Neonatal Circumcision

Randomized Trial of a Sucrose Pacifier for Pain Control

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Objective: To assess the effectiveness of oral sucrose via a nipple compared with no treatment and dorsal penile nerve block (DPNB) for alleviating pain in neonatal circumcision.

Design: Randomized control trial. Data analysis performed by investigators blinded to the 3 treatment groups.

Setting: University teaching hospital, General Care Nursery.

Patients: One hundred nineteen full-term male, normal birth weight neonates, 12 hours old or older.

Interventions: No treatment (our standard care), DPNB, or oral sucrose prior to circumcision.

Main Outcome Measures: Differences between groups in heart rate and oxygen saturation changes from baseline during specified intervals of the circumcision procedure. Differences between groups in loss of data due to episodes of excessive motion.

Results: Sucrose gave significant (P<.001) pain relief compared with the no treatment control throughout most of the circumcision and particularly in the early stages of the procedure. Overall, the average difference in the elevation of heart rates during the circumcision operative procedure among the 3 groups and the 95% confidence intervals (CIs) were as follows: control vs DPNB, 27.1 beats/min (17.6, 36.6) and control vs sucrose, 9.7 beats/min (0.1, 19.3). Furthermore, newborns who received either DPNB or sucrose had less loss of oxygen saturation data due to excessive motion during the procedure than the no-treatment controls. The total percentages of lost data due to excessive motion in the 3 groups were 31% for control, 10% for DPNB, and 8% for sucrose. Relative risk and 95% CIs were: DPNB vs control, 0.32 (0.23, 0.43); sucrose vs control, 0.26 (0.18, 0.36). Differences in oxygen saturation among the 3 groups during the circumcision operative procedure were statistically (P<.001), but perhaps not clinically, significant. However, the analysis did not include missing data due to excessive motion, which occurred predominantly in the no-treatment control group.

Conclusion: Sucrose on a pacifier is an inexpensive and effective method for pain relief in neonatal circumcision when DPNB is not desirable.


CIRCUMCISION, an operation performed on more than 80% of newborn males in the United States,1 is usually undertaken without administering an analgesic agent. Although it is widely acknowledged that neonates experience pain during circumcision, as documented by cardiovascular, hormonal, and behavioral changes,2 physicians have been reluctant to use analgesics for a variety of reasons.3 Dorsal penile nerve block (DPNB) has been used effectively for pain relief in neonatal circumcision since 1978,4 but the American Academy of Pediatrics has not endorsed its use. The 1989 American Academy of Pediatrics Task Force on Circumcision stated, local anesthesia adds an element of risk and data regarding its use have not been reported in large numbers of cases. . . . It would be prudent to obtain more data from large controlled series before advocating local anesthesia as an integral part of newborn circumcision.5

In 1991, Schoen (chairman of the American Academy of Pediatrics Task Force) and Fischell6 recommended that methods to relieve pain during circumcision must have almost no risk to be acceptable. They found attractive the work of Blass and Hoffmeyer7 which showed that a nipple dipped in sucrose was efficacious for pain relief during neonatal circumcision. Schoen and Fischell6 concluded that “in view of the noninvasive, risk-free nature of a sucrose-flavored pacifier, this technique deserves wide-spread evaluation of its effectiveness.”
SUBJECTS AND METHODS

SUBJECTS

The study subjects, 120 healthy male newborns from the General Care Nursery of the University of Chicago Hospitals, had been delivered at 38 or more completed weeks’ gestation; had a birth weight of more than 2500 g; a 5-minute Apgar score of 8 or higher; and a postnatal age of 12 hours or older. Their mothers had given informed written consent both for circumcision and for participation in the study. The newborns were randomized equally to 1 of 3 groups. Infants born to opiate addicts were excluded. All infants were recruited during March and April 1997. The protocol was approved by the Institutional Review Board of the University of Chicago Hospitals.

TECHNIQUE OF CIRCUMCISION

Circumcisions were performed by an obstetrical resident under the supervision of an attending physician using the Gomco clamp procedure (Gomco, St Louis, Mo). Ninety percent of the circumcisions were performed by 2 residents (C.E. and N.M.), who were coinvestigators. Ten other residents performed from 1 to 4 circumcisions each. In general, infants were not fed for at least 30 minutes prior to the procedure.

TECHNIQUE OF DPNB

The procedure is described in detail, with graphics, by Fontaine and Toffler. After the infant was placed on the restraint board (Circumstraint, Olympic Medical, Seattle, Wash), a total of no more than 0.8 mL of 1% lidocaine without epinephrine was injected into the dorsolateral penile root with a 1-mL tuberculin syringe and a 26G 3⁄8 needle. After a delay of 3 minutes, the circumcision was performed. All DPNBs were performed by 3 study-team investigators (C.E., N.M., and M.H.).

OF ORAL SUCROSE

The pharmacy prepared a bulk solution of 50% sucrose from sucrose USP/NF (Spectrum Chemical Co, Gardena, Calif) and then packaged 10 mL of the 50% sucrose solution in 15-mL amber glass sealable vials (Wheaton Uni-Dose Vials, product No. 226732, Wheaton Industries, Millville, NJ). The sealed, individual-dose vials of 50% sucrose were kept in the nursery refrigerator for easy access; they were restocked every 1 to 2 weeks. After first being restrained on the circumcision board, those infants randomly assigned to treatment with the oral analgesic received a premature nipple (Ross Products Division, Abbott Laboratories, Columbus, Ohio) dipped in the 50% sucrose solution, with a 2×2-cm sterile gauze pad inside the nipple moistened by the fluid. After 2 minutes of sucking, the circumcision was begun. Throughout the circumcision procedure, including during crying episodes, the nipple was held in the infant’s mouth by an assistant; periodically, the gauze pad was moistened with the sucrose solution. The vials contained enough sucrose to keep the gauze moistened and to allow for spillage. The cost per vial of sucrose was about $1.40.

MONITORING

Heart rate (based on electrocardiographic wave form) and oxygen saturation were continuously recorded using a monitor (PC ScoutMonitor 90309 with dual-channel internal recorder, SpaceLabs Medical, Redmond, Wash) via neonatal electrocardiographic electrodes and an infant oxygen transducer (Oxisensor II, Nellcor Incorporated, Pleasanton, Calif). The oxygen saturation transducer was placed on the infants’ right big toe in all cases. Baseline recording began in the infant’s crib 2 to 5

Results

Maternal and infant data for the 3 study groups are shown in Table 1. Infants randomized to the 3 groups were comparable in terms of gestational age, birth weight, route
minutes before placing the infant on the restraint board and continued throughout the procedure; most babies were released from the board within 10 minutes. Each phase of the circumcision was noted on the paper-strip chart: initial restraint; injection of lidocaine or oral sucrose on a nipple, as applicable; skin preparation for the procedure with antiseptic and drape; lateral clamping of the foreskin; lysis of adhesions; dorsal clamping of the foreskin; dorsal cutting; retraction of the foreskin with further lysis of adhesions; application of the Gomco bell and clamp; excision of the foreskin; Gomco clamp removal; removal of the bell; and placement of the petrolatum dressing.

The printer recorded the heart rate and oxygen saturation data continuously in wave form and in digital form every 20 seconds. Performance of the infant oxygen saturation transducer is known to be compromised by excessive motion. When excessive motion of the infant caused loss of interpretable data, the printer recorded a question mark. Oxygen saturation data were affected by motion much more than the heart rate data because of limitations of pulse oximetry technology. Mean heart rate and oxygen saturation were calculated from the digital output for a given interval. If the heart rate or oxygen saturation data were not interpretable for at least half of a given interval, then the mean for that interval was not calculated. The paper-strip data were analyzed by investigators who were blinded to the group assignments.

OUTCOME MEASURES

Response to pain was assessed by the change in infant heart rate and oxygen saturation from baseline. For every infant, the mean heart rate and oxygen saturation for each interval of the circumcision were calculated. Mean values between groups were compared. Frequencies of missing oxygen saturation data due to excessive motion of the infants in the 3 comparison groups were analyzed separately.

HEART RATE

The data, with 95% CIs, are shown in the Figure. Overall, there was a statistically significant difference in the heart rates of the 3 groups (repeated measures ANOVA, P < .001). While formal neurobehavioral analysis was beyond the scope of this project, we noticed that most babies were asleep during the baseline period. The baseline and restraint period heart rates of the 3 groups were not different. No comparison was made during the treatment interval. During the preparation for surgery, the heart rate in the no-treatment control group was about 12 bpm higher than in the group who had received sucrose (P = .006) and about 15 bpm higher than in the group who had received DPNB (P = .002). The difference between the sucrose group and the DPNB group was not statistically significant (P = .80). During lateral clamping and lysis of adhesions,

STATISTICAL METHODS

Power Calculation

Data from previous studies10,14 suggested that a reasonable estimate of the treatment effect for each of the outcomes would be as follows:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean (±SD)</th>
<th>Mean (±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Elevation in Heart Rate, bpm</td>
<td>Fall in Oxygen Saturation, %</td>
</tr>
<tr>
<td>Control</td>
<td>35 ± 30</td>
<td>15 ± 8</td>
</tr>
<tr>
<td>Treatment</td>
<td>15 ± 12</td>
<td>8 ± 7</td>
</tr>
</tbody>
</table>

where treatment indicates DPNB or sucrose and bpm is beats per minute.

A sample size of 40 in each group would provide greater than 95% power to detect differences of this magnitude for each of the outcomes (increased heart rate/decreased oxygen saturation) between the control and treatment groups. In addition, the proposed sample size of 40 in each group would provide greater than 90% power to detect differences between the 2 treatment groups of 10 bpm or more given the following parameters: mean heart rate elevation (±SD) in dorsal block treatment equals 10 ± 10 bpm and mean heart rate elevation (±SD) in sucrose treatment equals 20 ± 15 bpm. The type I error (α) was fixed at .05 for all of the above calculations.

Randomization

We prepared, then shuffled, 120 (40 control, 40 DPNB, and 40 sucrose groups) opaque unmarked envelopes containing the group assignments. After an infant was placed on the restraint board, the envelope was opened. There was 1 exclusion: an infant randomized to sucrose was not circumcised. After the operator visualized the location of the meatus, she thought the surgery was contraindicated.

Data Analysis

Mean heart rate and oxygen saturation were compared between groups using the repeated measures analysis of variance (ANOVA) procedure of the SAS statistical software. The characteristics of the infants in the 3 groups were compared using the χ² test, Fisher exact test, or ANOVA. All reported P values correspond to 2-tailed tests.

Table 1. Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>No Treatment (n=40)</th>
<th>DPNB† (n=40)</th>
<th>Sucrose (n=39)</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neonates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>39.7±1.0</td>
<td>39.4±1.2</td>
<td>39.5±1.1</td>
<td>.59</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>3361±454</td>
<td>3473±512</td>
<td>3336±452</td>
<td>.39</td>
</tr>
<tr>
<td>No. of vaginal deliveries</td>
<td>35</td>
<td>34</td>
<td>33</td>
<td>.92</td>
</tr>
<tr>
<td>Apgar score at 5 min</td>
<td>9.0±0.2</td>
<td>8.9±0.3</td>
<td>8.9±0.3</td>
<td>.38</td>
</tr>
<tr>
<td>Age at circumcision, h</td>
<td>24.1±14.2</td>
<td>23.8±14.4</td>
<td>27.3±28.6</td>
<td>.70</td>
</tr>
<tr>
<td>Duration of surgery, min</td>
<td>4.7±1.3</td>
<td>4.9±1.7</td>
<td>4.9±1.1</td>
<td>.78</td>
</tr>
<tr>
<td><strong>Mothers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>24.1±6.2</td>
<td>24.4±5.2</td>
<td>23.2±7.0</td>
<td>.67</td>
</tr>
<tr>
<td>No. black</td>
<td>33</td>
<td>37</td>
<td>36</td>
<td>.33</td>
</tr>
</tbody>
</table>

*Values are expressed as mean±SD unless otherwise indicated. †DPNB indicates dorsal penile nerve block. ‡P corresponds to results of analysis of variance for continuous data and χ² or Fisher exact test for categorical data.
the average heart rate in the no-treatment control group was about 12 bpm higher than in the sucrose group (P values <.005), and 22 and 24 bpm higher than in the DPNB group (P values <.001). Again, differences between the sucrose and the DPNB groups were not statistically significant (P values <.15). From the intervals of dorsal clamping of the foreskin through the tightening of the Gomco clamp, the heart rates in the control group were, on average, 10 to 15 bpm higher than in the sucrose group (P values <.02) and 27 to 33 bpm higher than in the DPNB group (P values <.001); differences between the sucrose and the DPNB group were statistically significant (P values <.03). At the latter part of the procedure, from excision of the foreskin to placement of the dressing, the heart rate in the control group was 13 to 23 bpm higher than in the DPNB group (P values <.002), but not significantly different from that in the sucrose group (P values >.22).

To express our findings in a way comparable with Taddio et al., we first calculated differences in heart rate from the baseline for each subject during the 8 steps of the circumcision operative procedure, from lateral clamping through excision of foreskin. We then calculated the mean change from baseline for each subject and used ANOVA to compare the means of the changes in heart rate for the subjects in the 3 comparison groups. No significant values

To express our findings in a way comparable with Taddio et al., we first calculated differences in heart rate from the baseline for each subject during the 8 steps of the circumcision operative procedure, from lateral clamping through excision of foreskin. We then calculated the mean change from baseline for each subject and used ANOVA to compare the means of the changes in heart rate for the subjects in the 3 comparison groups. No significant differences were found among the 3 groups during the entire experiment. However, as in the case with heart rate, we also compared differences in oxygen saturation from baseline among the 3 comparison groups during the circumcision operative procedure, i.e., lateral clamping through excision of the foreskin (Table 3). Overall, there were statistically significant differences among the 3 groups (ANOVA F test, P <.001). The average change,

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Treatment (n=40)</th>
<th>DPNB† (n=40)</th>
<th>Sucrose (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>137.1±12.5</td>
<td>134.1±12.3</td>
<td>122.0±13.2</td>
</tr>
<tr>
<td>Oxygen saturation, %</td>
<td>95.6±2.4</td>
<td>96.3±2.2</td>
<td>95.1±3.2</td>
</tr>
</tbody>
</table>

*Values are expressed as mean±SD.
†DPNB indicates dorsal penile nerve block.
‡P corresponds to analysis of variance F tests for comparing the changes in heart rate or oxygen saturation from baseline in the 3 groups; differences in baseline averages of heart rate and oxygen saturation were not statistically significant in the 3 groups.

OXYGEN SATURATION

In contrast to the heart rate data where the percentage of missing data at any given time interval was typically small (<10%), a substantial proportion of oxygen saturation data were missing due to excessive motion. Furthermore, this loss of data was found significantly more often in the no-treatment control group. We analyzed the results according to the percentage of intervals in each group with missing oxygen saturation data. During the interval of lysis of adhesions, 23 of 40 infants in the control group experienced loss of data as compared with 9 of 40 in the DPNB, and 4 of 39 in the sucrose groups (Table 3). The difference in the frequency of missing data between the DPNB and the sucrose groups was not statistically significant (P=.14). The total percentages of intervals with missing data due to excessive motion throughout the circumcision in the 3 groups were 31% for control, 10% for DPNB, and 8% for sucrose. Relative risk and 95% CI were as follows for the groups: DPNB vs control, 0.32 (0.23,0.43); sucrose vs control, 0.26 (0.18,0.36). The intervals during which the no-treatment control infants experienced the most loss of data were from lateral clamping through tightening of the Gomco. There was a marked decrease in their lost data from the interval of excision of the foreskin to placement of the dressing.

Perhaps because of the small numbers of recorded oxygen saturation, mainly in the no-treatment control group, repeated measures ANOVA showed no significant (P =.64) difference among the 3 groups during the entire experiment. However, as in the case with heart rate, we also compared differences in oxygen saturation from baseline among the 3 comparison groups during the circumcision operative procedure, i.e., lateral clamping through excision of the foreskin (Table 3). Overall, there were statistically significant differences among the 3 groups (ANOVA F test, P <.001). The average change,
with 95% CI, in the oxygen saturation percentage from baseline for the no-treatment control was −2.5 (−15.8 to 3.12) whereas the corresponding change for the DPNB group was −0.8 (−4.3 to 5.5), and for the sucrose group was 0.7 (−6.8 to 12.5). Differences between both the DPNB and the sucrose groups and the control group were statistically significant at the .05 level; however, the difference between the DPNB and the sucrose group was not statistically significant (P = .09). Average differences and the 95% CIs between groups were as follows: no-treatment control vs DPNB, −1.7 (−3.5, to −0.0); no-treatment control vs sucrose, −3.3 (−5.0 to −1.6). While these differences in oxygen saturation are statistically significant (P < .001), they probably do not constitute clinically important differences. However, as noted above, the recorded oxygen saturation data did not include missing values due to excessive motion. Therefore, differences in the oxygen saturation changes among the 3 groups might have been greater than our estimates suggest. Specifically, the oxygen saturation for the no-treatment control group might have been substantially lower had we been able to measure oxygen saturation for those infants who became agitated.

### COMMENT

We have confirmed and extended the work of Blass and Hoffmeyer7 that oral sucrose on a nipple is effective in reducing the pain of circumcision. When compared with a group receiving a nipple dipped in water or a no-treatment control group, these investigators showed that sucrose treatment resulted in a statistically significant overall reduction in the percentage of time crying, but they did not present their data according to specific intervals of the operation. Nor did they compare sucrose with DPNB. We have shown the treatment effects during each interval of the procedure and compared sucrose with DPNB and no-treatment control.

Because DPNB can be considered the standard for pain relief during circumcision, we chose to compare oral sucrose with DPNB, as well as with a no-treatment control. We did not compare sucrose with the lidocaine–prilocaine hydrochloride combination drug cream (EMLA) because topical therapy is not practical in our setting since the cream has to be applied at least 1 hour prior to the procedure. The obstetrical residents in our institution who do the circumcisions usually do not know 1 hour ahead of time when they will be free to do the procedure. We have shown that, overall, sucrose was effective in reducing the pain of circumcision. In fact, as assessed by the degree of elevation in heart rate, sucrose was as effective as DPNB in the initial intervals of the circumcision, ie, lateral clamping and lysis of adhesions. Throughout the procedure, until excision of the foreskin, sucrose had statistically significant (P < .001) analgesic benefits when compared with the no-treatment controls, as assessed by heart rate. Furthermore, infants who received oral sucrose showed a statistically significant (P < .001) reduction in excessive movement associated with crying and agitation as compared with the no-treatment controls; this effect of sucrose was at least as profound as that of DPNB.

We do not know why the relative benefit of sucrose in alleviating pain as assessed by heart rate elevation appeared to diminish toward the end of the circumcision. The interval of the procedure during which sucrose was no better than the no-treatment control was the point when the infants in all 3 groups showed a reduction in heart rate; however, the heart rate decrease in the sucrose group was less pronounced. As well, during this interval, the excessive motion that had been present in the no-treatment controls markedly diminished.

Smith et al17 comment that “sucrose effectiveness is characterized by rapid onset and slow offset: Calm endures well after sucrose termination.” Under an experimental condition studying the effect of sucrose infused through a pacifier on the spontaneous crying of newborns, they showed the calming effect of sucrose lasted at least 5 minutes after termination of treatment. It is not clear what the duration of the effect of sucrose is under our experimental conditions.

We did not study sucking rate in relation to heart rate. In a controlled, quiet environment study of term 1- to 2-day old neonates, Lipsit et al18 have shown that when sucking for no fluid, the neonates’ heart rates increased to a mean of 123.8 bpm, significantly over the mean basal level of 116.3 bpm, and rose significantly higher to 146.6 bpm with sucrose sucking. In different experimental conditions, Smith et al17 and Blass19 found that in normal term infants who were crying at the start of testing, intraoral infusions of sucrose were calming and resulted in a decrease in heart rate. Sucrose was equally calming when delivered with or without a pacifier; the calm was more enduring than that caused by a pacifier alone. Because of the variable effects on heart rate of a pacifier and sweet taste, it would be worthwhile to assess the effectiveness of the sucrose pacifier for pain relief by a measure other than heart rate. (The facial activity score might not be feasible in the presence of a pacifier.) Studies of the long-term effects of analgesia with sucrose on postsurgical feeding and sleeping behavior and on pain response to later immunizations would be valuable.20

Two groups of investigators have reported the putative effectiveness of the topical combination lidocaine–prilocaine cream compared with placebo control for circumcision.11,16 The most recent report16 concludes that the topical combination lidocaine–prilocaine cream is safe and that it reduces the pain of circumcision, as measured by the facial activity score, during 4 of 9 intervals of the surgical procedure. The topical therapy was not compared with the standard, DPNB. This topical combination of lidocaine–prilocaine was no more effective than
placebo control, as assessed by the facial action score, during the painful interval of lysis of adhesions, suggesting that it may not be as efficacious as sucrose which gives notable analgesia during this interval. Taddio et al\textsuperscript{16} did not present heart rate data for each interval of the circumcision, but the overall heart rates from the forceps application through foreskin cutting showed a difference of 10 bpm between the topical combination lidoca-n-prilocaine treatment group and the placebo control, which is comparable to the effect of sucrose compared with no-treatment control in our study (9.7 bpm). We have confirmed the well-known superiority of DPNB for relieving the pain of circumcision. However, as a result of our findings, we recommend oral sucrose on a nipple as a safe and inexpensive method of pain relief for neonatal circumcision in the instances when either physicians or parents are not comfortable with DPNB. We have confirmed the effectiveness of oral sucrose in reducing the signs of pain and have shown its benefits as compared with DPNB and with no-treatment control.

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The PC Scout Monitor 90309 with dual-channel internal recorder was generously loaned to us by SpaceLabs Medical for the duration of the project.

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REFERENCES


REFERENCES


Correction

Incorrect Author Affiliation and Block Quotation Notation Missing. In the article titled “Neonatal Circumcision: Randomized Trial of a Sucrose Pacifier for Pain Control” published in the March issue of the ARCHIVES (1998;152:279-284) an error occurred in Dr Ellman’s affiliation. She should have been listed as being affiliated with the Department of Obstetrics and Gynecology and not as having an affiliation with the Department of Pediatrics. Another error occurred on page 279, left-hand column, with the quotation from the 1989 American Academy of Pediatrics Task Force, that begins on line 19. A block quotation should have been set for the words following “stated.” The material that begins with the word “local” and ends with “circumcision.” should all have been set as a block quotation. The journal apologizes for the error.