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## EFFICACY AND SAFETY OF LIDOCAINE-PRILOCAINE CREAM FOR PAIN DURING CIRCUMCISION

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### ABSTRACT

**Background** Neonatal circumcision is a painful surgical procedure often performed without analgesia. We assessed the efficacy and safety of 5 percent lidocaine-prilocaine cream (Emla) in neonates undergoing circumcision.

**Methods** We carried out a double-blind, randomized, controlled trial in 68 full-term male neonates: 38 were assigned to receive lidocaine-prilocaine cream, and 30 to receive placebo. One gram of lidocaine-prilocaine or placebo cream was applied to the penis under an occlusive dressing for 60 to 80 minutes before circumcision. Behavioral (facial activity and time spent crying) and physiologic (heart rate and blood pressure) responses were recorded during the procedure. Blood samples were obtained at various times after drug application for measurements of methemoglobin and plasma lidocaine, prilocaine, and *o*-toluidine (a metabolite of prilocaine).

**Results** A total of 68 and 59 neonates were included in the safety and efficacy analyses, respectively. Demographic characteristics such as gestational age and birth weight did not differ between the lidocaine-prilocaine and placebo groups. During circumcision, the neonates in the lidocaine-prilocaine group had less facial activity ( $P=0.01$ ), spent less time crying ( $P<0.001$ ), and had smaller increases in heart rate ( $P=0.007$ ) than the neonates in the placebo group. Facial-activity scores were 12 to 49 percent lower during various steps of the procedure in the lidocaine-prilocaine group. As compared with neonates in the placebo group, infants in the lidocaine-prilocaine group cried less than half as much and had heart-rate increases of 10 beats per minute less. Blood methemoglobin concentrations (expressed as a percentage of the hemoglobin concentration) were similar (1.3 percent) in both groups. Lidocaine and prilocaine were detected in plasma in 23 (61 percent) and 21 (55 percent) of the infants treated with lidocaine-prilocaine cream, respectively.

**Conclusions** Lidocaine-prilocaine cream is efficacious and safe for the prevention of pain from circumcision in neonates. (N Engl J Med 1997;336:1197-201.)

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MANY physicians are reluctant to administer analgesic drugs to neonates undergoing circumcision, despite evidence that this procedure causes intense pain.<sup>1-3</sup> The most frequently cited reasons are lack of familiarity with techniques of administration and the actions and side effects of analgesic drugs in this age group. There also appears to be a perception that circumcision is a minor procedure that is unworthy of analgesia.<sup>1,2</sup>

A safe and effective analgesic that is easy to administer is needed. One alternative is a 5 percent lidocaine-prilocaine cream (2.5 percent lidocaine and 2.5 percent prilocaine, Emla, Astra, Mississauga, Ont., Canada), which is a eutectic mixture of local anesthetics — that is, a mixture whose melting point is lower than the melting points of either lidocaine or prilocaine. Unlike previous formulations, this formulation allows the use of high concentrations of the anesthetic bases without concern about local irritation, uneven absorption, or systemic toxicity. Lidocaine-prilocaine cream produces reliable analgesia for various cutaneous procedures including venipuncture,<sup>4,5</sup> lumbar puncture,<sup>6</sup> and vaccination.<sup>7,8</sup>

In the one reported trial of lidocaine-prilocaine cream for circumcision, neonates who received the anesthetic had significantly lower levels of facial activity, which is used to estimate pain in these patients; cried less during the procedure; and had smaller increases in heart rate and higher oxygen-saturation values than neonates who received a petrolatum place-

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bo.<sup>9</sup> However, the data were collected by an observer who was aware of treatment assignment. Moreover, methemoglobin concentrations were not measured in the study, and there is a concern that lidocaine–prilocaine cream may cause methemoglobinemia in neonates. We therefore undertook this study to investigate the efficacy and safety of lidocaine–prilocaine cream for pain during circumcision in neonates.

## METHODS

The study subjects were 68 healthy white male neonates ( $\geq 37$  weeks' gestation; birth weight,  $\geq 2500$  g) undergoing circumcision. We excluded neonates with jaundice or methemoglobinemia and those receiving methemoglobin-inducing, analgesic, or sedative drugs. The protocol was approved by the ethics boards of the Hospital for Sick Children and Women's College Hospital, and the parents gave informed written consent for their infants to participate.

### Study Procedures

The lidocaine–prilocaine and placebo creams were provided by Astra. The lidocaine–prilocaine cream was composed of a 1:1 mixture of lidocaine and prilocaine that was emulsified in water and thickened to produce a suitable consistency. The placebo cream was identical, except that the active ingredients were replaced with coconut oil.

The neonates were randomly assigned to receive lidocaine–prilocaine or placebo cream. One milliliter (1 g) of study cream was drawn into a 3-ml syringe. One third of the dose was applied to the lower abdomen. The penis was then extended upward and gently pressed against the abdomen. The remainder of the dose was applied to a Tegaderm dressing that was placed over the penis and taped to the abdomen, so that the cream surrounded the penis. After 60 to 80 minutes, the dressing was removed and the cream was wiped away with a tissue. Local skin reactions were recorded.

Circumcisions were performed by one of three study-team pediatricians in the nursery treatment room. The procedure was standardized and divided into 13 periods of observation: base line, restraint of the infant by a circumcision board (Circumstraint, Olympic Surgical, Seattle), application of antiseptic, application of forceps, lysis of adhesions, dorsal incision, application of the clamp (Gomco, St. Louis), pulling of skin through the clamp, tightening of the clamp, cutting of foreskin, removal of the clamp (five minutes after the foreskin was cut), application of petrolatum dressing, and removal of restraints.

The infant's facial expressions were continuously recorded during the procedure with a video camera (model PV-S770A-K, Panasonic, Mississauga, Ont.) positioned approximately 60 cm from his face. A model AS3 monitor (Datex-Engstrom, Helsinki, Finland) was used to monitor the heart rate. Blood pressure was monitored noninvasively with a Critikon Dinamap monitor (model 1846SX, Johnson and Johnson, Peterborough, Ont.) interconnected with the cardiorespiratory monitor.

A heparin-treated blood sample (1 to 1.5 ml) was collected from each neonate 1.25, 2, 4, 6, 10, or 18 hours ( $\pm 15$  minutes) after the study drug was applied, according to a preassigned randomization code, for measurements of methemoglobin and plasma lidocaine, prilocaine, and *o*-toluidine (a metabolite of prilocaine that causes methemoglobinemia).

The neonates were observed for adverse effects every 8 hours for up to 24 hours after the circumcision. The parents were contacted by telephone two weeks after the circumcision and interviewed about adverse effects with a standardized questionnaire.

### Assessment of Pain

The facial activity of the neonates, which reflects the amount of pain experienced, was assessed by a research assistant unaware

of the treatment assignments who was trained to use the Neonatal Facial Coding System reliably ( $\kappa$ , 0.93;  $P < 0.001$ ).<sup>10-12</sup> The presence or absence of 10 discrete facial actions — bulging of the brow, squeezing the eyes closed, nasolabial furrowing, opening the mouth, vertically stretching the mouth, horizontally stretching the mouth, pursing the lips, holding the tongue taut, quivering of the chin, and protrusion of the tongue — was scored from the videotape in 2-second intervals for the first 20 seconds of each phase of the circumcision or for the entire duration of the phase if it lasted less than 20 seconds. The research assistant could stop and start the videotape as many times as needed to score each facial action. The recorded image had a running time clock.

A summary score of facial activity was devised to compare facial expressions between groups. First, raw scores of each facial action were expressed as the proportion of time each action was observed during each phase of the circumcision. Then facial actions correlating poorly with other actions ( $r < 0.15$ ) were removed in a stepwise fashion with principal-components analysis, leaving six facial actions (bulging of the brow, squeezing the eyes closed, nasolabial furrowing, vertically stretching the mouth, holding the tongue taut, and opening the mouth) that accounted for 64 percent of the variability in infants' responses. These six scores were weighted according to the raw coefficients from the factor analysis and totaled to arrive at an overall facial-activity score ranging from 0 to 1.226.

Secondary outcome measures included the duration of crying during each phase of the procedure and physiologic (heart rate and blood pressure) changes. The duration of crying was calculated from the videotape as the percentage of time an infant cried during each phase of the circumcision, with scores ranging from 0 to 100 percent. The mean heart rate was calculated for each phase from raw data recorded directly onto a laptop computer with the Datex AS3 Datacollect program (Puritan Bennett, Pickering, Ont.). Systolic and diastolic blood pressures were measured in each infant at base line and during lysis of adhesions.

### Laboratory Analyses

Blood methemoglobin was measured with a co-oximeter (model 482, Instrumentation Laboratory, Lexington, Mass.) and expressed as a percentage of total hemoglobin. All samples were stored on ice for six hours or less before analysis. The 95 percent confidence interval reported by the manufacturer was  $\pm 1$  percent, and the standard deviation 0.5 percent. The remainder of the blood sample was centrifuged, and the plasma was separated and frozen at  $-20^\circ\text{C}$ . Plasma lidocaine, prilocaine, and *o*-toluidine were measured simultaneously by high-performance liquid chromatography.<sup>13</sup> For each compound, the limit of detection was 20 ng per milliliter and the within-day coefficient of variation ranged from 3.1 to 8.3 percent.

### Statistical Analysis

Facial-activity scores, the duration of crying, and heart rate were compared between groups with repeated-measures analysis of covariance, in which seven of the circumcision phases (application of forceps, lysis of adhesions, dorsal incision, application of the clamp, pulling of skin through the clamp, tightening of the clamp, and cutting foreskin) were included and the base-line value was the covariate. Univariate and multivariate effects were examined. Methemoglobin concentrations were compared by Student's *t*-test. Blood pressure was analyzed by analysis of covariance. The characteristics of the infants in the two groups were compared by chi-square test or Student's *t*-test. Analyses were performed with SAS computer software. Statistical tests were two-tailed.

## RESULTS

The characteristics of the 68 neonates, 38 in the lidocaine–prilocaine group and 30 in the placebo group, were similar (Table 1). Eight neonates were treated with lidocaine–prilocaine cream in an un-

**TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF THE NEONATES IN THE LIDOCAINE-PRILOCAINE AND PLACEBO GROUPS AND THEIR MOTHERS.\***

CHARACTERISTIC	LIDOCAINE-PRILOCAINE (N=38)	PLACEBO (N=30)	P VALUE
Neonates			
Gestational age — days	278±9	276±9	0.36
Birth weight — g	3604±401	3548±442	0.59
Postnatal age — days	1.3±0.8	1.6±0.9	0.13
5-Minute Apgar score	9.1±0.3	9.1±0.3	0.54
Vaginal delivery — no. (%)	29 (76)	19 (63)	0.24
Mothers			
Age — yr	32±4	33±4	0.40

\*Plus-minus values are means ±SD.

blinded fashion and were included only in the safety analysis. Fifty-nine neonates were included in the efficacy analysis: 29 in the lidocaine-prilocaine group and 30 in the placebo group. One neonate in the lidocaine-prilocaine group was excluded because he was not circumcised on the day the cream was applied. Fifty-five of the neonates were circumcised by the same pediatrician. The mean (±SD) interval between the removal of the cream and circumcision was 13±16 minutes in the lidocaine-prilocaine group and 10±11 minutes in the placebo group (P = 0.35).

The duration of the procedure (i.e., from the application of forceps to cutting of the foreskin) was 9±1 minutes in the lidocaine-prilocaine group and 9±2 minutes in the placebo group (P = 0.34).

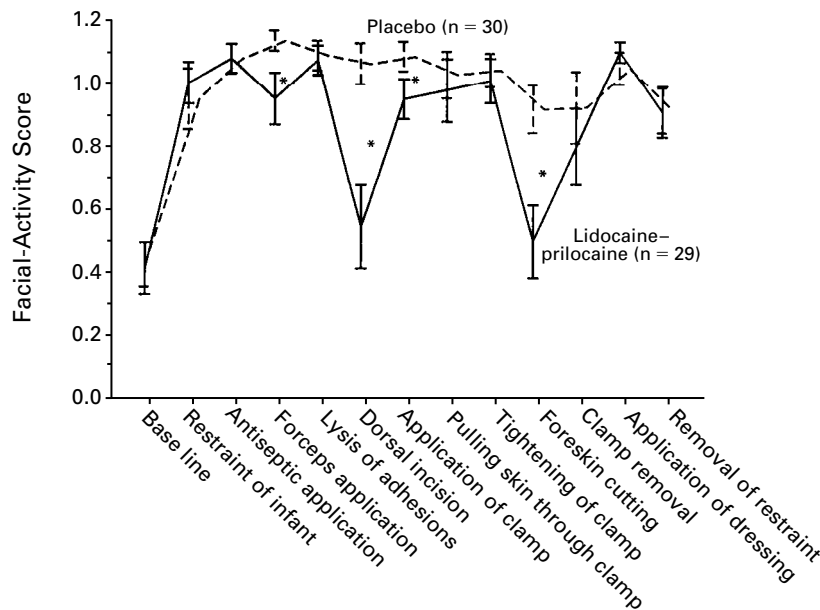
**Infants' Response to Pain**

The facial-activity scores recorded during circumcision are shown in Figure 1. The scores increased in both groups and remained high in the placebo group throughout the procedure. During surgery, the scores were lower in the lidocaine-prilocaine group than the placebo group (P = 0.01). The lidocaine-prilocaine group had 12 to 49 percent less facial activity (P<0.001) than the placebo group during forceps application, dorsal incision, application of the clamp, and foreskin cutting.

The lidocaine-prilocaine group spent less time crying during the procedure than the placebo group (P<0.001) (Table 2); they cried less (P<0.05) during six of the circumcision phases. They also had a smaller increase in heart rate overall (P = 0.007) (Table 2) and during five of the circumcision phases (P<0.05).

**Adverse Effects**

None of the neonates had any clinical signs of methemoglobinemia. The mean methemoglobin concentration was 1.3±0.6 percent in the lidocaine-



**Figure 1.** Mean Facial-Activity Scores during Circumcision in the Lidocaine-Prilocaine and Placebo Groups.

A higher score indicates that the infant experienced more pain. The asterisks indicate a significant difference (P<0.001) between the groups. P = 0.01 for the overall comparison between groups. Bars indicate 95 percent confidence intervals.

**TABLE 2.** RESPONSE TO CIRCUMCISION IN THE LIDOCAINE-PRILOCAINE AND PLACEBO GROUPS.\*

CHARACTERISTIC	LIDOCAINE-PRILOCAINE	PLACEBO	P VALUE
Increase during procedure in percentage of time spent crying (%)†	21±27	46±25	<0.001
No. of infants	29	30	
Increase in heart rate (beats/min)†	7±13	17±16	0.007
No. of infants	19	20	
Increase in systolic blood pressure (mm Hg)†	11±17	14±21	0.22
No. of infants	22	16	
Increase in diastolic blood pressure (mm Hg)†	19±22	24±33	0.16
No. of infants	22	16	

\*Plus-minus values are means ±SD. Vigorous body movements during the procedure and errors in the storage of data by computers prevented the acquisition of physiologic data on some neonates, as indicated.

†The increase is the increase from base line.

**TABLE 3.** PLASMA LIDOCAINE AND PRILOCAINE CONCENTRATIONS IN THE LIDOCAINE-PRILOCAINE GROUP.

HOURS AFTER APPLICATION	LIDOCAINE*		PRILOCAINE*	
	ng/ml	No. OF SAMPLES WITH UNDETECTABLE LEVELS/TOTAL No. OF SAMPLES†	ng/ml	No. OF SAMPLES WITH UNDETECTABLE LEVELS/TOTAL No. OF SAMPLES†
1-1.5	46 (38-91)	2/7	35 (24-74)	2/7
1.75-2.25	50 (41-100)	0/6	33 (29-68)	1/6
3.75-4.25	96 (30-135)	1/7	62 (29-81)	1/7
5.75-6.25	48 (21-103)	3/7	49 (24-107)	4/7
9.75-10.25	21, 28	4/6	25, 45	4/6
17.75-18.25	—	5/5	—	5/5

\*Values are medians, with ranges given in parentheses.

†The limit of detection was 20 ng per milliliter. Each of the 38 infants donated one blood sample.

prilocaine group and 1.3±0.2 percent in the placebo group (P=0.80). There were no differences between groups at any time during sampling.

Twenty-three (61 percent) of the neonates in the lidocaine-prilocaine group had detectable plasma lidocaine concentrations, and 21 (55 percent) had detectable plasma prilocaine concentrations. The highest concentrations were detected within four hours after drug administration (Table 3). No neonate had detectable concentrations 18 hours after drug application. The metabolite *o*-toluidine was undetectable in all infants.

Mild pallor at the site of application of the cream was observed in 12 (32 percent) of the neonates in

the lidocaine-prilocaine group, as compared with 4 (13 percent) in the placebo group (P=0.08). One neonate in the lidocaine-prilocaine group had mild edema, and one had a local infection that was successfully treated with a topical antibiotic.

## DISCUSSION

We found that applying lidocaine-prilocaine cream to the penis reduced the pain of circumcision in neonates, as measured by facial activity, the duration of crying, and heart-rate changes, confirming the results of a previous small trial.<sup>9</sup> Although the use of lidocaine-prilocaine cream was associated with an overall decrease in pain, the magnitude of the effect varied during the procedure: it was less effective during phases associated with extensive tissue damage such as lysis of adhesions and tightening of the clamp. The neonates in the lidocaine-prilocaine group still had pain during the circumcision, albeit at an attenuated level. The efficacy of lidocaine-prilocaine cream is affected by the method of application and the dosage. Uneven distribution of cream may cause variations in the tissue concentrations of lidocaine and prilocaine and subtherapeutic anesthetic concentrations in some regions.

Alternative methods of analgesia for circumcision include dorsal penile nerve block with lidocaine and subcutaneous infiltration of lidocaine in the foreskin. These techniques are more effective than applying lidocaine-prilocaine cream, decreasing the amount of time infants spend crying by up to 70 percent and preventing large increases (of up to 60 beats per minute) in the heart rate.<sup>14-16</sup> Both techniques, however, are rarely used because they require skills that most physicians have not acquired. Moreover, the injections themselves are considered painful and are associated with the risk of systemic toxicity due to inadvertent injection of the local anesthetic into a blood vessel.

Neonates have immature reductase enzyme pathways that predispose them to methemoglobinemia from oxidizing agents such as metabolites of prilocaine. However, we found no changes in blood methemoglobin concentrations up to 18 hours after the application of lidocaine-prilocaine cream. These results are consistent with those in previous studies of both preterm and full-term neonates that used single doses of 0.5 to 1.25 g of cream applied for 0.5 to 2 hours.<sup>17-21</sup> There have been only two reports of methemoglobinemia in infants in association with this treatment, and in both cases the doses of lidocaine-prilocaine cream were high.<sup>22,23</sup> In our study, the plasma concentrations of lidocaine and prilocaine were considerably below those considered toxic (>5000 ng per milliliter).<sup>24</sup> In addition, *o*-toluidine, the metabolite believed to cause methemoglobinemia, was not detected in any neonate.

Our study was limited to white neonates. In a pre-

vious study investigating racial differences in the effectiveness of lidocaine-prilocaine cream, black subjects had a smaller reduction in pain than whites, presumably because of the increased density of the stratum corneum.<sup>25</sup>

Physicians may be reluctant to use lidocaine-prilocaine cream when techniques (Mogen clamp and Plastibel) other than the one we employed are used for circumcision. However, we believe that the use of lidocaine-prilocaine cream is justified given that the extent of tissue damage is similar regardless of which technique is used, that lidocaine-prilocaine cream poses little risk to the infant, and that the cream blocks afferent nociceptive input for several hours after administration. Other interventions that comfort the infant (e.g., the use of a pacifier and the administration of sucrose) should also be used.<sup>26,27</sup> Acetaminophen may be effective for the postoperative control of pain.<sup>28</sup>

One of the reasons commonly cited for not using analgesia during neonatal circumcision is that the pain experienced by the infants is inconsequential. However, untreated pain from circumcision has been linked to short-term alterations in sleeping, feeding, and crying patterns.<sup>29-31</sup> In addition, circumcised infants have more pain during routine vaccinations at four to six months of age than uncircumcised infants.<sup>32,33</sup> Thus, circumcision may affect an infant's behavior months after the event.

In conclusion, the application of lidocaine-prilocaine cream decreased pain during circumcision and had no adverse effects. Lidocaine-prilocaine cream offers an alternative to nerve block that is relatively easy to administer. We recommend that its use be considered routinely in neonates undergoing this procedure, in order to decrease their pain.

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