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Comparison of dorsal penile nerve block alone and in combination with lidocaine–prilocaine cream in neonates undergoing circumcision: a randomized controlled study

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ABSTRACT

Background Suboptimal neonatal circumcision analgesia causes a significant stress response. There is continued search for more effective analgesia for neonatal circumcision. We aimed to determine whether lidocaine–prilocaine cream (LPC) prior to dorsal penile nerve block (DPNB) offers better analgesia than DPNB alone.

Methods A prospective randomized study of 72 neonates undergoing plastibell circumcision was randomized into two groups of 36 each. Group I received DPNB alone with 4 mg/kg plain lidocaine. Group II had 1 g LPC applied to the phallus 1 hour before DPNB. Serum cortisol levels were measured 30 min preoperatively and 30 min postoperatively. Heart rate (HR) and peripheral arterial oxygen saturation (SpO_2) were noted at 30 min preoperatively, after DPNB injection, after excising the prepuce, and at 30 min thereafter. The primary outcome measure was change in serum cortisol levels, while secondary outcomes were changes in HR and SpO_2.

Results Both groups had increased mean serum cortisol levels, decreased mean SpO_2 and increased mean HR from baseline. The rise in mean serum cortisol level was significantly lower in group II (8.09±4.53 µg/dL) than that in group I (11.42±7.83 µg/dL) (p=0.034). Changes in SpO_2 and HR were significantly less in group II than that in group I patients (p<0.05), except for HR changes at 30 min after excision of the prepuce (p=0.086).

Conclusion These data suggest that neonates who received LPC prior to DPNB experienced significantly less pain from plastibell circumcision than those who had DPNB alone.

Trial registration number PACTR201906554747665.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Circumcision in neonates is a painful procedure.
⇒ Dorsal penile nerve block (DPNB) alone provides circumcision analgesia but has painful steps in its administration.

WHAT THIS STUDY ADDS

⇒ Application of lidocaine–prilocaine cream (LPC) prior to DPNB results in significantly reduced pain from neonatal plastibell circumcision.
⇒ Use of LPC prior to DPNB in neonates is practicable and safe.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ LPC prior to DPNB may be preferred to DPNB alone for neonatal circumcision analgesia.

INTRODUCTION

Circumcision is the surgical removal of the prepuce in the male human. Approximately 30% of the total world male population is circumcised, with rates as high as 87% in sub-Saharan Africa.[1 2] It is often performed with suboptimal or no analgesia in neonates despite the evidence that the procedure is painful and traumatic for the child.[3–5] Optimal analgesia will make the patient calm and the surgeon more meticulous during the procedure, thereby improving outcome.[6 7]

Several modalities have been used to minimize pain of routine circumcision in neonates. General anesthesia is effective but has high relative risks. Regional techniques such as caudal and pudendal blocks are also effective but rather invasive.[8] Dorsal penile nerve block (DPNB) and topical anesthetics such as lidocaine–prilocaine cream (LPC) are safe and commonly used techniques.[9] Many studies have shown that DPNB is more effective than topical LPC.[10 11] However, there are painful steps in its use as well as documented incomplete block up to 13% and complete block failures up to 7%.[12 13] DPNB elicits pain at the time of administering the

block due to the trauma of the needle prick. Additionally, it is significantly less effective during circumcision steps involving trauma to the ventral aspect of the penis because this surface is partly supplied by the perineal nerve, which is not affected by the block.[13 14] In the study center, we previously used DPNB alone with similar anecdotal experience. This study thus aimed to determine the effectiveness of DPNB with or without LPC for neonatal circumcision analgesia using serum cortisol levels, heart rate (HR) and peripheral arterial oxygen saturation (SpO_2) changes as indicators of pain.

We hypothesized that LPC administered prior to DPNB for neonatal circumcision will provide better analgesia by reducing the pain of the block injection and obviating probable sources of block failure. It may also provide additional analgesia extending throughout the procedure and postoperatively up to 2 hours or more after removing the cream.[14 15] Moreover, LPC is easy to administer in newborns. However, there is increased cost and waiting time.[15]

METHODS

Study design

The present study is a prospective, double-blind, randomized controlled trial performed according to the principles of good clinical practice and the International Declaration of Helsinki. The study is registered in the Pan Africa Clinical Trials Registry and reported according to the Consolidated Standards of Reporting Trials statement.

Study protocol

The study was carried out between March and August 2018 at the Pediatric Surgical Unit of Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), Ile-Ife, Nigeria. The babies included in the study were healthy term male neonates. Exclusion criteria included congenital anomaly of the phallus, preputial complications, jaundice, untreated bleeding disorders, and circumcision method other than the plastibell. Parents of eligible patients were interviewed, and written consent was obtained. The patients were randomly allocated by a nurse at the clinic into group I or II using the closed-envelope technique. Seventy-two cards labeled either group I or group II were sealed in an opaque envelope and placed in a basket with a block size of 4 and an allocation ratio of 1:1 for consecutive parents to pick from. The nurse was not aware of which was the treatment group until the end of the study. Subjects were naturally blinded to the group allocation since they were all neonates. Recruitment continued consecutively until the sample size was obtained. Thirty-six patients were included in each group.

Intervention

All the included neonates were fasted for 1.5–2.0 hours before the procedure. Baseline HR and SpO_2 were recorded while the babies were calm on their mothers' laps. Venous blood (1.5 mL) was taken 30 min before circumcision using a 21 G needle into a 2.5 mL plain bottle and kept at room temperature until it clotted. Baseline samples were collected between 08:30 and 09:30 to ensure similar diurnal values.

LPC (EMLA cream 5%, batch number TE6950), which contains 25 mg lidocaine and 25 mg prilocaine, was applied as a thick coating circumferentially on the prepuce and penile shaft down to the base and covered with occlusive dressing. The neonates were left with their parents/caregivers for 60 min, after which the dressings were removed and the patients were taken to the operating theatre. They were strapped on a neonatal restraining device in a warm and quiet operating suite. Using a 23 G needle, DPNB was administered by subcutaneous injection of plain lidocaine (NCI Lidocaine Injection BP; batch number 60277) at the 2 0'clock and 10 0'clock positions at a ratio of 50:50. The circumcision was carried out in the standard fashion starting 5 min after the block. The plastibell device (Hollister) was used throughout. The duration of the procedure was recorded in minutes from the application of forceps for adhesiolysis to the end of excision of the prepuce. HR and SpO_2 were noted at the end of DPNB, at excision of prepuce and at 30 min thereafter. Readings were taken from the lowest SpO_2 and highest HR within 1 min after DPNB and after excision of the prepuce.

Group I: Patients received only DPNB with 4 mg/kg plain lidocaine 1%.

Group II: Patients received 1 g topical EMLA cream 5% 1 hour prior to DPNB with 4 mg/kg plain lidocaine 1%.

The babies were then dressed up and breast fed. At 30 min after circumcision, another 1.5 mL of blood was taken and allowed to clot as previously described. The clotted blood samples were spun at 3000 revolutions per minute for 5 min. Supernatant serum was decanted into labeled plain bottles and stored at −75°C.

Postinterventional follow-up

All patients were observed for 30 min and placed on paracetamol syrup 15 mg/kg every 6 hours for 3 days. The parents were given phone contact in case of complications. They were followed up at the clinic on day 6 to detect complications such as skin rashes and hematoma.

Outcome measures

The primary outcome measure was the change in serum cortisol levels from baseline to postoperative values. Secondary outcomes were changes in HR and SpO_2 from baseline to the end of DPNB injection, after excision of the prepuce and 30 min thereafter.

Serum cortisol levels were measured from pooled samples by a microplate enzyme immunoassay using an Accu-Bind ELISA Microwells Cortisol Test Kit by a chemical pathologist who was blinded to the group assignment. HR and SpO_2 were measured using a handheld pulse oximeter (Lifebox, model number AH-M1, SN.

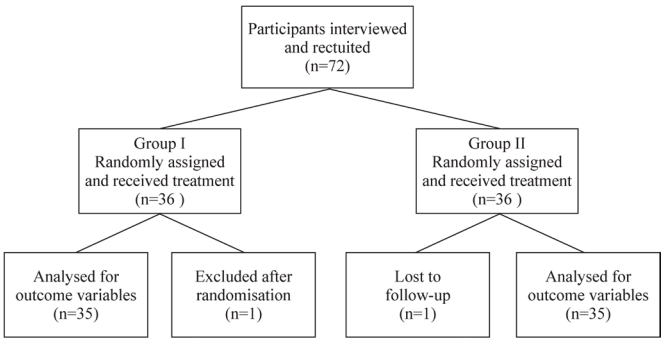

Figure 1 Flowchart of the participants.

M21846172EN by Acare Technology Co.), with a neonatal probe attached to the left wrist. Charting of the HR and SpO_2 at the different points was performed by either of two perioperative nurses who were blinded to the group allocation.

Statistical methods

Sample size was calculated based on the prevalence of male circumcision in Nigeria (0.84) as reported by Okeke *et al*,[2] estimated population size from yearly average number of neonates who had circumcision in OAUTHC obtained from records of preceding 4 years (96) and standard deviation (SD) of 1.96, which corresponds to 95% confidence interval (CI). After adding a possible attrition rate of 10%, a minimum sample size of 72 was obtained.

Data collected into a predetermined proforma were analyzed using IBM Statistical Package for Social Sciences V.22. Changes in serum cortisol levels, HR and SpO_2 between the two groups were compared using a two-tailed independent sample t-test. Numerical variables are presented as the mean±SD. A p value of <0.05 was considered significant with a CI of 95%.

RESULTS

Totally, 72 neonates were recruited and designated group I (n=36) and group II (n=36). Seventy patients completed the study and were analyzed (figure 1). There was a 1.4% attrition rate. One patient in group I had on-table slippage) of the plastibell ring, necessitating conversion to the free-hand technique. This patient was excluded due to a change in circumcision method. The parent of one of the patients in group II left with the baby before follow-up vital signs and blood sampling at 30 min after circumcision. This patient was excluded due to incomplete data. The patients aged from 7 days to 28 days and weighed 2.2–4.5 kg. There were no significant differences in the mean age or weight distribution between the groups (t(68): 1.943 and −1.883; p=0.056 and 0.064, respectively) (table 1).

Table 1 Baseline demographic characteristics of subjects in both groups

Parameter	Group I (n=35)	Group II (n=35)	P value
Mean age (days)	17.66±5.36	15.11±5.58	0.056
Mean weight (kg)	3.24±0.51	3.48±0.55	0.064

Table 2 Serum cortisol levels before and after surgery and comparison of both groups

Variables	Group I (n=35)	Group II (n=35)	P value
Mean serum cortisol (µg/dL)			
Baseline	9.32±4.60	7.96±4.77	0.227
Postoperative	20.74±9.14	16.05±6.76	0.017
Difference at postoperative	11.42±7.83	8.09±4.53	0.034

Baseline serum cortisol levels ranged between 0.58 µg/dL and 19.01 µg/dL (8.64±4.70). The mean was 9.32±4.60 µg/dL in group I and 7.96±4.77 µg/dL in group II (p=0.227). Postoperative serum cortisol levels ranged from 3.79 µg/dL to 40.89 µg/dL (18.40±8.31). The mean was 20.74±9.14 µg/dL in group I and 16.05±6.76 µg/dL in group II (p=0.017). The postoperative values were 123% and 102% higher than the baseline values in group I and group II, respectively. The difference in the mean cortisol change from baseline to postoperative stage between the two groups was statistically significant (t(68): 2.160, p=0.034) (table 2).

Baseline SpO_2 ranged from 91% to 100%. There was no significant difference in the baseline values between the two groups (p=0.685). Group II showed a significantly smaller decline in SpO_2 than group I in all the three stages (p=0.006, 0.006 and 0.003 at DPNB injection, excision of prepuce and postoperative respectively). The trend of changes from baseline through the different stages is reflected in figure 2.

There was no significant difference in the baseline HR between groups I and II (p=0.261). The difference in the mean HR at each of the three stages change from baseline was higher in group I than that in group II, but this difference was not statistically significant in the postoperative stage (p=0.086). Figure 3 shows the trend of HR changes.

The duration of circumcision was 5–13 min (9.43±2.00). There was no significant difference in the mean duration between the groups (p=0.477).

One patient in group I had a hematoma at the site of dorsal penile injection. There were 2 cases of glans edema, with 1 in each group. The glans edema in group II necessitated removal of the plastibell ring on postoperative day (POD) 2, while the other was only noticed at the follow-up clinic on POD 6 when the plastibell ring had completely separated. All complications were managed conservatively with complete resolution. No patient in either group reported a need for rescue analgesics.

The addition of LPC to the procedure resulted in an additional waiting time of an hour and an additional cost of $2.00 (N720.00) per patient.

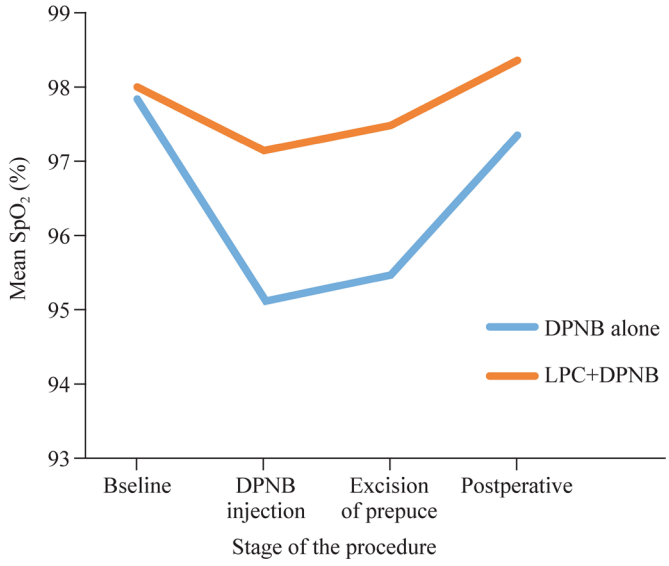

Figure 2 Mean decrease in SPO_2 percentages from baseline for the two groups. Group I circumcised with DPNB; group II circumcised with DPNB after application of LPC. DPNB, dorsal penile nerve block; LPC, lidocaine–prilocaine cream; SPO_2, peripheral arterial oxygen saturation.

DISCUSSION

Serum cortisol has been used to study the effectiveness of DPNB for neonatal circumcision analgesia.[16 17] This study used changes in serum cortisol, SpO_2 and HR to compare the effectiveness of DPNB alone and in combination with LPC in 70 neonates undergoing plastibell circumcision. We found increases in serum cortisol levels of 123% and 102% from baseline in group I (DPNB alone) and group II (DPNB with prior LPC), respectively. There was a decline in SpO_2 and a rise in HR from baseline at the different stages of the procedure. These changes were greater for patients

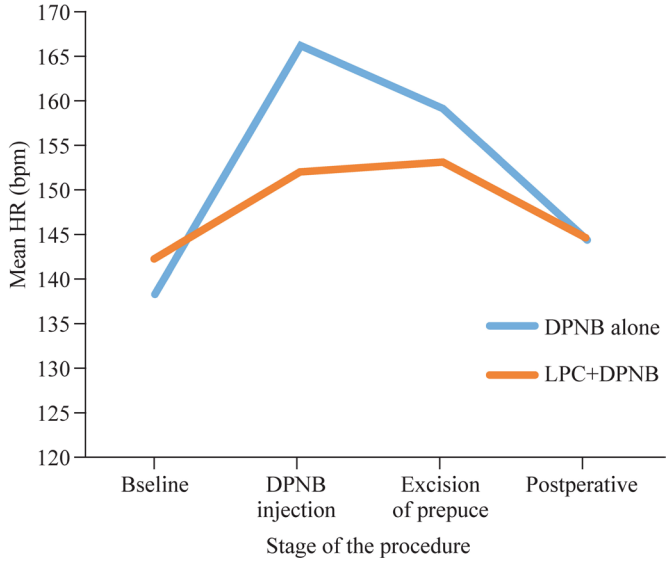

Figure 3 Mean increase in HR from baseline for the two groups. Group I circumcised with DPNB; group II circumcised with DPNB after application of LPC. DPNB, dorsal penile nerve block; HR, heart rate; LPC, lidocaine–prilocaine cream.

in group I than those in group II at the stage of DPNB injection, after excision of the prepuce and at 30 min after plastibell circumcision.

Higher cortisol values from baseline than either group in the current study have been documented in unanesthetized neonates.[16 17] A study on 24 neonates aged 1–3 days compared an unanesthetized control with DPNB.[16] They reported a rise of 106% for the DPNB group and 131% for the control group. Talbert *et al* recorded a 167% increase in serum cortisol in unanesthetized neonates 4–6 hours old at 40 min postoperatively.[17] This marked increase in cortisol in unanesthetized neonates in their study suggests that both DPNB alone and DPNB with prior LPC in the current study provide analgesia for neonatal circumcision. However, Kara *et al* reported only a 58% rise in serum cortisol from baseline in 5- to 17-year-old boys who underwent circumcision under intravenous general anesthesia.[18] There are no reports on serum cortisol level changes in neonates who underwent circumcision under DPNB with prior LPC in our literature search.

The postoperative rise in serum cortisol levels from baseline values in all patients in the current study is probably secondary to pain and stress response. A 2004 Cochrane review of 35 clinical trials involving 1997 newborn circumcisions concluded that the different local and regional techniques of analgesia reduced pain but did not eliminate it.[19] However, the significant difference in serum cortisol level change from baseline between the groups in this study shows that administering LPC prior to DPNB further reduces pain from circumcision in neonates.

Changes in SpO_2 and HR from baseline to values after DPNB injection, after excision of prepuce and at 30 min thereafter in both groups showed similar patterns to the changes in serum cortisol levels. Although the change in mean HR did not reach statistical significance at 30 min postoperatively, overall changes in SpO_2 and HR at the three stages from baseline between the groups further suggest that LPC provided sufficient analgesia to significantly enhance the efficacy of DPNB. LPC likely reduced the pain of needle injection and anesthetic infiltration and provided analgesia for the ventral aspects of the penis by blocking perineal nerve supply. The pain of anesthetic injection and insufficient analgesia of perineal nerve branches of the pudendal nerve have been attributed as causes of DPNB failure in a study on older children.[14]

Serour *et al*, in their work on children 7–16 years old, reported a significant anesthetic effect of LPC (EMLA) at the point of skin needle penetration but not at the point of anesthetic agent infiltration during dorsal penile injection.[14] Their study was able to assess the degree of pain at both points using verbal rating scales, as the children were old enough to voice the extent of discomfort or pain at each point. This was not feasible in this study on neonates. Although their conclusion was that LPC had no benefit in dorsal penile block, they suggested that a more superficial block than the subpubic technique that was used may give better outcome. Our study used a more superficial needle insertion technique at the penile base, where the dorsal

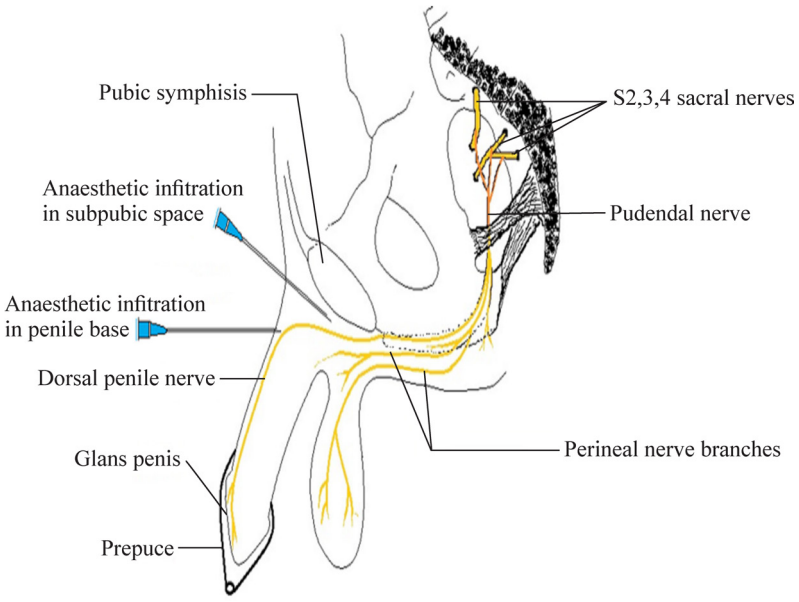

Figure 4 Sagittal section of penile innervation showing the course and depth of the dorsal penile nerve and two different points of dorsal penile nerve block.

penile nerve lies just beneath Buck's fascia (figure 4). Bjering *et al* observed a depth of 5 mm skin analgesia to needle insertion after LPC application to an area of the forearm in volunteers aged 24–28 years.[20] This is likely sufficient to reach the two dorsal penile nerve branches at this location in neonates and thus reduces the pain of both needle penetration and anesthetic infiltration.

We observed no major complications from the circumcision or local anesthetics used. This is consistent with other reports on circumcision using appropriate analgesia and techniques in hospital settings.[2 21–23] Methemoglobinemia is a rare but fatal complication of prilocaine and lidocaine administration that may manifest as cyanosis, respiratory distress or simply bruising of the hands and feet, especially in young infants.[24] Although these were not recorded in any of our patients, we were limited by the inability to measure the levels of the local anesthetics, their metabolites or methemoglobin in the postoperative blood samples. This may help detect subclinical complications of the use of this combination of local anesthetic agents. A larger study may provide a sufficient sample to also compare complication outcomes between the two groups.

In conclusion, the application of LPC prior to DPNB provided significantly more effective analgesia than DPNB alone for neonatal plastibell circumcision. This may justify the additional waiting time and cost occasioned by the addition of LPC. In the absence of contraindications to its use, LPC prior to DPNB may be preferred to DPNB alone.

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Contributors IOO conceived the research idea. IOO, CCN and AMS drew the initial draft. All authors contributed significant intellectual content to the drafting, review, analysis and interpretation of data. They all approved the final draft and agreed to be accountable for all aspects of the article. IOO is responsible for the overall content as the guarantor.

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Competing interests A full dissertation of this project was presented to the West African College of Surgeons.

Patient consent for publication The participants gave informed consent to participate in the study before taking part.

Ethics approval This study involves human participants and was approved by research and ethics committee of Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria (dossier number IRB/IEC/0004553).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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