Analgesic Effect of Oral Glucose in Neonates

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ABSTRACT

The International Association for the Study of Pain, has defined pain as "an unpleasant sensory and emotional experience connected with actual or potential tissue damage or described in terms of such damage". It was thought that the newborn baby does not experience pain because of incompletely developed nervous system. However, it has been shown that neurological system known to be associated with pain transmission and modulation, is intact and functional. A study was conducted in our center to study the analgesic effect of administration of oral glucose in various concentrations, in neonates undergoing heel punctures, for collection of blood for investigations. This was compared with the analgesic effects of breast milk (which contains lactose). 125 full term normal neonates with no history of birth asphyxia or underlying neurological abnormality, requiring heel punctures for collection of blood for various investigations were selected for the study. They were matched for gestational age, birth weight and sex distribution and divided into 5 groups of 25 each. One group comprised control subjects and was administered sterile water. 3 groups were administered 1 ml of varying strengths of glucose solutions i.e. 10%, 25% and 50% respectively. The last group was given 1 ml of expressed breast milk (EBM). Prior to heel pricks, state of arousal, baseline heart rate (HR) and transcutaneous oxygen saturation (SpO_2) were recorded by pulse oximeter in each neonate. Autolet, a mechanical device for capillary sampling, was used for heel pricks to give equal strength of painful stimulus in each procedure. Audio tape recorder was used to record the cry. The oral solution was administered slowly over 30 seconds by means of a syringe placed in the mouth. Heel puncture was done after 2 minutes, taking all aseptic precautions. HR and SpO_2 were monitored using pulse oximeter. Pain response was assessed, by recording duration of crying, change in HR, change in SpO_2 and facial action score after the procedure. Mean duration of cry and total cry over 5 minutes was significantly less in groups given 25% and 50% glucose solutions as compared to the control group and babies given EBM. Difference in mean increase in HR, fall in SpO_2 were statistically significant between control group, EBM group and neonates given 25% and 50% glucose solutions respectively. Compared to control group, all other administered solutions (10%, 25%, 50% glucose and EBM) were found to reduce physiological and behavioral responses in neonates undergoing heel punctures. 25% and 50% glucose solutions were found to have maximal analgesic effect and both were found to be equally effective. EBM and 10% glucose solution have an equal analgesic effect but less than 25% or 50% glucose. This simple, cheap and safe method of oral analgesia can be easily used in neonates undergoing heel prick procedures during routine neonatal care.

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Key Words : Analgesic effect; Breast milk; Glucose; Neonates

Introduction

"To cure sometimes, to relieve often, to comfort always", is a 15th century French description of the role of the physician. Although the relief of pain is felt to be a cardinal principle of compassionate medicine, yet in practice, pain management is often an ignored aspect of care. Though this unfortunate state has improved somewhat for older children and adults, yet neonatal pain continues to receive limited attention and is treated far less vigourously than in older children and adults.

The myth regarding neonatal pain suggests that because of neurological immaturity, neonates do not experience pain. However, studies have shown that pain pathways as well as cortical and subcortical centers, necessary for pain perception are well developed late in gestation and physiological and behavioural responses to pain are well documented in neonates [1-3]. Neonates either sick or well, require a number of painful therapeutic and diagnostic procedures and cry vigorously during these procedures. The medical and the para-medical staff usually ignore pain felt during these procedures. However, neonates have significant alteration in heart rate (HR), blood pressure (BP), palmar sweating (PS), plasma renin activity (PRA) and plasma cortisol level during such procedures [4].

A wide variety of pharmacological and non-pharmacological interventions are available for management of pain in infants. Pharmacological agents are usually not employed for pain relief in neonates due to the adverse effects they can produce. Non-pharmacological intervention is a more feasible alternative. Various studies [5-7] have shown that administration of oral sucrose, a disaccharide, raises the pain threshold, presumably mediated by endogenous opioids and could be used for that purpose. However, sucrose is not routinely used in neonatal care and is not readily available in the neonatal nursery. Glucose is a monosaccharide widely used by intravenous (IV) route in neonatal care unit but not as an oral solution. The present study was undertaken to find out the effect of oral administration of glucose, in different strengths, on pain relief in neonates requiring a heel prick test and to compare it with breast milk administration which

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contains the disaccharide lactose.

Material and Methods

Healthy term neonates between 1 to 7 days of life, requiring heel prick method for collection of blood, were included in the study. The neonates were divided into 5 groups, each group consisting of 25 neonates each (total 125). Gestational age of each neonate was determined, using date of LMP of the mother, antenatal ultrasound findings and clinical assessment using the New Ballard Score [8]. Detailed antenatal and perinatal data was recorded for each neonate from the clinical records. Neonates with following characteristics were excluded from the study :-

Age <24 hrs or >7 days

Gestational age <37 weeks

Apgar score of <7 and <8 at 1 and 5 min respectively.

Neonates with oxygen requirement > 40%

Analgesic or sedative drug given within 5 days

Neurological symptoms like seizures, listlessness, altered sensorium etc.

Neonates were randomly distributed into 5 groups as under :

Group 1 : Control group - neonates received 1 ml of sterile water before heel prick.

Group 2 : Test group - neonates received 1 ml of 10% glucose before heel prick.

Group 3 : Test group - neonates received 1 ml of 25% glucose before heel prick.

Group 4 : Test group - neonates received 1 ml of 50% glucose before heel prick.

Group 5 : Test group - neonates received 1 ml of expressed breast milk (EBM) before heel prick.

Glucose solutions utilized were the same used for IV use and EBM was obtained from the baby's mother. Heel pricks were performed on the neonates in a warm quiet nursery. A pulse oximeter was applied to the neonate's foot, to monitor SpO_2 as well as HR during the procedure. Baseline HR and SpO_2 were recorded for each neonate before giving the heel prick. Audio tape recorder was used to record the crying. Duration of crying was measured for each neonate using a stopwatch.

Autolet, a mechanical device for capillary sampling, was used for heel pricks to obviate the difference between the strength of painful stimuli applied while giving the heel prick. The stylet was placed in the spring-loaded cartridge, which was then held against the heel pad and the spring was released; the stylet pierced the skin, causing bleeding and was immediately withdrawn. The autolet gives a fixed depth of puncture (2.4mm) unlike the manual method. This reduces the risk of calcaneal osteomyelitis.

State of arousal of each neonate was assessed before heel prick as per Prechtl and Beintema [9] behavioural state / wakefulness.

State 1 - Eyes closed, regular respiration, no movements (quiet sleep).

State 2 - Eyes closed, irregular respiration, gross movements, no crying (active sleep).

State 3 - Eyes open, regular respiration, no gross movements (quiet awake).

State 4 - Eyes open, irregular respiration, continual gross movements, no crying (active awake).

State 5 - Eyes open or closed and crying (active crying).

Every effort was made to ensure that the neonate was State 3.

The oral solution was warmed to 37°C before it was given. The solution was administered slowly over a period of 30 seconds by means of a syringe placed in the mouth. The heel pad was cleaned with 1% betadine solution, followed by alcohol using a sterile swab. Two minutes after giving the oral solution, the heel was squeezed and then lanced with sterile autolet. Audio tape recorder was switched on simultaneously to record the cry of the infant. HR and SpO_2 were monitored using pulse oximeter. Pain response was assesssed by recording the following parameters :

1. Duration of crying : Duration of 1st cry was recorded from the 1st burst of sound till the neonate became silent again. Total crying time over a period of 5 minutes after the prick was also noted.

2. Change in HR : It was recorded as the difference between the maximum HR achieved during the procedure and the baseline HR.

3. Change in SpO_2 : Recorded as the maximum change, either increase or decrease after heel prick, from the baseline SpO_2.

4. Facial action score : Four facial actions as mentioned below were noted to determine the facial score of each neonate :

a. Brow bulge : Bulging, creasing and vertical furrows above and between brows, occurring as a result of lowering and drawing together of eyebrows.

b. Eye squeeze : Squeezing of eyelids, bulging of the fatty pads above infant's eyes is pronounced.

c. Nasolabial furrow : Upward pulling and deepening of nasolabial furrow.

d. Opening of the mouth : Any separation of lips was scored as opening of the mouth.

Each response was given a score of 1 (one) if present and 0 (zero) if absent. Total score was noted by adding score of each parameter. Data thus collected, was tabulated and analyzed. A statistical comparison was made using ANOVA and multiple comparison tables.

Results

A total of 125 term normal neonates, divided into 5 groups of 25 each, were studied. None of the neonates had birth asphyxia or birth trauma. There was no alteration of neurological status in either of them. Each group of neonates underwent heel pricks for collection of blood samples and

was administered different strengths of glucose and EBM as pain relieving agents. Group 1 was used as control.

Effect on duration of 1st cry : Mean duration of 1st cry was maximum in group 1 and minimum in group 3 (Table 1). Difference in mean duration of 1st cry was statistically significant ($p<0.05$) between all groups except when group 2 compared to group 5 and group 3 to group 4.

Table 1

Duration of first cry after heel prick

Group	Mean (sec)	SD	F statistic ANOVA	p Value
1	34.88	5.239		
2	27.92	5.131		
3	17.06	5.635	48.054	0.000
4	18.28	3.846		
5	29.84	6.725		

Mean duration of 1st cry is maximum in group 1 (control group) and minimum in group 3 (25% glucose)

Effect on total duration of cry : Mean total duration of cry is depicted in Table 2. It was maximum in group 1 and minimum in group 2. It is statistically significant ($p<0.05$) between all groups except when group 2 is compared to group 5 ($p>0.05$) and group 3 to group 4 ($p>0.05$).

Table 2

Total duration of cry over 5 min period after heel prick (n = 125)

Group value	Mean (sec)	SD	F statistic ANOVA	p
1	113.76	11.82		
2	101.00	9.99		
3	74.80	10.96	60.43	0.000
4	77.36	13.21		
5	104.56	9.16		

Mean duration of total cry is maximum in group 1 (control group) and minimum in group 3 (25% glucose)

Effect on HR : All groups showed significant increase in HR as shown in Table 3. Mean percentage increase in HR over baseline HR was maximum in group 1 and minimum in group 4. This is statistically significant ($p<0.05$) except when group 2 is compared to group 5 and group 3 to group 4.

Table 3

Change in heart rate after heel prick (n=125)

Group	Change in heart rate (beats per min)		F statistic (ANOVA)	p value
	Mean	SD		
1	31.48	6.66		
2	26.52	4.88		
3	17.88	2.92	48.14	0.000
4	16.80	3.01		
5	26.91	4.20		

All groups showed significant increase in heart rate during the heel prick test.

Mean and percentage increase in HR after heel prick, is maximum in group 1 and minimum in group 4 (50% glucose)

Effect on SpO_2 : All groups showed a significant ($p<0.05$) fall in mean SpO_2 after the heel prick (Table 4). Mean fall in SpO_2 was maximum in group 1 and minimum in group 4. This is statistically significant ($p<0.05$) except when group 2 is compared to group 5 and group 3 to group 4.

Table 4

Transcutaneous oxygen saturation before and after heel prick (n=125)

Group	Base line SaO_2% Mean ± SD	SaO_2 (%) after heel prick Mean ± SD	p value
1	97.8 ± 3.49	89.64 ± 6.31	< 0.05
2	98.2 ± 2.62	91.80 ± 8.20	< 0.05
3	96.9 ± 3.04	92.34 ± 5.49	< 0.05
4	97.9 ± 3.50	93.42 ± 7.42	< 0.05
5	97.6 ± 2.72	91.00 ± 6.45	< 0.05

Mean baseline transcutaneous oxygen saturation is maximum in group 2 (10% glucose) and minimum in group 3 (25% glucose)

Effect on facial expressions : Mean facial scores of all groups are shown in Table 5. Mean facial score was maximum in group 1 and minimum in group 3 and 4. It is statistically significant only when group 3 and 4 are compared to group 1 and 5.

Table 5

Fall in transcutaneous oxygen saturation after heel prick (n=125)

Group	Fall in SaO_2 (%) Mean ± SD	F statistic (ANOVA)	p value
1	8.16 ± 1.93		
2	6.40 ± 1.97		
3	4.56 ± 1.60	19.71	0.000
4	4.48 ± 1.19		
5	6.60 ± 1.87		

All groups showed a significant ($p < 0.05$) fall in mean transcutaneous oxygen saturation after the heel prick.

Mean fall in SpO_2 is maximum in group 1 (control group) and minimum in group 4 (50% glucose).

Discussion

Withdrawing of blood in neonates for investigations is a common procedure during their stay in the hospital. These procedures are known to cause pain in patients who can report it. Opioids or similar drugs are normally used to manage pain during intensive care. However, for less sick babies, efforts to relieve pain have not yet been widely or satisfactorily used. Pain in newborns can affect cardiovascular functions, metabolism, and intracranial pressure [1,2,10,11]. For these reasons as well as for ethical reasons, it seems essential to find a simple and acceptable method for relieving pain. An ideal method or drug for reducing pain in neonates should be easy to use and well tolerated; method of administration should be atraumatic; should have a rapid onset of analgesic effect and should have minimal side effects.

Detection and qualification of pain in neonates is

difficult. In this study, four easily detectable parameters were used to assess pain while doing heel punctures in newborns. They were namely, duration of crying, change in HR, change in oxygen saturation, and facial expressions.

Various studies [5-7] have shown that infants given oral sucrose, cry less during heel pricks and these effects can be blocked by naltrexone, an opioid antagonist, suggesting a link between the orogustatory effect of sweet solution orally and endogenous opioid pathways. However, sterile solution of sucrose - a disaccharide, is not normally available in the nursery/postnatal ward. This study aimed to provide pain relief orally with a sweet solution i.e. glucose (a monosaccharide), which is normally used in the neonatal unit and for intravenous use. It has the advantage of being sterile and is readily available. Different strengths of this solution and EBM (which contains a disaccharide-lactose) were used and their analgesic effects were compared. A control group was administered only sterile water in the same quantity. Only normal full term babies matched for gestational age, sex and birth weight were used. Compared to control group, all groups showed a significant ($p<0.05$) reduction in duration of 1st cry. Maximum effect was seen in babies given 25% glucose, showing a 51% decrease in duration of 1st cry as compared to the control group. However, the difference was not significant ($p>0.05$) when group 2 (10% glucose) was compared to group 5 (EBM) and group 3 (25% glucose) was compared to group 4 (50% glucose). In a similar study by Skogsdal et al [12], in neonates with more than 30 weeks gestation and of age between 24 hours and 30 days, mean duration of 1st cry was found to be 35 seconds in neonates given no treatment, while it was 10 seconds in neonates given 25% glucose. In another study Haouari et al [6], using oral sucrose as an analgesic agent, found decrease in duration of 1st cry in neonates given 12.5%. 25% and 50% solutions, which are comparable with our study. However, unlike our study, thier study showed maximum effect with 50% solution as compared to 25% solution. Ramenghi et al [7] have shown similar results using sucrose solution.

Total cry time over a 5 min period after heel prick was significantly ($p<0.05$) reduced in all groups as compared to the control group. The difference among the various groups was also statistically significant ($p<0.05$), except when group 2 (10%) glucose was compared to group 5 (EBM) and group 3 (25%) was compared to group 4 (50%). This shows that 25% and 50% glucose when given orally are comparable in their analgesic effect and 10% glucose and EBM have a comparable analgesic effect. Our results are similar to the results of Blass et al [5], Haouari et al [6] and Ramenghi et al [7], the only difference being that all these studies had used sucrose solutions for analgesic.

Similar effects were seen in change in HR after heel punctures, where difference in change in HR was statistically significant ($p<0.05$) in all test group as compared to control group. Also, that 25% glucose was as effective as 50% glucose and 10% glucose was equally effective as EBM as an analgesic but less so as compared to the other 2 glucose groups. Various other workers have reported similar effect on HR during painful procedures in neonates [12-14]. Newborns in all 5 groups experienced a significant ($p<0.05$) fall in SpO_2 during the procedure. Mean fall of SpO_2 was maximum in control group and minimum in 50% glucose group. Singh et al [14] and Williamson et al [15] found a similar fall in SpO_2 in their respective studies. Neonates in all groups expressed pain in the form of change in their facial expressions. Mean facial score during the procedure was maximum in control group and least in 25% and 50% glucose group. This is comparable to the study of Ramenghi et al [7].

Findings in this study strongly suggest that EBM and all strengths of glucose solutions administered orally cause pain relief in healthy term neonates undergoing heel punctures and there is dose response effect of increasing concentration of glucose solution but a plateau is reached at 25% concentration. Difference in all the parameters measured was highly significant ($p<0.05$), except for facial scores, between the control group and the test groups. Although the mechanisms mediating the effect of glucose could not be studied, many studies by different authors have shown a primary role of endogenous opioids in pain relief [2,5,16]. This study and previous studies on animals [16,17] suggest a pre-absorptive mechanism. In all probability it is based on sweet taste perception, a human sense well developed even among premature infants at birth[18]. To conclude, increasing concentration of glucose and EBM have been found to have analgesic effect in full term neonates undergoing heel punctures for routine investigations and can probably be used to provide pain relief in other simple painful procedures. It is a cheap method and has the advantage of being easy to use, has no side effects and is well accepted by neonates.

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