received no anesthetic (mean mtHB concentration 1.3±0.6 % in EMLA cream group and 1.3±0.2 % in placebo group, $P = 0.80$)[15]. Although another study showed no significant difference in the mean mtHB concentration among infants who received EMLA cream (1.3%) (2 grams for at least 90 minutes) and those who received placebo (0.6%) or injected lidocaine for DPNB (0.7%) or injected lidocaine for ring block (0.4%), two infants in the EMLA cream group had mtHB levels of 2.4% and 4.5%, respectively, and no treatment was required[22]. A third study showed that although levels of methemoglobin increased from baseline in infants treated with EMLA cream prior to circumcision, they did not exceed normal values[23].

Though we do not have the capacity to measure serum mtHB concentration at our facilities, the two newborns discussed here did not develop any pallor or cyanosis, findings known to develop as a result of methemoglobinemia when serum levels of mtHB exceed about 5%. For other clinical signs and symptoms of methemoglobinemia to become apparent, mtHB levels usually exceed 30%[24]. Searching PubMed “eutectic mixture of local anesthetic” or “EMLA” and “methemoglobinemia”, we find two case reports of infants developing methemoglobinemia after application of EMLA cream for NMC: in one case 3.5 grams were applied for an hour and in another case an unknown amount was applied for 3 hours. In both cases the infants were noted to have changes in skin color that prompted testing for methemoglobinemia. Both infants had methemoglobin levels of 16%. No treatment other than supplemental oxygen was required and no other sequelae were noted[25, 26]. A published, systematic review of EMLA cream in neonates, not limited to use for NMC, found no clinically significant cases of methemoglobinemia, with a maximum measured value of 16%[27].

The question remains as to what local anesthetic would be safe to use in neonates experiencing local tissue edema secondary to EMLA cream. As both lidocaine and prilocaine have been independently reported to cause tissue edema, we do not feel comfortable recommending other preparations of prilocaine or lidocaine (either injectable or topical) in individuals who have had this reaction to EMLA cream. The US Food and Drug Administration recommends avoiding benzocaine in children less than 4 months of age[28]. Although tetracaine is an ester-type (while lidocaine and prilocaine are both amide-type) local anesthetic and this may suggest reduced risk of cross-reactivity[29], tetracaine has not been studied in NMC so we cannot currently recommend its use. Infants with localized reactions to EMLA cream may have to wait until they are old enough to undergo the procedure under general anesthesia if so desired.

It is important to emphasize that NMC is an elective procedure and should only be undertaken when providers can ensure there are no unnecessary risks resulting from the conditions under which it is performed. Providers must be encouraged to evaluate each neonate carefully and be willing to abandon the procedure in circumstances such as the one described here.

Conclusions

Although EMLA cream has a number of advantages over injectable formulations and serious adverse reactions are extremely rare, providers should be aware that one potential side effect is marked edema resulting in the complete loss of anatomical landmarks

necessary for safe NMC. It is not clear whether this is related to duration of application. We do not recommend re-challenge with EMLA cream.

Acknowledgments

Funding: Supported by NIH 5K23AI084579 from the National Institutes of Allergy and Infectious Diseases (Dr. Plank). The larger study was supported through the President's Emergency Plan for AIDS Relief (PEPFAR) grant U2GPS000941-01, Programme No. 08-P0157. The content is solely the responsibility of the authors and does not necessarily represent the official views of PEPFAR or the National Institutes of Health. The study sponsors had no role in the study design, in the collection, analysis and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication.

Abbreviations

DPNB	Dorsal penile nerve block
EMLA	Eutectic mixture of local anesthetic
mtHB	methemoglobin
NMC	Neonatal male circumcision
WHO	World Health Organization

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1a


1b


1c

Figure 1.

Infant 1: a) about 2 hours after application of EMLA, with localized bullous edema of distal foreskin with obliteration of normal anatomical landmarks; b) ventral aspect of penis showing spread of edema along median raphe. Note obliteration of the perimeter of the coronal sulcus that would usually be apparent beneath the foreskin: c) Follow-up 96 hours later reveals normal uncircumcised penis and discernable coronal sulcus.


2a


2b

Figure 2.
Infant 2: a) about 2 hours after application of EMLA, with localized bullous edema of distal foreskin with obliteration of normal anatomical landmarks: b) Follow-up 24 hours later reveals normal uncircumcised penis.

Figure 3.
Typical reaction to EMLA with mild edema of the distal foreskin.