Analgesic Effect of Oral Glucose in Preterm Infants During Venipuncture—A Double-blind, Randomized, Controlled Trial

by Laxmikant S. Deshmukh *and* Rekha H. Udani
Department of Neonatology, Seth G.S. Medical College and KEM Hospital, Parel, Mumbai–12, India

Summary

The aim of the present study was to evaluate the effect of different concentrations of glucose on measures of neonatal pain during venipuncture. A randomized, double-blind, placebo controlled trial was carried out at the neonatal intensive care unit at the King Edward Memorial Hospital. Sixty healthy preterm infants of gestation age 28–37 weeks and postnatal age 2–28 days were randomized to receive 2 ml of one of three solutions (sterile water, 10 per cent wt/vol. glucose and 25 per cent wt/vol. glucose) in the mouth 2 min before venipuncture. There was a significant reduction in duration of first cry in the babies given 25 per cent glucose compared with controls and those given 10 per cent glucose. There was no significant effect on heart rate, respiratory rate or oxygen saturation. It is concluded that concentrated glucose solution seems to reduce pain and may be a useful and safe analgesic for minor procedures in neonates.

Introduction

It has long been debated whether the newborn baby can feel pain. We now know that the anatomical structures for proprioception and the neurochemical systems associated with pain perception are present and functional at the lowest gestational ages when they can survive.[1] Physiological and behavioral responses to pain in newborns are well documented.[2,3] Furthermore, an increased effect of noxious stimulations has been suggested due to the lack of inhibition in the neonatal spinal cord.[4]

Many newborn babies, particularly preterm, undergo venipuncture quite frequently and it is therefore important to find an easy and reliable method to reduce the pain caused by venipuncture and similar procedures. The administration of sucrose with and without non-nutritive sucking has been the most frequently studied non-pharmacological intervention of procedural pain in neonates, but sucrose is not otherwise used in neonatal care. Glucose (dextrose) is a monosaccharide widely used and universally available but is usually not given as an oral solution. The present study was undertaken to determine if an oral dextrose solution could reduce physiological and behavioral expression of pain after venipuncture.

Acknowledgements

We thank Dr P. M. Pai, Dean Seth G.S. Medical College and K.E.M. Hospital for granting us permission to publish this article.

Correspondence: Dr Laxmikant S. Deshmukh, 120, Samarth Nagar, Aurangabad 431 001 (M.S.), India.
E-mail: <Isdeshmukh@123india.com>.

Materials and Methods

A double-blind, randomized, placebo controlled trial was carried out in the neonatal intensive care unit of King Edward Memorial Hospital, Mumbai, over an 8-month period from December 1997 to July 1998.

Patients

Based on the results of a previous study,[5] we calculated that to achieve a reduction of more than 50 per cent in the duration of cry with a power of 90 per cent, the sample size needed to be 15 in each group.

A total of 60 neonates were enrolled in the study. The inclusion criteria were: gestational age <37 weeks (as assessed by New Ballard Score); postnatal age <4 weeks but with a maturity score <37 weeks; breathing spontaneously in room air; and clinically stable.

Babies with age <24 h, an analgesic or sedative given within 5 days, on ventilator or oxygen treatment, or gross congenital malformations or neurologic symptoms, were excluded from the study. In babies delivered under general anaesthesia a minimum washout period of 48 h was established.

Procedure

Newborns were randomized to three groups using sealed envelopes, to receive by mouth using a sterile syringe preloaded with a coded solution of 2 ml of sterile water (group W), 10 per cent dextrose [Parenteral Drugs (India) Ltd.] (group D10), or 25 per cent dextrose [Parenteral Drugs (India) Ltd.] (group D25). Both glucose solutions were originally produced for intravenous use.

Two min after administration of an oral solution venipuncture was performed while the infant was still awake. A 2-min interval has been demonstrated to be the most effective delay period between sucrose administration and tissue damaging stimulation.[6] All venipunctures were ordered by the responsible physician as part of patient care and performed by a trained resident. All venipunctures were scheduled at least 1 h after feeding and when infants were in state 3 or 4 arousal according to the Prechtl and Beintema scale.[7] The infants were not removed from the incubator or crib in which they were normally cared for, during the procedure.

Monitoring

For pain assessment physiological parameters of heart rate (HR), respiratory rate (RR) and transcutaneous oxygen saturation by pulse oximetry were recorded. The duration of first cry (a behavioral parameter) defined as audible distressed vocalizations with a continuous pattern before a quiet interval of 5 s soon after the painful stimulus, was recorded over first 5 min following venipuncture, using a stop clock.

The monitoring was done continuously from 30 min before the procedure. Three time points were selected for the analysis of the physiological status—just prior to and soon after oral solution was administered, and 5 min after venipuncture.

Statistical analysis

The data were analysed using SPSS-OC, version 7.0. The decoding was done only after analysis of the data. Comparisons were made between three groups using unpaired *t*-test. A p value of < 0.05 was taken as significant.

Results

Sixty neonates (20 in each of the three groups) were enrolled for the study. There was no significant difference between the groups for sex, gestational age, and age at the time of venipuncture. The birthweight of the babies in the D25 group was higher compared with the other two groups (Table 1).

Physiological variables (Table 2)

There were no significant differences in heart rates, respiratory rates, or oxygen saturation between or within the groups at baseline, post-solution administration, or 5 min after venipuncture.

Duration of first cry

For the three groups, the mean (SD) duration of first cry during the first 5 min after venipuncture was 85.5 s (44.15), 68.95 s (42.51) and 40.50 s (38.98) for the W, D10 and D25 groups, respectively. Two babies in the D25 group and one each in the D10 and W groups, did not cry. There was no significant difference in duration of first cry between W and D10 groups ($p = 0.23$); however, it was significantly less for D25 compared with D10 ($p = 0.034$) and compared to water ($p = 0.002$).

There were no adverse effects observed, such as vomiting, abdominal distension, or NEC following the use of oral glucose.

Discussion

Most of the preterm neonates admitted in the nursery are subjected to a variety of invasive procedures, of which the most common is venipuncture. If intensive care is required, it is usually accepted that morphine or similar drugs should be given to relieve the pain. However, for babies who are less sick, efforts to relieve pain have not yet been widely or satisfactorily taken. Pain in the newborn child can be associated with risks. These include effects on cardiovascular function as well as changes in metabolism and intracranial pressure.[6] For this reason, as well as for ethical reasons, it seems essential to find a simple and acceptable method of reducing pain. This method should be easy to use and well tolerated.

TABLE 1
Baseline characteristics of the treatment groups [(mean SD)]

	Treatment groups		
	W ($n = 20$)	D10 ($n = 20$)	D25 ($n = 20$)
Birthweight (g)*	1532.5 (179.33)	1172.5 (274.73)	1706.5 (253.42)
Gestational age at birth (weeks)	34.55 (1.53)	34.05 (1.51)	34.2 (1.36)
Sex ratio (M: F)	1.5:1	0.7:1	0.7:1
Age at time of venipuncture (days)	7.55 (4.03)	7.95 (3.00)	6.05 (2.89)
Antibiotherapy* (%)	07 (35)	10 (50)	16 (80)

W = sterile water (control), D10 = 10% glucose, D25 = 25% glucose.
*$p < 0.05$.

TABLE 2
Physiological parameters at various time points and their change from baseline

Time point	Treatment group			*p* value
	W (n = 20)	D10 (n = 20)	D25 (n = 20)	
Heart rate				
Baseline	142 (20)	142 (19)	144 (20)	NS
PS	148 (16)	148(12)	151(15)	NS
VP5	152 (20)	145(18)	142(15)	NS
(VP5-B)	09 (21)	03 (16)	02 (15)	NS
(PS-B)	05 (14)	06 (17)	08 (15)	NS
Respiratory rate				
Baseline	45 (15)	53 (14)	46 (9)	NS
PS	41 (10)	47 (8)	45 (3)	NS
VP5	46 (15)	49 (13)	48 (7)	NS
(VP5-B)	0.35 (25)	–4.0 (15)	1 (8)	NS
(PS-B)	–4.0 (18)	–2.0 (13)	–070 (10)	NS
Oxygen saturation (%)				
Baseline	94 (2)	95 (2)	96 (2)	NS
PS	94 (2)	94 (3)	95 (2)	NS
VP5	94 (4)	94 (3)	95 (3)	NS
(VP5-B)	-0.73 (5)	–2 (3)	0 (3)	NS
(PS-B)	0 (2)	–1.65 (3)	–0.3 (2)	NS

NS = not significant; PS = post-solution, immediately after administration of solution; VP5 = 5 min after venipuncture; VP5-B = change from baseline to 5 min after venipuncture; PS-B = change from baseline to post-solution.

Various scales have been derived for pain detection in the newborn.[8] In the present study, we used three physiological parameters: heart rate, respiratory rate, and oxygen saturation, and the behavioral parameter of duration of first cry, since these are important parameters in most scales and can be easily used in clinical practice.

The present study, unlike that of Skogsdal, *et al*.,[5] did not show any significant change in heart rate with the use of glucose. Although, heart rate changes have been used for response evaluation to pain relief, this reflex response is unpredictable, since newborn infants have a parasympathetic dominance compared with later in life. Therefore, a paradoxical bradycardia in response to stress might occur.[6]

In the present study, there was no significant effect on respiratory rate and oxygen saturation. This could be because of the lack of significant stress following venipuncture, as suggested in recent reports.[9]

Duration of crying induced by a noxious stimulation is considered a valuable measure of pain in full term neonates, and has therefore been frequently used in pain studies. Extension of this tool for the assessment of pain to preterm infants is reasonable in the absence of any obvious impairment to vocalization.[10]

As in our study, other workers have used duration of first cry to assess the efficacy of pain relief in full term as well as preterm infants. In all these studies, sucrose as well as glucose reduced the duration of first cry significantly, indicating an analgesic effect.[6,10]

The effectiveness of a 2-min interval between glucose administration and the noxious stimulation agrees with other studies, suggesting a mechanism activated by the presence of the solution in the mouth rather than gastric or metabolic mediations.[10] With a mild sweet solution, our results did not show any significant analgesic effect, suggesting that a strong flavour seems to be necessary to elaborate the analgesic response.[10]

The experimental studies support the notion that the analgesia elicited by an oral sweet solution can be mediated by the activation of endogenous opioids and can be antagonized by opioid antagonists, such as naltrexone.[11]

References

1 Anand KJS, Carr DB. The neuroanatomy, neurophysiology and neurochemistry of pain, stress, and analgesia in newborns and children. Pediatr Clin N Am 1989; 36: 795–822.
2 Kabra NS, Udani RH. Evaluation of physiological and behavioral response to pain following heel prick with different techniques for Dextrostix assessment in healthy preterm neonates. Indian Pediatr 1999; 36: 1135–41.
3 Anand KJS, Hickey PR. Pain and its effects in the human neonate and fetus. New Eng J Med 1987; 317: 1321–29.
4 Fitzgerald M. Development of pain mechanisms. Br Med Bull 1991; 47: 667–75.

5 Skogsdal Y, Eriksson M, Schollin J. Analgesia in newborns given oral glucose. Acta Pediatr 1997; 86: 217–20.
6 Stevens B, Taddio A, Ohlsson A, Einarson T. The efficacy of sucrose for relieving procedural pain in neonates—a systematic review and meta-analysis. Acta Pediatr 1997; 86: 837–42.
7 Prechtl H, Beintema D. The neurologic examination of the full term newborn infant. London, SIMP, Heinemann, Clin Dev Med 1964; 12.
8 Stevens B, Johnston C, Petreyshen P, Taddio A. Premature infant pain profile: development and initial validation. Clin J Pain 1996; 12: 12–22.
9 Larsson BA, Tannfeldt G, Largercrantz H, Olsson GL. Venipuncture is more effective and less painful than heel lancing for blood tests in neonates. Pediatrics 1998; 101: 882–86.
10 Abad F, Diaz N, Domerech E, Robayana M, Rico J. Oral sweet solution reduces pain related behaviors in preterm infants. Acta Pediatr 1996; 85: 854–58.
11 Blass EM, Ren K, Zhou R, Dubrier R. Suckling and sucrose ingestion suppress persistent hyperalgesia and spinal Fos expression after forepaw inflammation in infant rats. Proc Natl Acad Sci USA 1997; 94: 1471–75.