

Dorsal Penile Nerve Block vs Topical Placebo for Circumcision in Low-Birth-Weight Neonates

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Objective: To investigate the efficacy and safety of dorsal penile nerve block (DPNB) and eutectic mixture of lidocaine (EMLA) for palliation of pain associated with circumcision in low-birth-weight infants.

Design: Randomized, blinded, controlled trial.

Setting: Intensive care nursery (step down unit) at Georgetown University Medical Center, Washington, DC.

Participants: Fifty neonates with weights of 1600 to 2500 g at the time of circumcision who were discharged from the hospital between May 1994 and June 1995 were randomly assigned to the DPNB, EMLA, or control group. Twenty-five infants who were otherwise eligible were excluded because of parental refusal of consent to participate.

Interventions: Infants in the DPNB and EMLA groups received anesthesia with subcutaneous injection of 1% lidocaine hydrochloride or topical EMLA, respectively. The control group received sham anesthesia with topical placebo (acid mantle cream).

Main Outcome Measures: Changes in physiologic variables (heart rate, blood pressure, oxygen saturation, and respiratory rate) and behavioral score 20 minutes before, during, and 5 and 20 minutes after circumcision between DPNB and control groups. Surgical complications and adverse effects were also monitored.

Results: Fifty infants were enrolled in the study: 19 randomized to the DPNB group, 19 to the control group, and 12 to the EMLA group. Enrollment into the EMLA group was suspended early because of redness and blistering of the foreskin in 2 infants, and this entire group was excluded from further analysis. The clinical course was similar in all groups of infants. All circumcisions were performed without complication or technical difficulty. Statistically significant differences were noted in heart rate, respiratory rate, and behavioral score when comparing the DPNB group with controls during and after circumcision.

Conclusion: Dorsal penile nerve block is safe and effective in controlling pain associated with circumcision in low-birth-weight infants.

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RESULTS OF several studies demonstrate the efficacy of anesthesia in providing pain relief in term infants and children undergoing circumcision. Topical lidocaine hydrochloride (30%) was investigated by Weatherstone et al,¹ dorsal penile nerve block (DPNB) with 1% lidocaine was studied by

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Maxwell et al² and Stang et al,³ and eutectic mixture of local anesthetics (EMLA: a mixture of 1% lidocaine and prilocaine hydrochloride for topical anesthesia) was used by Lee and Forrester⁴ and Benini et al.⁵ All studies demonstrated efficacy, as noted by smaller increases in physiologic variables in anesthetized vs control groups. However, none included low-birth-weight in-

fants and at the time this study was conducted, none included infants with birth weights of less than 2000 g.⁶ With earlier hospital discharge of smaller, preterm infants and parental requests for circumcision in this group of patients, this study was undertaken to investigate the safety and efficacy of using DPNB and EMLA as anesthetic agents in low-birth-weight infants.

RESULTS

Of 50 infants enrolled in the study, 12 were randomized to the EMLA group, 19 to the DPNB group, and 19 to the control group. Two infants in the EMLA group developed an apparent allergic hypersensitivity rash of the foreskin, which consisted of erythema with mild blister formation. These 2 infants were not circumcised, did not complete the study, and were dropped from analysis. Subsequent to these reac-

PATIENTS AND METHODS

This study was conducted as a randomized, blinded, controlled trial of infants born at Georgetown University Medical Center, Washington, DC, with weights of 1600 to 2500 g at the time of circumcision. Infants with congenital anomalies were excluded. After informed consent was obtained, infants were randomized, using randomization tables, to the DPNB, EMLA, or control group. Because of complications during the study, randomization to the EMLA group was discontinued. To maintain the blinded nature of the study, the DPNB and control groups received placebo (acid mantle) cream and the EMLA group received EMLA cream. Eutectic mixture of local anesthetics or acid mantle cream was applied to a 1 to 2 cm² surface area of the foreskin 1 hour before circumcision. Using a 1-cm³ tuberculin syringe with a 27-gauge needle, 0.4 cm³ of 1% lidocaine was injected subcutaneously to each side of the base of the dorsal penis, on the lateral sides (2- and 10-o'clock positions), according to standard technique 5 minutes before circumcision. A total of 0.8 cm³ of 1% lidocaine without epinephrine was used for DPNB. After the placebo or EMLA cream was applied, plastic wrap was applied loosely over the infant's foreskin and left undisturbed for 1 hour. The investigator (M.H. or S.K.) monitoring the infant's physiologic variables and behavior was not present during application of the placebo or EMLA cream or during administration of the DPNB injection.

The behavioral scale included 8 behavioral state variables: sleep state, cry, facial expression, torso movement, soothability, response to distress, need for tactile stimulation, and environmental noise. Interventions required to comfort infants, including vocalization, touch, and offering a pacifier, were recorded for each infant. Each variable was scored on a scale of 1 to 6 points, and scores were totaled for each infant. Before beginning the study, investigators (M.H. and S.K.) who would later administer the behavioral scale observed several infants simultaneously with another investigator (I.K.) to agree on common definitions

and to ensure minimal interobserver variability in scoring of the behavioral scale. Formal interobserver variability assessment was not done before the study, and scoring for each infant was done by a single observer (M.H. or S.K.) during the study. However, post-hoc scores assigned by the individual observers provide reassuring data regarding interobserver variability (**Table 1**).

Each infant was monitored for 20 minutes before, during, and after circumcision, during which time the behavioral score and physiologic variables were recorded. Physiologic data, including heart rate (HR), respiratory rate (RR), blood pressure (BP), and oxygen saturation, obtained from continuous monitoring by Marquette monitors were recorded every 5 minutes before and during circumcision and 5 and 20 minutes after circumcision. For each patient, the 5-minute observations before and during circumcision were averaged, resulting in 4 time points used in the final analysis: before, during, and 5 and 20 minutes after circumcision. All circumcisions were performed in standard fashion by a single obstetrician (T.P.) using a 1.1- or 1.3-cm Gomco clamp.

At the end of the 20-minute precircumcision period, a 1-cm³ blood sample was obtained by heelstick to determine β -endorphin levels. The infants were allowed to calm down for 10 minutes, then the circumcision was performed. β -Endorphin levels were obtained again at the end of the postcircumcision period.

Power analysis using an α of .05 and a β of 90%, with a difference in HR of 30 beats/min and a mean systolic BP difference of 15 mm Hg, indicated that a cohort of 30 neonates would be required to demonstrate a significant difference between study and control groups.

Continuous variables were analyzed by analysis of variance for repeated measures with post-hoc Scheffé and paired *t* tests. The Fisher exact test was used for categorical variables, and the Mann-Whitney *U* test was used for ordinal scale data.

The protocol was approved by the Georgetown University Medical Center institutional review board, and informed consent was obtained from the parents of each patient enrolled in the study.

tions, the institutional review board requested discontinuation of EMLA enrollment, and the study continued with only the DPNB and control groups. Because of the small number of patients in the EMLA group, no meaningful statistical comparisons could be made, and these patients were excluded from further analysis. Thirty-eight patients were thus included in the final analysis.

Demographic data are shown in **Table 2**. There were no statistically significant differences between the groups when comparing birth weight, gestational age, age and weight at circumcision, and postconceptional age at circumcision. Mean weight at circumcision was approximately 2000 g, mean postconceptional age was 36 weeks, and mean \pm SD duration of the procedure was 8 ± 2 minutes.

Precircumcision data show that the DPNB and control groups were similar with respect to HR, RR, oxygen saturation, BP, and behavioral score (**Figure 1** through **Figure 5**). Statistically significant differences were noted, however, in physiologic and behavioral variables during the circumcision. When comparing HR (Figure 1),

Table 1. Behavioral Score Interobserver Comparison*

	Before Circumcision	During Circumcision	After Circumcision
Study group	12.7 \pm 3.0	18.7 \pm 5.4	18.7 \pm 5.5
Investigator 1	11.7 \pm 2.3	19.1 \pm 5.6	18.4 \pm 6.7
Investigator 2	15.2 \pm 4.7	19.1 \pm 5.9	19.4 \pm 4.8

*Data are given as mean \pm SD.

there was a statistically significant difference between study and control group infants during circumcision compared with baseline HR ($P < .001$). Five minutes after circumcision there remained a statistically significant elevation of the control group infants' HR compared with baseline ($P < .05$), whereas the DPNB group infants' HR remained stable. Twenty minutes after circumcision, the control group infants' HR was approaching baseline, whereas the HR for the DPNB group infants was increased ($P < .01$) compared with their baseline HR.

Table 2. Demographic Data of Study Participants*

	Group	
	DPNB (n = 19)	Control (n = 19)
Birth weight, g	1728 ± 534	1733 ± 533
Gestational age, wk	32.6 ± 3.0	32.2 ± 2.8
Age at circumcision, d	27.3 ± 25.0	25.3 ± 26.8
Weight at circumcision, g	2076 ± 266	2049 ± 220
Postconceptional age at circumcision, wk	36.0 ± 1.9	35.5 ± 1.6

*Data are given as mean ± SD. DPNB indicates dorsal penile nerve block.

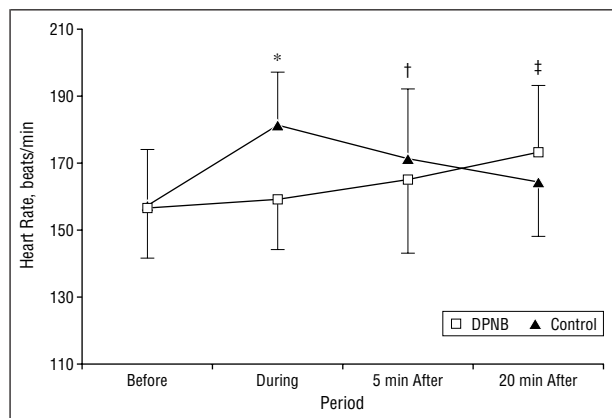


Figure 1. Asterisk denotes the mean ± SD heart rates of control vs dorsal penile nerve block (DPNB) infants during circumcision, $P < .001$; dagger, control infants vs baseline, $P < .05$; and double dagger, the heart rates of DPNB infants vs baseline, $P < .01$.

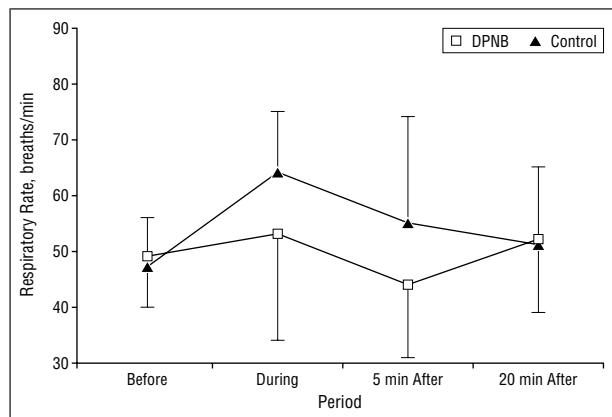


Figure 2. Note the mean ± SD respiratory rates of control vs dorsal penile nerve block (DPNB) infants during circumcision, $P < .01$.

Increases in RR (Figure 2) were also noted in control group infants during circumcision ($P < .01$) compared with DPNB group infants and baseline. These differences were no longer present 5 minutes after circumcision, with RR returning to baseline 20 minutes after circumcision.

Although oxygen saturation decreased slightly in the control group during circumcision compared with the DPNB group, the difference was not statistically significant, and no difference between groups was noted 5 and 20 minutes after circumcision (Figure 3).

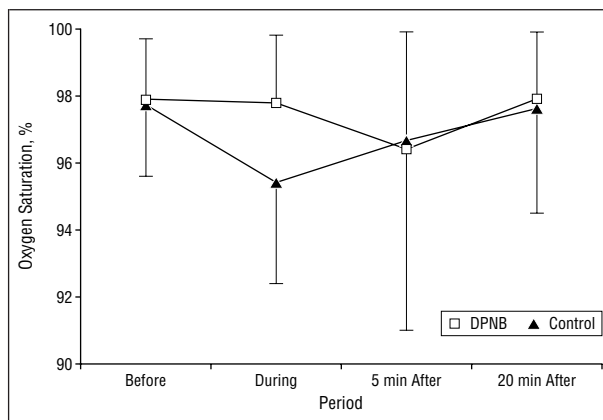


Figure 3. No significant difference in mean ± SD oxygen saturation between control and dorsal penile nerve block (DPNB) groups.

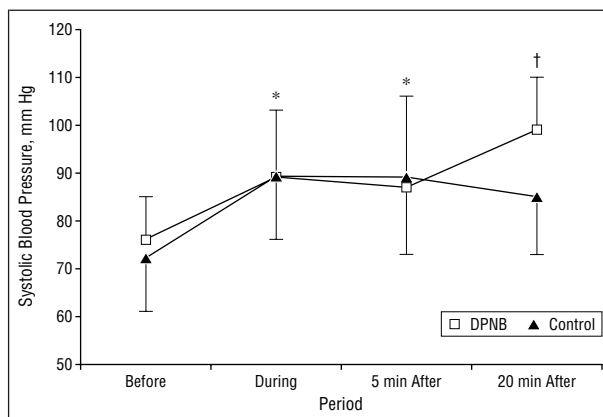


Figure 4. Asterisk denotes the mean ± SD systolic blood pressure of dorsal penile nerve block (DPNB) and control infants during and 5 minutes after circumcision compared with baseline, $P < .001$; dagger, the systolic blood pressure of DPNB infants 20 minutes after circumcision compared with baseline.

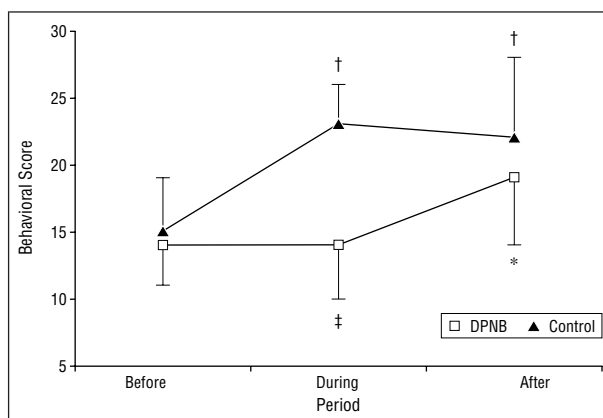


Figure 5. Asterisk denotes the mean ± SD behavioral scores of dorsal penile nerve block (DPNB) infants before vs after circumcision, $P < .001$; dagger, the behavior score of control infants before vs during and after circumcision, $P < .001$; and double dagger, the behavior score of DPNB vs control infants during circumcision, $P < .01$.

Systolic BP (Figure 4) increased significantly in both groups compared with baseline during circumcision ($P < .001$). This increase persisted 5 minutes after circumcision ($P < .001$). Twenty minutes after circumci-

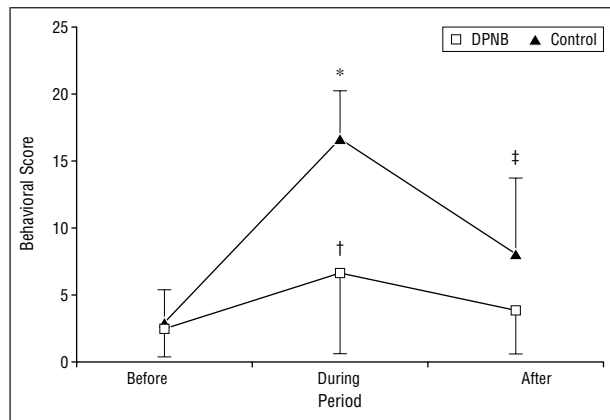


Figure 6. Asterisk denotes mean \pm SD crying component of behavioral score for control vs dorsal penile nerve block (DPNB) infants and for control infants before vs during and after circumcision, $P < .001$; dagger, crying component of DPNB infants vs baseline, $P < .02$; and double dagger, crying component of control infants vs baseline, $P < .001$.

sion, the control group's systolic BP was trending toward baseline and was no longer significantly higher than baseline. However, the DPNB group's systolic BP 20 minutes after circumcision demonstrated a secondary elevation that was statistically significant (mean, 22 mm Hg higher; $P < .001$) compared with baseline. Because this secondary rise in the DPNB group was not detected until final data analysis, the time for return to baseline was not evaluated.

The control group's behavioral scores (Figure 5) were elevated during and after ($P < .001$ for both) circumcision compared with baseline and the DPNB group during circumcision ($P < .001$). The DPNB group infants' behavioral scores remained stable during circumcision but increased significantly ($P < .001$) after circumcision compared with baseline.

The most dramatic differences were demonstrated in the crying component of the behavioral score (Figure 6). Crying contributed significantly to the total behavioral score when comparing control and DPNB infants. Although the crying component was elevated for the DPNB and control groups compared with baseline, the difference between groups during circumcision remained significant. Compared with baseline, the control group's cry component remained elevated during and after circumcision, whereas the DPNB group's score returned to baseline after circumcision. During foreskin clamping, 80% of the DPNB group remained quiet; only 18% cried. In comparison, 95% of the control infants cried and were inconsolable during foreskin clamping ($P < .001$, Figure 7).

β -Endorphin levels were not significantly lower after circumcision in the DPNB group compared with controls. In fact, no trends were noted when comparing endorphin levels between groups. Mean \pm SD levels for the DPNB and control groups were 294 ± 140 vs 280 ± 137 pmol/L before circumcision and 326 ± 165 vs 305 ± 130 pmol/L after circumcision, respectively.

No complications were encountered in the DPNB group related to injection (hematoma, skin sloughing, or urinary retention), and there were no complications related to the use of lidocaine (arrhythmia, hypotension, or seizures).

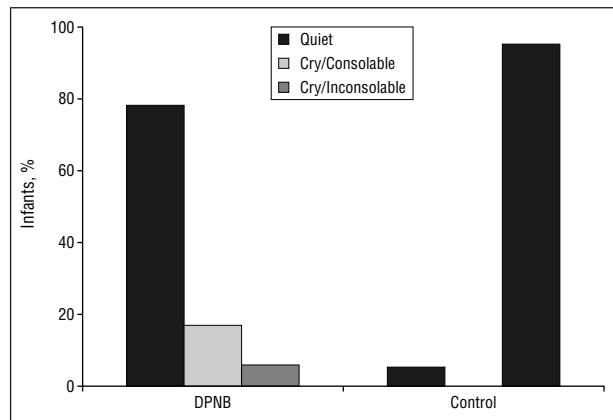


Figure 7. Behavior at foreskin clamping of dorsal penile nerve block (DPNB) (quiet) vs control (unconsolable) infants, $P < .001$.

COMMENT

Advances in technology with increased survival of small, preterm infants have allowed earlier hospital discharge of these infants. A concomitant increase in the number of preterm boys has parents requesting circumcision before hospital discharge. In the group of infants studied, we found circumcision with DPNB as an anesthetic agent to be safe and efficacious. The physiologic changes we observed in the control infants during circumcision, including increases in HR^{2,7,8} and behavioral score,¹ are similar to those seen in studies performed in term and preterm⁶ infants. These HR changes have also been demonstrated in response to other painful procedures performed in term infants.⁹⁻¹¹

The lack of difference in systolic BP between the groups was not expected and was contrary to that seen in term infants in previous studies.^{1,2} We speculate that, although DPNB may be effective in providing pain relief, restraint, presensitization to procedures in neonatal intensive care unit patients, decreased vagal tone present in preterm infants, and lack of mature regulatory central control of BP could contribute to the differences seen in BP changes associated with pain responses in preterm vs term infants. The lack of difference in systolic BP may also be a reaction to the infant's restraint during circumcision, thereby obscuring any noticeable difference in BP between groups. In addition, the late rise in BP and HR 20 minutes after circumcision in the DPNB group suggests that the anesthetic effect may wear off as expected because no epinephrine was used to delay its absorption.

Oxygen saturations also demonstrated no significant difference between the DPNB and control groups, another contrast to findings in studies of term infants.^{2,7,8} Masciello⁸ speculated in term infants that the statistical difference in oxygen saturation between anesthetized and control groups was caused by increased crying and increased intrathoracic pressure, resulting in decreased oxygen saturations. It is possible that preterm infants are unable to generate a significant degree of increased intrathoracic pressure during a crying episode because of decreased rib cage stability and intercostal muscle strength. Together with an increased RR and sub-

sequent increased minute ventilation, this could possibly compensate for any decrease in oxygen saturation when comparing the DPNB and control groups. In addition, the loss of signal and discounting of observed values at precisely the times when saturations are lowest may be an alternate explanation for the absence of significant decreases in saturation in these infants.

The crying component of the behavioral score reflects similar differences as those seen in term infants. All infants were provided with attempts to comfort them during circumcision, including vocalization, touch, and offering a pacifier. Infants in the control group who were inconsolable remained so despite the intervention provided.

β -Endorphin level elevations in term infants have been demonstrated by Weatherstone et al¹ and have been used as an objective measure of stress response in term infants. β -Endorphin levels were not elevated after circumcision in the control group compared with the anesthesia group. There may be a wide range in resting β -endorphin levels in preterm infants that may mask precircumcision and postcircumcision differences, precluding the use of β -endorphin level as a measure of stress response in preterm infants. Restraint procedures and heelstick for blood drawing may also cause elevations in β -endorphin levels, masking any noted difference between groups before and after circumcision. Cortisol levels have also been noted to be elevated after circumcision in unanesthetized term infants.^{8,12} Absorption of lidocaine, with mean \pm SD lidocaine levels of 0.08 ± 0.02 ng/mL, as noted in previous studies in term infants,^{2,13} are well below the toxic range and therefore were not measured in this study.

No complications were encountered in the DPNB group related to injection (hematoma, skin sloughing, or urinary retention), and there were no complications related to the use of lidocaine (arrhythmia, hypotension, or seizures). The erythematous blistering reaction in the 2 EMLA patients may be a hypersensitivity reaction that has been noted as an adverse reaction associated with the use of EMLA.¹⁴ Use of EMLA in older patients has resulted in similar erythematous reactions without blistering.¹⁵ We are concerned that this reaction may occur more commonly in preterm neonates possibly secondary to differences in skin sensitivity to the components of EMLA.

The results of this study demonstrate that DPNB can be used safely and effectively to provide anesthesia during circumcision in preterm infants with weights at the time of circumcision of 1600 to 2500 g. Use of an oral analgesic (eg, acetaminophen) may be beneficial in controlling pain after the analgesic effect of DPNB diminishes. This would be an area for further study in the pain

management of preterm neonates. Because of the apparent hypersensitivity reactions in the EMLA group, caution should be exercised when using this agent in preterm infants. The American Academy of Pediatrics strongly recommends administering analgesia for all painful procedures. Use of DPNB is an effective method of decreasing pain in preterm and term neonates.

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