A randomized, controlled trial of a eutectic mixture of local anesthetic cream (lidocaine and prilocaine) versus penile nerve block for pain relief during circumcision

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OBJECTIVE: We set out to compare a eutectic mixture of local anesthetic cream (lidocaine and prilocaine) to dorsal penile nerve block with lidocaine for anesthesia during circumcision.

STUDY DESIGN: In a double-blind study, term newborns were randomized to local anesthetic cream and sodium chloride solution dorsal penile nerve block (n = 31) or to placebo cream and lidocaine dorsal penile nerve block (n = 29). Pain was assessed by determination of heart rate, respiratory rate, and behavioral distress scoring. Group differences were evaluated with repeat-measures analyses of variance.

RESULTS: Distress scores and heart rates were significantly higher in the eutectic mixture group than in the lidocaine group. Respiratory rates were higher in the eutectic mixture group but did not reach statistical significance.

CONCLUSIONS: Distress scores and heart rates were significantly higher in infants treated with the anesthetic mixture than in infants treated with lidocaine. Dorsal penile nerve block with lidocaine is a more efficacious means of providing anesthesia for neonatal circumcision than the mixture of local anesthetics. (Am J Obstet Gynecol 1999;181:1506-11.)

Key words: Neonatal circumcision, pain, lidocaine, EMLA

Neonatal circumcision remains one of the most common surgical procedures in the United States with approximately 64% of male newborns undergoing the procedure (National Center for Health Statistics, 1997 Aug). Whereas complication rates are low, ranging from 0.2% to 5%, the pain of circumcision without anesthesia is increasingly recognized as a significant side effect.[1-3] The American Academy of Family Physicians[4] acknowledged in its 1996 statement that neonatal circumcision is painful and that local anesthetic techniques alleviate intraoperative pain while posing little additional risk to the infant. The recently released American Academy of Pediatrics[3] statement on neonatal circumcision also called for the use of pain relief for this procedure. Furthermore, the American Academy of Pediatrics Committee on Anesthesia[5] declared in its statement about the use of pain relief medications in infancy that "…the decision to withhold such medication should be based on the same criteria used for older children."

There is considerable evidence that newborns who are circumcised without analgesia or anesthesia experience pain and physiologic stress.[3, 4, 6, 7] Neonatal physiologic responses to circumcision pain include changes in heart rate, respiratory rate, blood pressure, and oxygen saturation.[8-10] Behavioral distress has been documented by changes in the infant's postoperative behavior and by changes in the duration, pitch, and urgency of intraoperative infant crying.[2, 10-13]

In recognition of the need to provide effective and safe pain relief during circumcision, a number of studies have been conducted.[7, 9, 10, 14-18] Both EMLA (Astra USA, Inc, Westborough, Mass) cream and dorsal penile nerve block with lidocaine have been demonstrated to be effective methods of pain relief for neonatal circumcision.[14, 16-19] Until recently, however, there were no published studies comparing the 2 pain relief methods.[20, 21] The purpose of this randomized, double-blind clinical trial was to evaluate the relative efficacy of EMLA cream in comparison to dorsal penile nerve block for pain relief during neonatal circumcision.

Methods

This study protocol was approved by the Clinical Investigation Committee of Rochester General Hospital. Healthy, appropriate-for-gestational-age, term male in-

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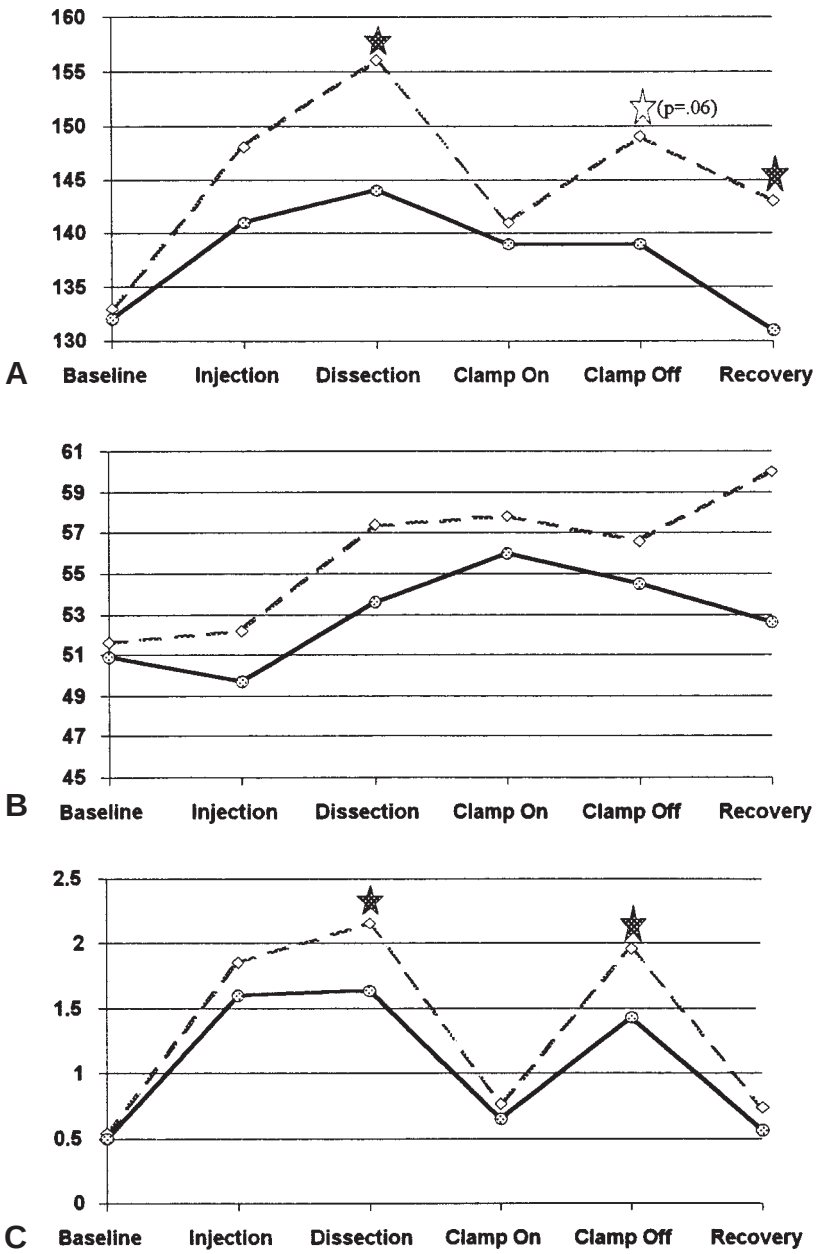

Fig 1. Group mean by stage of procedure; heart rate **(A)**, respiratory rate **(B)**, and behavioral distress scale **(C)** data. *Diamonds,* EMLA; *circles,* dorsal penile nerve block. *Dotted stars,* Individual stages of procedure for which statistically significant differences existed between study groups ($P \leq .05$). Statistical significance between procedures was as follows: **A,** $P = .05$; **B,** $P = .21$; **C,** $P = .04$.

fants whose parents requested circumcision were eligible for the study. Parental informed consent was obtained. Infants were randomized in a double-blind fashion to 1 of 2 study groups according to a random number list maintained in the hospital pharmacy. A total of 62 infants were randomized; however, only 60 infants completed the protocol. Before the procedure, tachypnea developed in 1 infant and another infant's parents withdrew permission for study participation. Infants were at least 24 hours old at the time of circumcision, and most (>85%) were discharged within 6 to 8 hours of the procedure.

One hour before the procedure and in accord with study group assignment, a pharmacy research nurse applied 1 g of either a placebo or EMLA cream to the distal half of the infant's penis.[19] The cream was then covered with an occlusive dressing. The placebo cream was selected to resemble EMLA cream as nearly as possible. Prefilled tuberculin syringes containing either sodium chloride solution or 1% lidocaine without epinephrine

Table I. Study group characteristics

Factor	*EMLA*	*Dorsal penile nerve block*	*Statistical significance**
Gestational age (wk)	39.8 ± 1.2	39.6 ± 1.3	*P* = .44
Birth weight (g)	3474 ± 476	3382 ± 508	*P* = .47
5-min Apgar score	8.9 ± 0.4	9.0 ± 0.4	*P* = .21
Age at circumcision (d)	2.0 ± 1.0	1.9 ± 0.9	*P* = .78
Procedural time (includes monitoring time) (min)	19.6 ± 3.6	18.4 ± 3.3	*P* = .19

*Analyses conducted with independent sample *t* test.

Table II. Mean differences (repeat-measures analysis of variance) between study groups for behavioral and physiologic outcomes

Variable	*EMLA (mean and SE)*	*Dorsal penile nerve block (mean and SE)*	*Mean difference (EMLA – Dorsal penile nerve block*)*	*95% Confidence interval*	*Statistical significance*
Distress scale	1.50 (0.09)	1.22 (0.09)	0.28	0.01 to 0.54	*P* = .040
Heart rate	146.9 (2.7)	139.0 (2.8)	7.9	0.1 to 15.6	*P* = .047
Respiratory rate	56.3 (1.6)	53.4 (1.7)	2.9	–1.7 to 7.5	*P* = .210

*Mean value for EMLA group minus mean value of dorsal penile nerve block group.

and labeled with the infant's name were also dispensed by the pharmacy. Pharmacy personnel responsible for randomization and the application and dispensing of medications had no other responsibilities in this study.

Blocks were administered by the surgeon performing the circumcision at the time of the procedure. The standard technique was used with administration of 0.4 mL on each side of the penis for a total volume of 0.8 mL of either sodium chloride solution or 1% lidocaine.[22] Twenty-nine infants were randomized to placebo cream and 1% lidocaine for dorsal penile nerve block, and 31 infants were randomized to EMLA cream and sodium chloride solution for dorsal penile nerve block.

Circumcisions were performed with the Gomco clamp (Allied Healthcare Products, St Louis, Mo) method. All procedures were performed by 1 of 3 investigators (K.F., P.G., D.Z.) who were experienced in both circumcision and dorsal penile nerve block. Infants were brought to a quiet room near the nursery. They were placed on the Circumstraint (Olympic Medical Co, Seattle, Wash) board, and their legs were restrained. A nurse held the infants' arms in flexion on the chest, and all infants were offered pacifiers. Infants were allowed to settle for up to 5 minutes before data collection was begun. Videotape recordings of the face and upper torso of the infants were made during all procedures. Heart and respiratory rates were recorded every 60 seconds. Heart rate monitoring involved the use of a Nellcor (Nellcor Puritan Bennett, Pleasanton, Calif) cardiorespiratory monitor. Respiratory rates were counted and recorded by a registered nurse. The procedure was divided into 6 stages beginning and ending with 2-minute baseline and recovery time periods. The second stage of the procedure entailed administration of the block, a 4-minute time period for the infant to settle after block administration, and then cleaning and draping of the surgical area. The third stage entailed separation of the prepuce from the glands and ended with the placement of the Gomco clamp. The fourth stage involved excision of the foreskin and clamp removal (clamps were left in place for a total time of 5 minutes). The fifth stage of the procedure included dressing placement and diapering of the infant. For the recovery period the infant remained unrestrained on the Circumstraint board.

When this study began, no comparative studies of these 2 methods of anesthesia were available. A total of 62 infants were randomized to ensure an adequate sample size for all the planned outcome measures (desired total N = 60). Sample size calculations were based on physiologic changes (heart rate) noted in other studies of circumcision with a total sample size of about 40 infants required.[7, 10, 14] Our actual n = ~30 infants per group provided 97% power with $\alpha = .05$ to detect a 10-beat (SD 10) difference between groups. Calculations indicated that 30 infants per group would also provide 86% power to detect a 35% difference in distress scores between groups (a change of 1.12-1.51 [SD .49]).[18] There were no adverse outcomes or complications in any infants who completed the study protocol; however, the sample size was inadequate to detect significant differences in complication rates.

Outcomes for this study included physiologic and behavioral measures. Heart rate and respiratory rate were used as physiologic measures of pain with data recorded every 60 seconds during the procedure. Behavioral distress was assessed by reviewing the videotape of the procedure. Distress scores were assigned for every 30 seconds of the procedure. A score of 0 was assigned for

neutral or Brazelton states 1 to 4—a score of 1 for minimal fussiness (≤2 episodes of fussiness in 30 seconds), a score of 2 for moderate fussiness (≥3 episodes of fussiness in 30 seconds or a light rolling cry), and a score of 3 for a sustained cry or Brazelton state 6 over the 30-second interval.[18] A single observer (C.tH.), blinded to study group assignment and trained in Brazelton behavioral state assessment, reviewed each tape and assigned distress scores.

Analysis. Data were entered and analyzed with the SPSS (SPSS Inc, Chicago, Ill) version 8. Statistical tests used to make baseline comparisons of the study groups included the Student *t* test, χ^2 test, and Fisher exact test as appropriate.

Repeat-measures analysis of variance was used to compare differences between the study groups. For each outcome, individual data points obtained during specific stages of the procedure were first averaged to obtain a mean value for each specific stage (eg, mean heart rate at baseline). Repeat-measures analysis of variance was then used to evaluate differences between study groups for stages 2 to 6 of the procedure. In each analysis the baseline or stage 1 value was entered as a covariate with the study group entered as the between-group factor. Post hoc comparisons of specific stages of the procedure were made by use of the Tukey β level if the *P* value for the overall outcome (ie, heart rate, respiratory rate, or behavioral distress) was ≤ .05.

Results

The study groups were similar for a number of baseline and study-related factors. The groups did not vary in terms of gestational age, birth weight, age at circumcision, or procedure time (Table I).

Distress score and heart rate data were significantly different between treatment groups. There was no overall difference between the groups with regard to respiratory rate.

Mean differences between the study groups showed that both distress scores and heart rates were significantly higher in the EMLA study group in comparison with the lidocaine dorsal penile nerve block group. Respiratory rates were also higher in the EMLA group but did not reach statistical significance (Table II).

Fig 1 displays behavioral and physiologic outcomes at each stage of the procedure by study group. The lidocaine group had significantly lower distress scores both at dissection and with clamp removal in comparison with the EMLA group. In addition, the lidocaine group had significantly lower heart rates at dissection and during the recovery period. Post hoc analyses were not conducted on respiratory rate data because repeat-measures analyses did not demonstrate any significant overall group differences.

Comment

Recent years have seen the publication of a number of studies on pain relief for neonatal circumcision. Whereas the issue of routine performance of neonatal circumcision will undoubtedly continue to engender debate, pain control for the procedure is increasingly recognized as a standard of care.[3, 4, 23] This study provides empiric evidence about the relative efficacy of 2 recognized, safe, and effective pain relief methods for neonatal circumcision. Two other randomized trials compared EMLA and lidocaine, but neither of the previously published studies was truly blinded. In both studies the surgeon for the procedure was not blinded to the intervention. Findings from both studies are thus subject to some potential bias; an investigator's belief that one method is more effective than the other could result in differential treatment of infants during circumcision.[20, 21] This study is the first double-blind, randomized comparative study of EMLA and lidocaine.

This study confirms findings from the 2 previously published studies by Butler-O'Hara et al[20] and Lander et al.[21] Infants treated with lidocaine in this study had significantly less behavioral distress during circumcision in comparison with infants treated with EMLA. Butler-O'Hara et al[20] found significantly lower scores on the Neonatal Infant Pain Scale, and Lander et al[21] found a significantly decreased crying time in the lidocaine group compared with the EMLA group. Physiologic findings in both studies support our findings with significantly lower heart rates in lidocaine-treated infants in comparison with EMLA-treated infants. The findings of Butler-O'Hara et al[20] were similar to those in this study in that they showed no significant differences for respiratory rate between study groups. The study of Lander et al[21] included a control or no-analgesia study group and the Butler-O'Hara et al[20] study included an unanesthetized comparison group (nonrandomized). There is substantial existing evidence that infants who undergo circumcision without anesthesia experience significant pain and that dorsal penile nerve block and EMLA are effective pain relief methods.[3, 4, 8, 11-14, 19] We chose not to include an unanesthetized study group.

To ensure that all personnel involved in this study were blinded to group assignment, we administered placebo blocks to the EMLA study group and placebo cream to the lidocaine group. Infants in the EMLA group thus incurred some additional manipulation and pain not normally encountered in the clinical setting of usual procedures. Other investigators, however, have shown that distress and physiologic response to block administration is short-lived and that infants return to baseline physiologic states within approximately 25 seconds.[7, 21] Infants were allowed to settle for several minutes after block administration, which was sufficient time to ensure that

block administration did not affect other comparisons between the groups. In addition, in clinical practice both block administration and recovery would normally occur in the infant's crib. To ensure reliable data collection for this study these stages were performed with the infant on the Circumstraint board.

These data also suggest that clamping and excision of the foreskin are a relatively nonstressful stage of circumcision. However, we believe this to be an artifact of the study protocol, which specified clamping over a 5-minute interval. Individual measurements recorded during each stage of the procedure were averaged. Thus the reported mean values for stage 4 (Fig 1, *Clamp On*), which began after placement of the clamp, may reflect a return of the infant to baseline behavioral and physiologic norms over the prolonged monitoring interval. Data from this study clearly demonstrate that infants in the dorsal penile nerve block group experienced less distress than EMLA-treated infants during other invasive aspects of the surgery.

The administration of a dorsal penile nerve block requires some experience to achieve adequate analgesia and results in minimal pain for the infant during anesthetic administration.[21] The pain associated with dorsal penile nerve block administration, however, can be alleviated by the concurrent administration of oral sucrose.[18] The application of EMLA cream, whereas it is a nonpainful procedure, entails some potential technical difficulties. Application of the adhesive, semipermeable dressing that covers the topical cream may be problematic. In addition, monitoring is required to ensure that the dressing and cream remain in place. In carrying out a research trial there may be little difficulty in consistently applying topical analgesia and performing procedures at appropriate time intervals. Busy obstetrics units, however, are likely to encounter many more difficulties with such seemingly mundane aspects of care. Given our long-term clinical experience with neonatal circumcision, anesthesia, and care of newborns, we believe that the administration of local anesthesia at the time of circumcision is an underrecognized benefit of dorsal penile nerve block.

To date, practitioner use of pain relief for neonatal circumcision, including dorsal penile nerve block, has been limited.[23, 24] The majority of obstetricians who provide pain relief during neonatal circumcision use dorsal penile nerve block (77%). Fewer than 25% of obstetrician-gynecologists who perform circumcision, however, use any form of pain relief as compared with 71% of pediatricians and 56% of family practitioners. It is of concern that the use of pain relief is so uncommon for a procedure performed by 70% of obstetricians.[24] In light of the available empiric evidence, effective anesthesia during neonatal circumcision should be the standard of care. The recent American Academy of Pediatrics statement calling for the universal use of anesthesia for neonatal circumcision is encouraging and will undoubtedly enhance pediatric use of anesthesia.[3] We encourage both The American College of Obstetricians and Gynecologists and the American Academy of Family Physicians to issue similar statements to their membership specifying the universal use of effective anesthesia for neonatal circumcision.

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