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Effect of lidocaine-prilocaine eutectic mixture of local anaesthetic cream compared with oral sucrose or both in alleviating pain in neonatal circumcision procedure

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ABSTRACT

Background: Neonatal circumcision is one of the oldest and most frequently performed surgical procedures on males. Newborns demonstrate strong endogenous reaction to pain and therefore modalities are being explored for optimum pain relief during circumcision. Pediatric nurses have a vital role for the use of these modalities and minimising the pain response during the neonatal minor procedures. **Aim:** The aim of this study was to assess the effectiveness of eutectic mixture of local anaesthetic (EMLA) cream compared with oral sucrose and both in alleviating pain in neonatal circumcision. **Materials and Methods:** This study was conducted in the Day Care Surgery Department of Maternity and Children Hospital, Dammam City, KSA. 90 full-term newborn males who underwent circumcision were divided randomly into three groups (30 each). Each group was assigned to receive a different type of analgesics such as EMLA cream (Group A), oral sucrose (Group B) or combination of EMLA cream and oral sucrose (Group C). Neonatal pain agitation and sedation scale (N-PASS) was used 5 min before, during and 5 min after the circumcision procedure to assess the neonatal response to pain. **Results:** N-PASS scores were significantly lower in Group C (median Group C = 5.2, Group A = 5.8, Group B = 8.5; $P < 0.001$). The endogenous response to pain in terms of escalation of heart rate and reduction in O_2 saturation were minimal among Group C ($P < 0.0001$). Duration of crying was comparable among all the groups. **Conclusion:** The combination of sucrose and EMLA cream revealed a higher analgesic effect and minimal adverse response to pain than either EMLA cream or sucrose alone during neonatal circumcision.

Key words: Eutectic mixture of local anaesthetic, neonatal circumcision, neonatal pain agitation and sedation scale score, pain, sucrose

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INTRODUCTION

Male circumcision is one of the oldest and most common surgical procedures world-wide and is undertaken for many reasons such as religious, cultural, social and medical.[1-3] Approximately, 30% of males are estimated to be circumcised globally, of whom an estimated two-thirds are Muslims.[4]

In recent years a number of authors have reported medical benefits of newborn circumcision including; a decrease in the number of infant urinary tract infections, immediate protection against inflammatory penile skin conditions such as balanitis, posthitis and balanoposthitis.[5] Male circumcision protects against penile cancer; human papilloma virus, herpes simplex virus type 2 and human immunodeficiency virus infections; and sexually transmitted diseases later on.[4-9]

Newborns undergoing circumcision demonstrate strong endogenous reaction and high intensity of pain response.[10] As a result of pain, newborns experience measurable physiologic (heart and respiratory rate and transcutaneous oxygen saturation) and behavioural responses (facial expression, crying patterns, irritability and poor feeding). These responses can be harmful to infant's behavioural and neurological development.[10-12] Pain and stress resulting in repeated disruptions can affect the infant's neurodevelopment, putting the child at risk for later emotional disturbances,

learning disorders, poor adaptive behaviour and attention deficits. There is also some evidence that neonatal pain experience may have far reaching effects even up to the preschool age and beyond.[12-15] Generation of free radicals in response to pain has been postulated to cause cerebral damage.[14] From the point of view of those caring for neonates and infants, pain has two important deleterious consequences. The first is the mistrust and fear towards the caregiver, generated by failure to prevent or relieve pain. Secondly, inadequate analgesia for initial procedures can decrease the effect of adequate analgesic doses in subsequent procedures.[14]

Despite evidence that circumcision is painful, the procedure continues to be performed in some settings without adequate analgesia. Analgesics are not administered routinely by health care workers in some settings because of concerns regarding the side-effects of drugs and perceived lack of importance of pain because of the immaturity of the central nervous system among neonates.[16] However, the American Academy of Paediatrics and American College of Obstetricians and Gynaecologists have recommended that, newborns should receive adequate, safe and effective analgesia during painful procedures such as circumcision. Several interventions, which include the use of pharmacologic and non-pharmacologic measures to relieve circumcision pain and discomfort have been suggested.[12]

The main aim of the present study was to assess the effect of eutectic mixture of local anaesthetic (EMLA) cream (2.5% lidocaine/2.5% prilocaine cream) alone compared with oral sucrose alone and with EMLA cream together with oral sucrose in alleviating pain and pain associated deleterious responses in neonatal circumcision procedure.

Because optimum pain assessment in neonates is difficult to perform, the pain-assessment tool used should be multidimensional, including measurements for both physiologic and behavioural indicators of pain, as neonates cannot self-report. Since paediatric nurses are in the unique position to help, educate parents regarding the care of their newborn, they must take responsibility for ensuring that each parent has accurate and unbiased information regarding circumcision procedure including options for pain control.[16]

MATERIALS AND METHODS

Following Institutional Review Board and Ethical Committee approval, this prospective randomised clinical trial was conducted in the Day Care Surgery Department of Maternity Children Hospital in Dammam City, Kingdom of Saudi Arabia. A convenience sample of 90 full term male infants, who were brought by their parents for circumcision to the above mentioned setting between January 2011 and April 2011 were included in the study. The selection of these early infants was based on certain criteria such as; gestational age of 38 weeks or beyond, 5-min Apgar score of 8 or higher, postnatal age of 12 h or older and birth weight >2500 g and to be free from jaundice, anomalies of the penis and analgesia or sedation in the previous 48 h. The sample was divided randomly into three groups and each group (30 neonates) was assigned to receive a different type of pain relieving modalities such as EMLA cream (Group A), oral sucrose (Group B) or combination of EMLA cream and oral sucrose (Group C).

Demographic data related to mothers and neonates were collected on a set proforma. Neonatal pain agitation and sedation scale (N-PASS) was used to assess the severity of pain and neonatal response to pain, 5 min before, during and 5 min after the circumcision for all newborns. The scale measures both physiologic (heart rate [HR], respiratory rate, blood pressure and oxygen saturation) and behavioural (crying irritability, behaviour state, facial expression and extremities tone) responses to pain.

Before 1 h of procedure, the envelope was opened to classify randomly the neonate to one of the groups in order to carry out the appropriate action. In Group A, 1 g of a topical mixture of lidocaine (2.5%) and prilocaine (2.5%) cream was applied to the shaft of the penis with an occlusive dressing 1 h before the procedure. In Group B, 2 ml of oral sucrose (24% weight by volume) were given through a dropper onto the tongue 2 min before the procedure. In Group C, both EMLA cream application and oral sucrose were used.

Circumcisions were performed by single paediatric surgeon using the Plasti Bell method to maintain uniformity. The video imaging of the neonate was carried out 5 min before, during and until 10 min after the procedure to show the newborn reaction to pain and duration of crying was recorded. The videotapes were reviewed by a second individual, unaware of the infant's treatment group assignment. A mean N-PASS score for each infant was then calculated by taking the mean of the five measured criteria. Physiologic and behavioural data were collected and analysed by a third individual who had not performed the circumcision nor scored the tapes.

Data analysis was performed utilising SPSS software, version 19.0. Data analysis included descriptive statistics on demographic data reporting in the form of frequencies, percentages, means, median and a standard deviation (SD). Combinations of ANOVA for quantitative data and Chi-square test for qualitative data have been used for the qualitative variables, $P < 0.05$ was considered to be statistically significant.

RESULTS

The sample distribution of neonates' characteristics was similar for the three randomised groups. No statistically significant differences were found between groups with regard to their age, weight, length, head circumference and chest circumference, gestational age and Apgar scoring [Table 1].

The N-PASS scores [Table 2] were significantly lower ($P < 0.001$) among the Group C neonates who received combination of EMLA cream and oral sucrose (median: 5.2) compared to Group A (EMLA group alone; median: 5.8) and Group B neonates (sucrose group alone; median: 8.5). There was no significant difference demonstrated between the three groups at baseline and post circumcision pain assessment.

However, significant differences were demonstrated in the physiological responses during the circumcision procedure between the three groups [Table 3]. Group B neonates demonstrated a greater increase in HR (mean ± SD was 205 ± 12.8) than Group A neonates (mean ± SD was 199 ± 9.99). Group C neonates had the lowest HR escalation (193 ± 7.91). Whereas, no significant difference in respiratory rate were noted among the three groups ($P = 0.9$). Decrease in oxygen saturation during the circumcision (from the baseline) was significantly different among the three groups ($P < 0.0001$). Duration of cry was comparable in all three groups with mean ranging between 7 and 8 min. Duration of cry was inversely proportional to neonates' postnatal age, gestational age and body weight ($P = 0.001$, $P = 0.03$ and $P = 0.05$, respectively) irrespective of the type of pain relieving modalities used [Table 4]. Other studied factors namely; age of neonates and Apgar score in 1 and 5 min had no statistically significant correlation with pain score during circumcision procedure.

DISCUSSION

Routine neonatal circumcision is a painful procedure. Recent research suggests that infants may be more vulnerable to the negative effects of pain than older children and adults.[14,15] Despite convincing evidence from recent research of the necessity to treat pain and to avoid early exposure to pain, neonates in some settings are still subjected to painful procedures and even surgery such as circumcision without adequate pain treatment.[12]

Table 1: Biological and anthropometric data of neonates

Neonatal biological factor	Group A (*n*=30) Mean±SD	Group B (*n*=30) Mean±SD	Group C (*n*=30) Mean±SD	Significant test
Age of neonates (days)	24.7±6.4	25.1±6.6	24.5±7.9	*P*=0.4
Gestational age (weeks)	38.9±0.7	38.7±0.7	39±0.8	*P*=0.2
Apgar score in 1st min	8.9±0.3	8.9±0.3	8.9±0.2	*P*=0.2
Apgar score in 5th min	All had value of 10	9.9±0.3	9.97±0.2	*P*=0.4
Weight/kg	3.8±0.3	3.8±0.24	3.7±0.3	*P*=0.3
Length in cm	50.3±1.9	49.8±1.6	50±1.4	*P*=0.5
Head circumference in cm	36.5±1.66	35.6±1.00	35.6±1.3	*P*=0.2
Chest circumference in cm	34.7±2.1	34±1.2	34±1.6	*P*=0.2

SD-Standard deviation

Table 2: Pain scores of different groups; before, during and after circumcision

Treatment group	Before 5 min mean±SD	During mean±SD	After 5 min mean±SD
Group A (*N*=30)	0.9±1.5	5.8±0.6	3.1±1.2
Group B (*N*=30)	0.9±1.2	8.2±1.4	4.5±1.4
Group C (*N*=30)	1.2±1.4	5.2±0.8	3.3±1.4
χ^{2a} (*P*)		54.514** (<0.001)	16.297** (<0.001)
Z_a (*P*)		Combination and EMLA 2.646** (0.008)	Combination and EMLA 0.731 (0.5)
		Combination and sucrose 6.237** (<0.001)	Combination and sucrose 3.052** (0.002)
	1.345 (0.5)	EMLA and sucrose 6.013** (<0.001)	EMLA and sucrose 3.803** (<0.001)

*The scale used for neonatal pain assessment is neonatal pain, agitation and sedation scale, the score of ≤3 consider (no pain) where score >3 indicate pain, **Statistically significant differences, SD-Standard deviation, EMLA-Eutectic mixture of local anesthetic

Table 3: Comparison between groups in relation to their physiological response to pain

Variables	Mean±SD			Significant test
	Group A	Group B	Group C	
Before circumcision				
Heart rate B/M	164±11.5	164±10.9	164±9.04	*P*=0.9
Respiratory rate C/M	46.4±4.2	47.3±3	46.3±4.2	*P*=0.5
Oxygen saturation %	98.5±1.7	98.8±1.4	99±1.4	*P*=0.2
During circumcision				
Heart rate B/M	199±9.99	205±12.8	193±7.91	*P*<0.0001*
Respiratory rate C/M	55.8±4.2	53.9±4.1	53.3±5.2	*P*=0.9
Oxygen saturation %	96.7±1.61	94±2.28	97.4±1.58	*P*<0.0001*
After circumcision				
Heart rate B/M	173±9.7	185.7±10.3	172±12.8	*P*<0.0001*
Respiratory rate C/M	50.7±3.9	50.7±3.9	49.6±4.2	*P*=0.4
Oxygen saturation %	98.4±1.6	96.6±1.4	98.3±1.9	*P*=0.5
Cry duration in minutes	7.43±1.71	8.39±1.81	7.9±1.59	*P*=0.2

*Statistically significant differences, SD-Standard deviation, B/M-beats per minute, C/M-cycles per minute

Table 4: Correlation between neonates' biological characteristics with cry duration during circumcision procedure

Variables	Group A *r* (*P*)	Group B *r* (*P*)	Group C *r* (*P*)
Age of neonates	−0.001 (0.996)	−0.360* (0.05)	−0.347 (0.06)
Gestational age	−0.193 (0.3)	−0.59* (0.001)	−0.216 (0.3)
Weight	0.058 (0.7)	−0.4 *(0.03)	−0.179 (0.3)
Apgar score in 1 min	−0.077 (0.7)	0.000 (1.000)	0.00
Apgar score in 5 min	−0.077 (0.7)	−0.143 (0.4)	0.00
Cry duration	0.200 (0.3)	0.273 (0.1)	−0.084 (0.7)

*Statistically significant differences

Reaction to pain in the neonatal period can be assessed by monitoring physiologic variables such as HR, respiratory rate and transcutaneous blood gases.[11,17] Multiple pain assessment tools have been developed to assess infant pain. In the current study, the N-PASS[17] was selected to assess multidimensional (physiologic and behavioural) responses to pain in newborns.

A number of studies have shown that orally administered sweet-tasting solutions such as sucrose and glucose, reduce signs of pain during painful procedures.[18-23] The local anaesthetic cream EMLA has recently been shown to be safe for use in neonates.[24,25] Quantitative studies have compared efficacies of these modalities in reducing of pain in neonates.[25]

In the literature, variable dosage of EMLA (ranged from 0.5 to 5 g) has been mentioned in the circumcision pain management, applied under an occlusive dressing for 45-90 min prior to the procedure.[24] In the present study, 1 g of EMLA cream was applied under an occlusive dressing for 60 min before circumcision procedure in order to ensure safety and effectiveness of the cream.

There are anecdotal reports in the literature proposing combination modalities for pain relief during circumcision. Mohan *et al.*, have recently used a combination of EMLA and oral sucrose in their cohort of neonatal circumcision and have demonstrated superior efficacy of the combination over individual agent which is consistent with the present study.[25] In our study, the mean N-PASS score was significantly lower in combined modality group (Group C = 5.2 ± 0.8) compared to single modality groups (EMLA cream alone = 5.8 ± 0.6 and oral sucrose alone 8.2 ± 1.4) [Table 4].

With regard to the effect of EMLA cream alone, Taddio *et al.*[24] randomly assigned neonates to 1 g of EMLA or a cosmetically identical placebo cream on the outside of the prepuce for 60-80 min before circumcision. Infants pre-treated with EMLA had lower ($P < 0.05$) facial action pain scores (assessed using the Neonatal Facial Coding System), per cent crying time and HR during surgery when compared with placebo. However, the finding of the present study demonstrated significant ($P < 0.001$) decrease in pain score of the neonates who received EMLA cream compared with neonates who received oral sucrose. The neonates treated with EMLA, showed lesser increase in HR and oxygen saturation than neonates who received oral sucrose.

Sucrose solutions have analgesic and calming properties in newborn infants.[18-23] However, Kass and Holman's research measuring pulse oximetry and HR, did

not support the idea that concentrated oral sugar solutions were effective at reducing the circumcision pain.[21] Furthermore, Stevens *et al*. showed that, the administration of oral sucrose before circumcision does not offer sufficient analgesia for all pain-related measures (HR, pulse oximetry, crying time and pain scores).[22]

The present study revealed that the neonates who received oral sucrose demonstrated a greater increase in HR and decrease in oxygen saturation because of excessive crying during the procedure, than those infants who received the EMLA cream alone. The group who received combination of EMLA cream and sucrose had a lowest HR and highest oxygen saturation.

In contrast, Herschel and colleagues found significant benefit from 50% of sucrose solution, administered through a nipple held in place during the procedure.[23] A potential flaw in this study is use of a nipple to deliver the sucrose. The suckling action of the infant on the pacifier alone may have produced analgesia.[26]

The present study eliminated the potential effects of suckling on pain-related behaviour and physiologic responses. It is possible that the sucrose may be a relatively weak analgesic that is more effective at calming infants during the recovery period after a painful procedure than during the actual procedure when pain is at its peak. However, it could have a synergistic effect on pain relief when used in combination with other modalities.

Neonatal pain response may vary with gestational age, state, severity of illness, repeated painful procedures. One study revealed that, there were different responses to painful stimuli (cry, facial activity, limbs movement and HR) in newborn with different gestational age (28 week, 33 week, 36 week and more).[26] In the current study, it was found that there was significant negative correlation between neonates' weight and gestational age to the degree of pain. This is consistent with Johnston and Stevens who stated that the HR during heel stick procedures was higher among infant born at 28 gestational age than infant who born at 32 weeks.[27]

CONCLUSIONS

It can be concluded that, the combination of EMLA cream and oral sucrose provides better pain reduction and minimal physiological disturbance during neonatal circumcision compared with EMLA cream alone or oral sucrose alone. The present study recommends that health-care institutions should develop and implement patient care policies to assess, prevent and manage pain in neonates during circumcision. The policy should address the importance of analgesia during neonatal circumcision in order to prevent short and long-term effects of neonatal pain.

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