Effect of oral sucrose in alleviating pain in preterm infants

Hiba Abdulwahid Dawood [(1)], Numan Nafie Hameed [(2)]
[(1)] PhD. student, Department of Pediatric Nursing, College of Nursing.
[(2)] Prof. Dr. College of Medicine, Baghdad University, and Consultant pediatrician in Children Welfare Teaching Hospital, Medical City.
hibaabdulwahid12345@gmail.com
numanalhamdani@yahoo.com

ABSTRACT
The purpose of this paper is to examine the effect of oral sucrose in alleviating pain among preterm infants, (2) identify the association between preterm infant's weight at time of intervention, maternal age, and pain intensity, and (3) investigate the difference in pain intensity between the groups of the preterm infant's gender. The researcher used the an interventional, randomized controlled trial design used to achieve the purpose of the study, the study was conducted at Medical City Complex/ Children Welfare Teaching Hospital/ NICU in Baghdad City throughout the period May 1st, 2022 to November 4th, 2022. Simple random sample of (42) preterm infants in NICU was selected into two groups, the nesting group 21 preterm infants and the control group 21 preterm infants. The scale of the study was the Premature Infant Pain Profile-Revised (PIPP-R) to assess pain, salivary cortisol used as indicator of pain. The study results exhibited that there were statistically significant differences in the PIPP-R and cortisol values for preterm infants in the oral sucrose group over time; the PIPP-R score for preterm infants in the oral sucrose group was noticeably less than that of the control group. The younger the mother at the oral sucrose group, the more intense the pain that her preterm infant can experience on heel stick procedure. The study concluded that oral sucrose was efficacious in alleviating the pain intensity and minimizing the salivary cortisol for the preterm infants after heel stick procedure than control group.

Introduction;

Infants with low-birth weight are more likely to have respiratory problems and CPAP failure (Hameed et al., 2014), increased risks of mortality, irreversible brain injury due to severe jaundice (Hameed et al.,2011), and blood transfusions due to immature body organs (Hameed et al., 2022). In preterm infants with is immune hemolytic diseases, the severity of extreme hyperbilirubinemia at admission substantially increases the probability of developing acute bilirubin encephalopathy and adverse outcomes at discharge. (Hameed & Hussein, 2021), in Iraq different guidelines of management the neonatal hyperbilirubinemia used in neonatal intensive care unit (Hameed et al., 2020).

Preterm birth is any birth before 37 complete weeks of gestation, or less than 259 days since the first day of the woman's last menstrual period (LMP) (World Health Organization [WHO], 2010). Premature birth results from a variety of unpredictable circumstances (Machado Júnior et al., 2014) such as vaginal bleeding (Kadhim & khairi, 2018). The nutritional status, psychosocial status, and the age of pregnant women during pregnancy are important variables contributed to the incidence of low birth weight (jeid & Abbas, 2018). The preterm infants need for special and immediate newborn care in delivery rooms (Hussein & Abbas, 2022) and need for promoting of breastfeeding due to the importance of breast milk for preterm infants (Hasan & abbas, 2018). The prematurity and small for gestational age (SGA) are risk factors for the development of respiratory distress syndrome (RDS) (Hameed & Mahmood, 2008). Preterm babies are particularly prone to pain since they are frequently delivered weeks or even months early. The neural system, like all other physiological systems, is underdeveloped in preterm newborns. Their pain-inhibitory systems are still undeveloped despite the fact that their pain-signaling pathways are there and completely functional, which prolongs and intensifies their pain (Fitzgerald, 2005). Many painful interventions and procedures are often required as part of the extensive treatment for them to survive. Research has exhibited that infants, particularly those born prematurely, sense pain and are able to recognize it from other tactile sensations (Weissman et al., 2009).

A sucrose solution (2 mL of 24% solution) is efficient for alleviating pain during painful procedures (venipuncture, heel lance, cannulation) in preterm and term newborns up to one month of age (Cooper & Petty, 2012). The sweet taste is believed to activate the endogenous opioid pathways, leading to the release of endogenous opioids. The

effectiveness of sucrose solution beyond 4-weeks of age for immunizations has not been consistently demonstrated in research (Wilson et al., 2013). When sucrose was given 2 minutes before to a painful stimulus, the effects lasted for 4 minutes, and the greatest reductions in physiologic and behavioral pain markers were observed (Stevens et al., 2013).

Research problem:

This study seeks to determine the effect of oral sucrose on pain intensity. At the neonatal intensive care unit (NICU), preterm infants often get a number of painful procedures (Simons et al., 2003). Accruing evidence demonstrates that preterm infants encounter pain (Giannakoulopoulos et al., 1999), and preterm infants differently express pain than full-term infants (Gibbins et al., 2014). Additionally, accumulating evidence suggests that prolonged exposure to unpleasant experiences during the newborn period is linked to important immediate and long-term effects (Cong et al., 2017).

The research seeks to answer the following questions:

1. What is the effect of oral sucrose in alleviating pain among preterm infants?

2. Can the preterm infant's weight at time of intervention, and maternal age predict the pain intensity the preterm infant has?

3. Are there differences in pain intensity between the groups of the preterm infant's gender?

Research objective:

to examine the effect of oral sucrose in alleviating pain among preterm infants, (2) identify the association between preterm infant's weight at time of intervention, maternal age, and pain intensity, and (3) investigate the difference in pain intensity between the groups of the preterm infant's gender.

Research hypotheses:

There are statistically significant differences in the pain intensity and salivary cortisol before and after heel stick between study and control groups.

Research methodology and study procedures:

Study Design:

An interventional, randomized controlled trial design used to achieve the purpose of the study, the study was conducted from the period of May 1st, 2022 to November 4th, 2022. Carried out in the Medical City Complex/ Children Welfare Teaching Hospital/ NICU in Baghdad City.

Study Sample:

Simple random sample of (42) preterm infants in NICU/ Children Welfare Teaching Hospital in Baghdad City.

Inclusion Criteria:

The inclusion criteria include preterm infants whose corrected gestational age from (32 - <37) weeks of pregnancy, those who do not experience any painful procedure for last 24 hours, do not receive any sedation for last 24 hours.

Exclusion Criteria:

The exclusion criteria addressed full-term infants whose corrected gestational age is >37 weeks, extremely preterm (< 28 weeks), very preterm (28–< 32 weeks), proven or suspected sepsis, major congenital malformations, all heart defect except neonatal Patent ductus arteriosus, who receive respiratory support.

Ethical Considerations*:*

The ethical approval was obtained from the Scientific Research Ethical Committee at College of Nursing-University of Baghdad, and written informed consent form used before data collection.

Study Instrument:

The Premature Infant Pain Profile-Revised (PIPP-R) is a well-validated measure used to assess pain in preterm and term infants. The PIPP-R includes three behavioral indicators (brow bulge, eye squeeze, and naso-labial furrow) and two physiological indicators (heart rate and oxygen saturation). Each indicator is rated on a 4-point Likert scale (0, 1, 2, and 3). The PIPP-R accounts for GA and baseline Behavioral State (BS) as contextual factors. The demographic data is body weight at time of intervention, preterm infants sex, and maternal age. The pain assessed objectively by using salivary cortisol kit for measure preterm infants pain, salivary cortisol as indicator of pain.

Data Collection Plan:

Before collecting study data, the mother/ relative of ten preterm infants who met the inclusion criteria were asked to involve their preterm infants in this study by giving informed consent. In NICU at Children Welfare Teaching Hospital, preterm infants

needing heel sticks were randomly assigned to either the study group or the control group. The study sample were randomly and equally selected in NICU.

Study procedure:

The student research gave one ml of 24% oral sucrose to the preterm infant two minutes prior to the heel stick, drop-by-drop via syringe over the anterior surface of the tongue which enable the preterm infant to swallow rates over a period of 1–2 minutes. Conducting the heel stick procedure with lancet approximately two minutes after administering the sucrose. The pharmacy at the study site supplies the syringes containing the oral sucrose solution, solutions are prepared and packaged in an identical matter, the SR will label each syringe with the preterm infants' study number and name to ensure added protection. Heel lancing was performed in the morning at the NICU where the study took place. The pain intensity was objectively measured using the salivary cortisol where its specimens were gathered before the heel lancing about 3-4 minutes, and after the heel lancing about 30 minutes. The transition from low light to bright light in the morning results in an increase in cortisol level

Group (n = 21) for each group	Preterm infant's body weight at time of intervention
	Mean (SD)
Oral Sucrose	1852.38 ± 520.48
Control	1710.95 ± 492.83

Preterm infant's gender	**Oral Sucrose Frequency (%)**	**Control Frequency (%)**
Male	8 (38.1%)	13 (61.9%)
Female	13 (61.9%)	8 (38.1%)

Results and discussion:

Table 1. ***Preterm infants' vital parameters (N = 42)***

The study results reveal that the preterm infant's body weight at time of intervention, those who are in the oral sucrose group scored higher (1852.38 ± 520.48) than control group. With respect to the preterm infants' gender, females outweigh males in oral sucrose (*n* = 13 (61.9%).

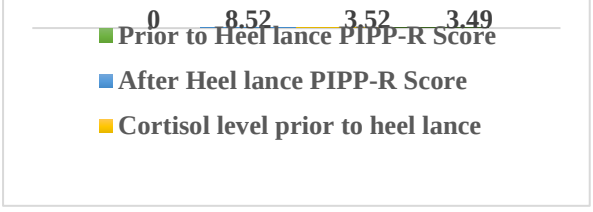
Table 3. ***Maternal age descriptive statistics***

	Oral Sucrose	Control
Mean (SD)	30.23 ± 7.02	29.33 ± 9.50

SD = Standard deviation

The study results reveal that the mean age of mothers in the oral sucrose group is 30.23 ± 7.02, and those in the control group is 29.33 ± 9.50.

Figure 1. ***PIPP-R and cortisol levels for the oral sucrose group over time***



The study results display there is a noticeable increase in the PIPP-R score for preterm infants in the oral sucrose group over time (Mean = 0; 8.52). For the cortisol level, there is a noticeable decrease in its value over time (3.52; 3.49) respectively.

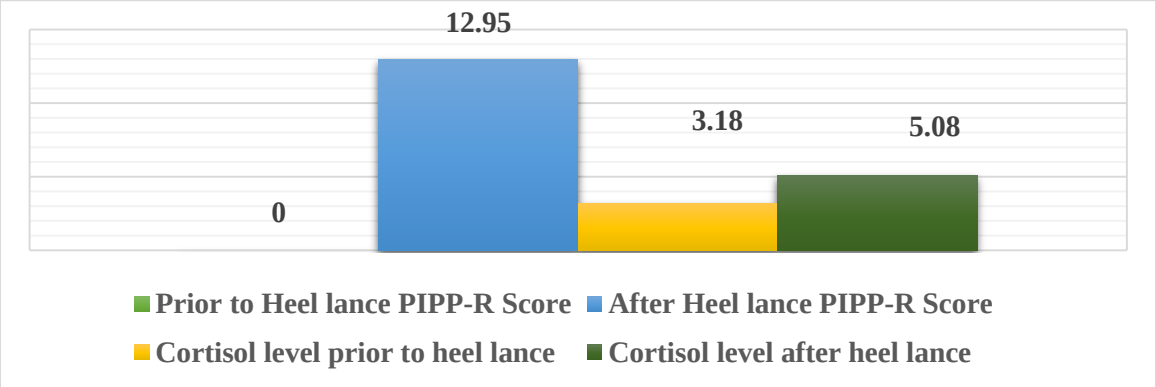
Table 4. ***Difference in the PIPP-R and cortisol scores for preterm infants in the oral sucrose group over time***

Paired Samples Test								
	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
PIPP-R Score Prior - After heel lance	-8.52381	2.54203	.55472	-9.68093	-7.36669	-15.366	20	.000
Saliva cortisol level prior - After heel lance	.02952	.82834	.18076	-.34753	.40658	.163	20	.872

df = Degree of freedom; Sig. = Significance; Std. Deviation = Standard Deviation; t = T-statistics

The study results exhibit that there is a statistically significant difference in the PIPP-R and oral sucrose values for preterm infants in the oral sucrose group over time (p-value = .000). On the other hand, there is no statistically significant difference in the cortisol level over time (p-value = .872).

Figure 2. ***PIPP-R and cortisol levels for the control group over time***



The study results display there is an extremely noticeable increase in the PIPP-R score for preterm infants in the control group over time (Mean = 0; 12.95). For the cortisol level, there is a noticeable increase in its value over time (3.18; 5.08) respectively.

Table 5. ***Difference in the PIPP-R and cortisol scores for preterm infants in the control group over time***

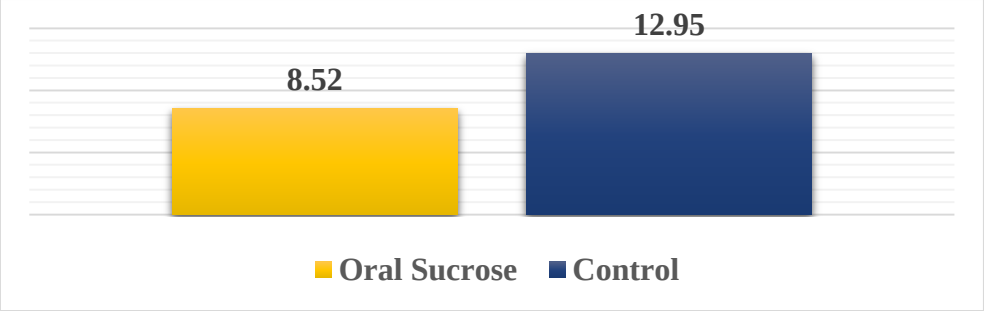
Paired Samples Test				
	Paired Differences	t	df	Sig. (2-tailed)

	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
PIPP-R Score Prior - After heel lance	-12.95238	3.02450	.66000	-14.32912	-11.57564	-19.625	20	.000
Saliva cortisol level prior - After heel lance	-1.89381	.87419	.19076	-2.29174	-1.49588	-9.928	20	.000

df = Degree of freedom; Sig. = Significance; Std. Deviation = Standard Deviation; t = T-statistics

The study results exhibit that there are statistically significant differences in the PIPP-R and cortisol values for preterm infants in the control group over time (p-value = .000, .000) respectively.

Figure 3. ***Mean scores of the PIPP-R after heal lance***



The study results demonstrate that preterm infants in the oral sucrose group experiences the lowest intensity of pain after heal lancing.

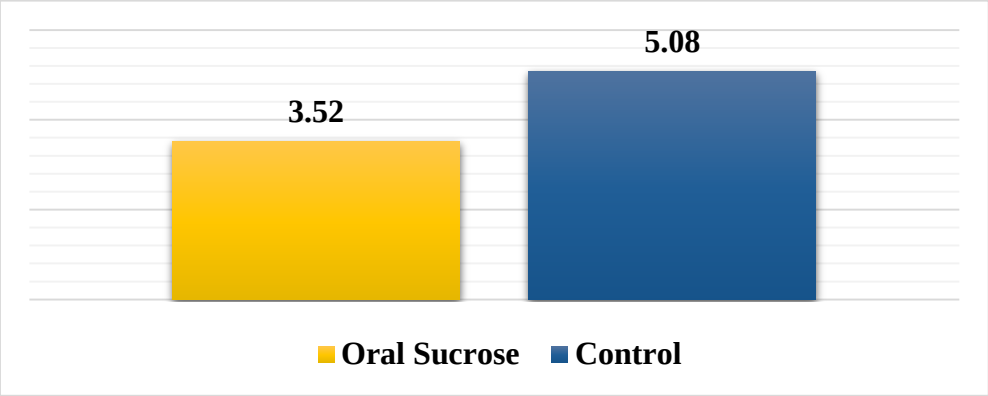
Table 6. ***Difference in the PIPP-R scores among the intervention groups and control group after heel lance***

One-Sample Test						
	Test Value = 0					
	t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
Oral Sucrose	15.366	20	.000	8.52381	7.3667	9.6809
Control	19.625	20	.000	12.95238	11.5756	14.3291

df = Degree of freedom; Sig. = Significance; Std. Deviation = Standard Deviation; t = T-statistics

The study results reveal that there are statistically significant differences in the PIPP-R scores among the Oral Sucrose group and control group (p-value = .000, .000) respectively.

Figure 4. ***Mean scores of the salivary cortisol after heal lance***



The study results demonstrate that the salivary cortisol value is lowest among preterm infants in the oral sucrose group (Salivary cortisol value = 3.52).

Table 7. ***Difference in the cortisol scores among the intervention groups and control group after heel lance***

One-Sample Test						
	Test Value = 0					
	t	Df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
Oral Sucrose	9.198	20	.000	3.52571	2.7261	4.3253
Control	10.562	20	.000	5.08048	4.0771	6.0838

df = Degree of freedom; Sig. = Significance; Std. Deviation = Standard Deviation; t = T-statistics

The study results reveal that there are statistically significant differences in the cortisol scores among the Oral Sucrose group and control group (p-value = .000, .000) respectively.

Table 8. ***Stepwise regression between the study variables and PIPP-R score for preterm infants in the oral sucrose group***

Coefficients[a,b]									
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	Correlations		
		B	Std. Error	Beta			Zero-order	Partial	Part
	Preterm infant's body weight at time of intervention	-.002	.001	-.384	-1.516	.148	.893	-.345	-.080
	Maternal Age	-.180	.084	-.630	-2.154	.046	.899	-.463	-.113
Preterm infant's body weight at time of intervention (control group)		-.001	.002	-.148	-.629	.538	.927	-.155	-.036

Maternal Age	.000	.088	.001	.004	.997	.928	.001	.000

a. Dependent Variable: After Heel Stick Pain Score Oral Sucrose
b. Linear Regression through the Origin

The study results display that the maternal age inversely predicted more the PIPP-R score (p-value = .046) in oral sucrose group.

Table 9. ***Difference in the PIPP-R between preterm infant's gender groups for preterm infants in the oral sucrose group***

Independent Samples Test									
After Heel Stick Pain Score Oral Sucrose	Levene's Test for Equality of Variances		t-test for Equality of Means						
	F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
								Lower	Upper
Equal variances assumed	2.433	0.135	0.487	19	0.632	0.56731	1.16471	-1.87045	3.00507
Equal variances not assumed			0.564	18.603	0.579	0.56731	1.00568	-1.54066	2.67527
Equal variances assumed (control group)	2.931	0.103	-0.641	19	0.529	-0.88462	1.37955	-3.77204	2.00281
Equal variances not assumed			-0.56	9.649	0.588	-0.88462	1.58072	-4.42413	2.6549

df = Degree of freedom; Sig. = Significance; Std. Deviation = Standard Deviation; t = T-statistics

The study results exhibit that there is no statistically significant difference in the PIPP-R values between the preterm infant's gender groups in the oral sucrose and control group over time.

Discussion:

The study results exhibited that there were statistically significant differences in the PIPP-R and cortisol values for preterm infants in the oral sucrose group over time. For the control group, there were statistically significant differences in the PIPP-R and cortisol values over time. However, the PIPP-R score for preterm infants in the oral sucrose group was noticeably less than that of the control group. These findings reflect the efficacy of the oral sucrose in alleviating the pain intensity. These findings are congruent with that obtained by Joung and Cho (2010) who concluded that the 24% oral sucrose resulted in lower pain scores in the experimental group than the control group after the painful procedure. In the same line, Stevens and others (2016) reported that oral sucrose is effective in reducing procedural pain from single events such as heel lance, venipuncture, and intramuscular injection in both preterm and term infants.

The dose used in this study is 1 ml is effective in alleviating the pain. This finding is consistent with that obtained by Stevens and others (2018) who concluded that the minimally effective dose of 24% sucrose required to treat pain associated with a single heel lance in the infants was 0.1 ml. For cortisol, the study finding is consistent with that of Gao and others (2021) who concluded that the salivary cortisol level decreased at discharge in preterm infants who received

oral sucrose combined with massage, music, non-nutritive sucking, and gentle human touch compared to those in routine care. The study results demonstrated that the maternal age inversely predicted more the PIPP-R score for preterm infants in the oral sucrose group. This finding implies that the younger the mother at the oral sucrose group, the more intense the pain that her preterm infant can experience on heel stick procedure. This finding could be explained as young mothers lack some mothering competencies including skin-to-skin care as demonstrated by Campbell-Yeo et al. (2022) as such competencies can alleviate the pain intensity these preterm infants experience.

Conclusions and Recommendations:

Conclusion:

The non-pharmacological pain management strategy of oral sucrose was efficacious in alleviating the pain intensity and minimizing the salivary cortisol for the preterm infants after heel stick procedure than control group. The younger the mother at the oral sucrose group, the more intense the pain that her preterm infant can experience on heel stick procedure.

Recommendations:

There is a pressing need to employ the non-pharmacological pain management strategies for alleviating the pain that the preterm infants experience on invasive procedures in the NICU across Iraq. Oral sucrose was efficacious in alleviating the pain intensity, easy to use and available in the NICU.

References :

1. Hameed, N. N., Abdul Jaleel, R. K., & Saugstad, O. D. (2014). The use of continuous positive airway pressure in preterm babies with respiratory distress syndrome: a report from Baghdad, Iraq. *The journal of maternal-fetal & neonatal medicine*, *27*(6), 629–632. https://doi.org/10.3109/14767058.2013.825595

2. Hameed, N. N., Na' Ma, A. M., Vilms, R., & Bhutani, V. K. (2011). Severe neonatal hyperbilirubinemia and adverse short-term consequences in Baghdad, Iraq. *Neonatology*, *100*(1), 57–63. https://doi.org/10.1159/000321990

3. Hameed, N. N., Ameen, H. K., & Faraj, S. (2022). Patterns and Determinants of Blood and Blood Products Transfusion in Neonate: An Experience of Single Institute. Open Access Macedonian Journal of Medical Sciences (OAMJMS), 10(B), 927–930. https://doi.org/10.3889/oamjms.2022.8641

4. Hameed, N. N., & Hussein, M. A. (2021). BIND score: A system to triage infants readmitted for extreme hyperbilirubinemia. *Seminars in perinatology*, *45*(1), 151354. https://doi.org/10.1016/j.semperi.2020.151354

5. Hameed, N. N., Yousif, H. N., & Fawzi, H. A. (2020). Assessment of adherence level for neonatal hyperbilirubinemia management by various physicians in Iraq: a multi-clinic study. *F1000Research*, *9*, 504. https://doi.org/10.12688/f1000research.24258.1

6. World Health Organization. 2010. ICD-10: international statistical classification of diseases and related health problems, tenth revision.

7. Machado Júnior, L. C., Passini Júnior, R., & Rodrigues Machado Rosa, I. (2014). Late prematurity: a systematic review. *Jornal de pediatria*, *90*(3), 221–231. https://doi.org/10.1016/j.jped.2013.08.012

8. Kadhim, S., & khairi, S. (2018). Relationship between Third Trimester Vaginal Bleeding Medical Causes and pregnancy Outcomes of Pregnant Women Attending Bint Al-Huda Hospital in Al-Nasiriya City. *Iraqi National Journal of Nursing Specialties*, *29*(1), 74–85. Retrieved from https://injns.uobaghdad.edu.iq/index.php/INJNS/article/view/244

9. jeid, S., & Abbas, I. (2018). Impact of Maternal Risk Factors on Birth Weight of Newborn in Two Maternity Hospitals in Baghdad City. *Iraqi National Journal of Nursing Specialties*, *19*(1), 55–64. Retrieved from https://injns.uobaghdad.edu.iq/index.php/INJNS/article/view/48

10. Hussein, W. A., & Abbas, I. M. (2022). Assessment of Nurse-Midwife's Knowledge and Performance Regarding Immediate Newborn Care in Delivery Rooms at Maternity Hospitals in Baghdad City. *Iraqi National Journal of Nursing Specialties*, *34*(2), 99–113. Retrieved from https://injns.uobaghdad.edu.iq/index.php/INJNS/article/view/579

11. Hasan, R., & abbas, I. (2018). Effectiveness of lactation counseling on maintenance of breastfeeding. *Iraqi National Journal of Nursing Specialties*, *25*(3), 20–34. Retrieved from https://injns.uobaghdad.edu.iq/index.php/INJNS/article/view/141

12. Hameed, N. N., & Mahmood, R. N. (2008). Respiratory Distress Syndrome

in Neonatal Care Units in Medical City. *Fac Med Baghdad*, 49(4) https://doi.org/10.32007/jfacmedbagdad.4941327

13. Fitzgerald, M. (2005). The development of nociceptive circuits. *Nature Reviews. Neuroscience*, *6*(7), 507–520. https://doiorg.ezproxy.okcu.edu/10.1038/nrn1701
14. Weissman, A., Aranovitch, M., Blazer, S., & Zimmer, E. Z. (2009). Heel-lancing in newborns: behavioral and spectral analysis assessment of pain control methods. *Pediatrics*, *124*(5), e921–e926. https://doi.org/10.1542/peds.2009-0598
15. Cooper, S., & Petty, J. (2012). Promoting the use of sucrose as analgesia for procedural pain management in neonates: A review of the current literature. *Journal of Neonatal Nursing*, *18*, 121–128.
DOI:10.1016/J.JNN.2012.05.003
16. Wilson, S., Bremner, A. P., Mathews, J., & Pearson, D. (2013). The use of oral sucrose for procedural pain relief in infants up to six months of age: a randomized controlled trial. *Pain management nursing: official journal of the American Society of Pain Management Nurses*, *14*(4), e95–e105. https://doi.org/10.1016/j.pmn.2011.08.002
17. Stevens, B., Yamada, J., Lee, G. Y., & Ohlsson, A. (2013). Sucrose for analgesia in newborn infants undergoing painful procedures. *The Cochrane database of systematic reviews*, (1), CD001069. https://doi.org/10.1002/14651858.CD001069.pub4
18. Simons, S. H., van Dijk, M., Anand, K. S., Roofthooft, D., van Lingen, R. A., & Tibboel, D. (2003). Do we still hurt newborn babies? A prospective study of procedural pain and analgesia in neonates. *Archives of pediatrics & adolescent medicine*, *157*(11), 1058–1064. https://doi.org/10.1001/archpedi.157.11.1058
19. Giannakoulopoulos, X., Teixeira, J., Fisk, N., & Glover, V. (1999). Human fetal and maternal noradrenaline responses to invasive procedures. *Pediatric research*, *45*(4 Pt 1), 494–499. https://doi.org/10.1203/00006450-199904010-00007
20. Stevens, B. J., Gibbins, S., Yamada, J., Dionne, K., Lee, G., Johnston, C., & Taddio, A. (2014). The premature infant pain profile-revised (PIPP-R): initial validation and feasibility. *The Clinical journal of pain*, *30*(3), 238–243. https://doi.org/10.1097/AJP.0b013e3182906aed
21. Cong, X., Wu, J., Vittner, D., Xu, W., Hussain, N., Galvin, S., Fitzsimons, M., McGrath, J. M., & Henderson, W. A. (2017). The impact of cumulative pain/stress on neurobehavioral development of preterm infants in the NICU. *Early human development*, *108*, 9–16. https://doi.org/10.1016/j.earlhumdev.2017.03.003
22. Joung, K. H., & Cho, S. C. (2010). The effect of sucrose on infants during a painful procedure. *Korean journal of pediatrics*, *53*(8), 790–794. https://doi.org/10.3345/kjp.2010.53.8.790
23. Stevens, B., Yamada, J., Ohlsson, A., Haliburton, S., & Shorkey, A. (2016). Sucrose for analgesia in newborn infants undergoing painful procedures. *The Cochrane database of systematic reviews*, *7*(7), CD001069. https://doi.org/10.1002/14651858.CD001069.pub5
24. Stevens, B., Yamada, J., Campbell-Yeo, M., Gibbins, S., Harrison, D., Dionne, K., Taddio, A., McNair, C., Willan, A., Ballantyne, M., Widger, K., Sidani, S., Estabrooks, C., Synnes, A., Squires, J., Victor, C., & Riahi, S. (2018). The minimally effective dose of sucrose for procedural pain relief in neonates: a randomized controlled trial. *BMC pediatrics*, *18*(1), 85. https://doi.org/10.1186/s12887-018-1026-x
25. Gao, H., Xu, G., Li, F., Lv, H., Rong, H., Mi, Y., & Li, M. (2021). Effect of combined pharmacological, behavioral, and physical interventions for procedural pain on salivary cortisol and neurobehavioral development in preterm infants: a randomized controlled trial. *Pain*, *162*(1), 253–262. https://doi.org/10.1097/j.pain.0000000000002015
26. Campbell-Yeo, M., Benoit, B., Newman, A., Johnston, C., Bardouille, T., Stevens, B., & Jiang, A. (2022). The influence of skin-to-skin contact on Cortical Activity during Painful procedures in preterm infants in the neonatal intensive care unit (iCAP mini): study protocol for a randomized control trial. *Trials*, *23*(1), 512. https://doi.org/10.1186/s13063-022-06424-4