Comparing sucrose solution with distilled water for pain management in premature infant venipuncture: randomized clinical trial

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Introduction and importance: Managing pain is critical, especially for premature infants undergoing frequent painful procedures. Uncontrolled pain can lead to lasting harm in growth, cognitive development, and future pain responses.

Methods: A double-blinded clinical investigation involving 150 premature infants was performed in a neonatal intensive care unit. They were randomly divided into three groups: Sucrose 20% (50 infants), distilled water (50 infants), and a control group (50 infants). The infants' behavioral responses were assessed using an infant pain measurement tool before, at 2, and 7 min after the intervention through direct observation.

Results: The study revealed that mean pain scores before, 2 min after, and 7 min after the intervention in the sucrose group were (4.78 ± 0.91), (3.18 ± 1.15), and (2 ± 1.02), respectively. In the distilled water group, scores were (4.66 ± 0.89), (3.04 ± 1.15), and (3.08 ± 1.10), while in the control group, they were (4.0 ± 0.79), (4.94 ± 0.79), and (4.72 ± 0.96). The trend of pain scores varied among the groups over time, with a significant difference in mean pain scores at different time points $(P < 0.001)$. Initially comparable, pain scores notably decreased after 2 min in the sucrose and distilled water groups $(P < 0.001)$, differing from the control group.

Conclusion: The study indicated that 20% sucrose and distilled water equally reduce infant pain post-venipuncture, suggesting their viability for clinical pain management. Distilled water, however, provides additional benefits, including economic considerations and ease of preparation.

Keywords: distilled water, pain management, premature infant, sucrose, venipuncture

Introduction

Annually, ~13 million preterm babies are born worldwide[1]. With the progression of medical advancements over the past two decades, the survival rate of low birth weight babies and those reliant on extensive medical care and prolonged hospital stays has increased[2]. Consequently, these infants are subjected to numerous painful procedures, with each baby enduring an average of 115 such procedures within the initial 14 days of

HIGHLIGHTS

- Pain represents one of the most intricate processes within the human body.
- Recent researches indicate that even short-term pain can have permanent adverse effects on premature and full-term infants.
- Managing infant pain is critical for both ethical reasons and due to the potential consequences.
- Both 20% sucrose solution and distilled water are equally effective in alleviating pain among premature infants.
- From an economical and practical standpoint, distilled water emerges as a preferred choice to alleviate pain among premature infants.

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hospitalization, amounting to ~16 procedures per day of hospitalization[3,4].

Pain represents one of the most intricate processes within the human body, encompassing diverse physical and psychological dimensions[5]. As per the definition put forth by the International Association for the Study of Pain, pain constitutes an unpleasant sensation and subjective experience linked to potential or actual tissue damage[6]. Babies often undergo painful procedures such as vitamin K1 injections, blood draws, and vaccinations[7]. Managing infant pain is critical for both ethical reasons and due to the potential consequences, including reduced oxygenation, hemodynamic instability, increased intracranial pressure, and intraventricular bleeding in the brain. Recent research indicates that even short-term pain can have permanent adverse effects,

prompting the medical community to seek ways to alleviate pain from diagnostic and therapeutic procedures in infants[8]. The reduction or prevention of pain represents a pivotal goal within infant-related medical sciences. Unaddressed infant pain can lead to enduring harm to cognitive growth and developmental aspects, as well as alterations in responses to future painful experiences[9].

Pharmacological methods typically involve using drugs such as paracetamol, acetaminophen, opioids, and local anesthetics for pain control. Despite being widely used, recent findings indicate that paracetamol might not effectively alleviate pain in infants during medical procedures. A review of eight studies involving 614 infants found that paracetamol didn't notably decrease pain from heel lance or examinations when compared to water, cherry elixir, or eutectic mixture of local anesthetic cream. While NSAIDs are common for pain relief in older children, they are limited in neonates due to risks like renal issues and gastrointestinal bleeding, especially in premature infants under six months. Regional anesthesia may reduce postoperative apnea and bradycardia but might not necessarily decrease opioid use later on[10].

On the other hand, non-pharmacological approaches focus on techniques like kangaroo care, gentle touch, swaddling, and sucrose solution administration to provide comfort and reduce pain perception in preterm infants. These non-pharmacological methods emphasize creating a soothing environment and promoting bonding between the infant and caregiver, ultimately enhancing pain management outcomes in this vulnerable population. Integrating both pharmacological and non-pharmacological strategies in a holistic approach can effectively address pain in preterm infants, ensuring their well-being and comfort during medical procedures and care[11].

Oral sucrose represents one of the non-medicinal approaches for oral pain relief. Its soothing impact typically endures for ~10 min, with the peak effect manifesting around 2 min after administration. Sucrose operates by stimulating the sweet taste receptors on the tongue, triggering the release of endogenous opioids. Additionally, it exerts a soothing influence through opioid receptors located on the tongue[12].

Research on sucrose's impact on infant pain shows mixed results. Taddio et al.[13]'s 2008 trial found it ineffective for newborns' muscle pain relief, while Isik et al.[14]'s study in Turkey contradicted this. Numerous studies have explored sucrose's utility in various concentrations for pain management, suggesting its potential to soothe infants during procedures[6–15]. However, the use of different sucrose amounts and concentrations across various procedures has been a recurring issue, hindering the establishment of an optimal concentration for infant pain relief[16,17].

To date, no study has addressed the determination of the most effective sucrose concentration.

In contrast, studies investigating the impact of distilled water on pain intensity have predominantly focused on adults. Previous researches have demonstrated the efficacy of subcutaneous and intradermal injections of distilled water in alleviating pain associated with acute kidney stone attacks, neck, shoulder, and back pain, as well as labor pain[18,19].

Given the conflicting findings and the dearth of evidence regarding the efficacy of distilled water injection in alleviating pain in newborns during venipuncture, it becomes imperative to conduct a comparative study. Such a study aims to assess the effectiveness of both methods concurrently, thereby identifying the most efficient intervention for relieving infant pain. Consequently, this study was undertaken in an interventional manner to evaluate the comparative impact of sucrose and distilled water in reducing pain among premature infants admitted to the NICU Medical Education Center in 2018.

Method and materials

Study design

A randomized controlled trial, conducted in a double-blind manner, was undertaken to meet the research goals. The primary aim was to assess the comparative impact of sucrose and distilled water on pain reduction among premature infants admitted to NICU Medical Education Center in 2018. Throughout the study, adherence to the CONSORT checklist was maintained to ensure the high-quality reporting of this randomized controlled trial[20].

Participants

This study, identified by the code IRCT202002225046615N1, is a double-blind clinical trial that was conducted after acquiring the essential permits and approval on 18 December 2019 from the research ethics committee (code: IR.UMSU.REC.1398.347). The participants consisted of premature infants hospitalized in the neonatal intensive care unit, all of whom were born in the latter part of 2018. Following a thorough explanation of the objectives, benefits, and drawbacks of the proposed plan and upon obtaining informed consent from their parents, the participants were enrolled in the study.

Inclusion criteria encompassed infants born between the 32nd and 36th week of pregnancy, weighing 1.5 kg or more, aged 1–2 days, with a first-minute Apgar score of 7–10, and no history of prior painful interventions such as resuscitation, blood drawing, circumcision, or injections. Additionally, infants successfully venipunctured in the forearm area for the first time were included.

Exclusion criteria involved feeding the baby within 30 min prior to venipuncture, administration of acetaminophen on the same day, or naloxone/phenobarbital within the last 48 h. Maternal opioid use, as well as the presence of cardiorespiratory and developmental issues in the baby, also led to exclusion. Furthermore, infants diagnosed with fructose and sucrose intolerance by a neonatal specialist were not included.

Sampling

In this study, the objective involves comparing the average pain intensity in two distinct groups of premature babies treated with sucrose and distilled water. To calculate the sample size, the following formula was employed. The study by Fatemeh Moradi and colleagues[21] provided the basis for estimating the average pain intensity in both groups. Specifically, 45 premature babies were initially designated for the study in each intervention group with 95% certainty and 80% test power. Considering the potential sample drop, a total of 50 babies were included in the study.

$$N = \frac{\left(z_{\alpha/2} + z_\beta\right)^2 \times \left(\sigma_1^2 + \sigma_2^2\right)}{d^2}$$

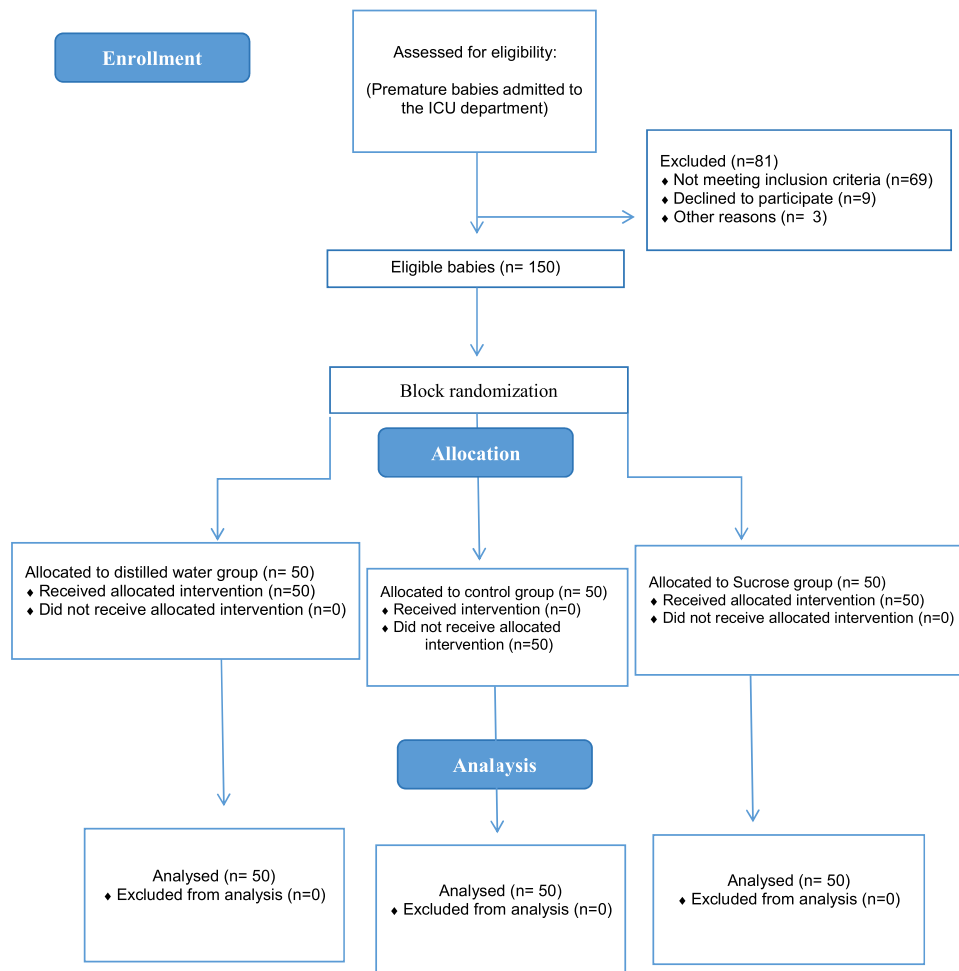$$N = \frac{(1.96 + 0.84)^2 \times (1 + 1.35^2)}{0.7^2} = 45$$

Figure 1. Diagram illustrating the method of enrollment, allocation, and analysis.

The sampling method employed was block randomization, and the process of selecting eligible samples spanned a period of 4 months, from December 2018 to March 2019 , and the entire research time lasted 6 months. Patient allocation into groups A, B, and C persisted until the sample size was fulfilled for all three groups. The flow diagram illustrating the enrollment of subjects into the study groups is presented in Figure 1.

Data collection

In this study, demographic information was obtained from the mothers' pregnancy records. Pain intensity was assessed by the researcher through direct observation and by utilizing the Neonatal Infant Pain Scale (NIPS). The NIPS serves as a behavioral assessment tool specifically designed for infants up to two months old, comprising six behavioral indicators: facial expression, crying, breathing patterns, arm movements, leg movements, and state of arousal. Each indicator is assigned a score based on observed behaviors, with the cumulative score determining the pain level. In this scale, a score of zero indicates the least pain, while seven indicates the maximum pain. The NIPS aids healthcare professionals in evaluating and addressing pain in non-verbal newborns. In this study, the pain intensity experienced by newborns during venipuncture was assessed using the NIPS, a validated method with proven reliability (Cronbach's alpha 0.88)[6].

Intervention

The researcher determined the infants' behavioral response by utilizing the infant-infant pain scale through direct observation. Subsequently, a baby from group A received half a ml of a 20% sucrose solution, prepared by dissolving 20 g of sucrose powder in 100 ml of distilled water, administered 2 minutes prior to vein extraction. Meanwhile, a baby from group B was prescribed half a cc of distilled water (manufactured by Shahid Ghazi Pharmaceutical Company, Tabriz—drug registration number (IRC) 7762655371647683—production serial number 1249, product expiration date 02/2025). Infants in group C did not receive any solution and served as the control group. The distilled water and sucrose solutions, labeled as codes 1 and 2, were stored together in identical packaging. Notably, neither the researcher nor the statistical analyst possessed knowledge of the solutions' identities. The nurse, the sole individual aware of the solution types, collaborated with the researcher to infusing the solutions to the mouth of infants using a 2 ml syringe without a needle tip. During infusing the sucrose solution, the baby's head was gently elevated, and the syringe was inserted into the front corner of the

mouth to facilitate easier swallowing. Following this, the researcher performed a vein sampling procedure two minutes later. The infants' behavioral responses were assessed using the NIPS tool, and a second measurement was taken 5 min after the venipuncture, using the same evaluation method. Importantly, the researcher conducted all blood sampling procedures. Throughout the study, any parental presence, hugging, comforting gestures, or verbal reassurance to the baby were deliberately excluded.

Statistical analysis

The study employed SPSS version 17 for data analysis. Quantitative data were presented as mean and standard deviation, while qualitative data were expressed as frequency and percentage. To compare the average pain intensity across the first, second, and control intervention groups, repeated measurements and the chi-square test were utilized for comparing qualitative variables among the three groups. After confirming normality using the Kolmogorov–Smirnov test with a P value greater than 0.05, indicating a normal distribution, parametric tests were selected for statistical analysis. One-way analysis of variance (ANOVA) was used to compare means across the three groups, and repeated measures were employed to compare means at three distinct time points: before, 2 min after, and 7 min after.

Results

Demographic characteristics

Findings revealed that in the control group, the gestational age at the time of the baby's birth averaged $50/1 \pm 92/33$ weeks, with a standard deviation. The birth weight (in kilograms) for this group was $23/0 \pm 27/2$, also with a standard deviation. The Apgar score in this group averaged $15/1 \pm 68/8$. Among them, 28 babies (56%) were female, and 22 babies (44%) were male. Within this group, 30 (60%) deliveries occurred naturally, while 20 (40%) were through cesarean section.

In the distilled water group, the gestational age at the time of the baby's birth was $42/1 \pm 82/33$ weeks, with a standard deviation. The birth weight (in kilograms) for this group was $27/0 \pm 29/2$, also with a standard deviation. The Apgar score in this group averaged $04/1 \pm 66/8$. Among them, 32 babies (64%) were female, and 18 babies (36%) were male. In this group, 27 (54%) deliveries were performed naturally, while 23 (46%) were through cesarean section.

For the sucrose group, the gestational age at the time of the baby's birth averaged $44/1 \pm 96/33$ weeks, with a standard deviation. The birth weight (in kilograms) for this group was $33/0 \pm 30/2$, also with a standard deviation. The Apgar score in this group averaged $11/1 \pm 70/8$. Among them, 30 babies (60%) were female, and 20 babies (40%) were male. Within this group, 28 (56%) deliveries occurred naturally, while 22 (44%) were through cesarean section.

The P value for the gestational age at the time of the baby's birth, birth weight (in kilograms), and APGAR Score between three group was 885/0, 865/0, and 0/984 respectively.

We utilized an ANOVA test to explore the relationship between gestational age, birth weight, and Apgar score across the sucrose, distilled water, and control groups. The results indicated

no significant variance in demographic variables among the three groups, indicating similarity in the desired variables ($P > 0.05$) (Table 1).

Additionally, we employed a chi-square test to assess the correlation between infants' gender and the method of delivery across the control, sucrose, and distilled water groups. Likewise, the results indicated no substantial distinction in demographic variables among the three groups, underlining similarity in the desired variables ($P > 0.05$) (Table 2).

Comparison of average pain score before, 2 and 7 min after the intervention

In Table 3, the average pain scores before the intervention, 2 min after the intervention, and 7 min after the intervention were (4.78 ± 0.91), (3.18 ± 1.15), and (3.02 ± 1.02), respectively, for the sucrose group. For the distilled water group, these scores were (4.66 ± 0.89), (3.04 ± 1.15), and (3.08 ± 1.10) respectively. In the control group, the scores were (4.84 ± 0.79), (4.94 ± 0.79), and (4.72 ± 0.96), respectively. Repeated measurement analysis of variance was performed to evaluate the pain scores at these three time points across the sucrose, distilled water, and control groups, and the results are outlined in Table 4.

Repeated measure analysis of pain scores

Table 4 presents the examination of three effects:
(1) The interaction effect of time and intervention: The statistical test reveals a significant interaction effect of time and intervention on average pain scores ($P < 0.001$). This indicates that the trend of the response variable (pain scores) over time differs among the three groups.

Table 1

Quantitative demographic variables of premature babies born in three groups

| P | SD ± mean | | | |
	Control	Distilled water	Group variable	Sucrose
0/885	33/92 ± 1/50	33/82 ± 1/42	33/96 ± 1/44	Gestational age at the time of the baby's birth (in weeks)
0/865	2/27 ± 0/23	2/29 ± 0/27	2/30 ± 0/33	Birth weight (in kilograms)
0/984	8/68 ± 1/15	8/66 ± 1/04	8/70 ± 1/11	APGAR Score

Table 2

Qualitative demographic variables of premature babies born in three groups

| P | Control | | Distilled water | | Sucrose | | Group variable | |
	%	N	%	N	%	N		
0/717	56	28	64	32	60	30	Girl	Sex of premature baby
	44	22	36	18	40	20	Boy	
0/827	60	30	54	27	56	28	Natural	Method of delivery of the mother
	40	20	46	23	44	22	Cesarean section	

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Table 3

Comparison of the average pain score before, 2 and 7 min after the intervention among the three group

7 min after intervention	2 min after intervention	Before intervention	Pain scores
			Group
3/02 ± 1/02	3/18 ± 1/15	4/78 ± 0/91	Sucrose 20%
3/08 ± 1/10	3/04 ± 1/15	4/66 ± 0/89	Distilled water
4/72 ± 0/96	4/94 ± 0/79	4/84 ± 0/79	Control

Mean and standard deviation of pain scores at three time points

(2) The effect of time: The significant value of the time variable being less than 0.05 rejects the assumption of uniformity across different time levels with a confidence level of up to 0.99. Consequently, a statistically significant difference was observed in the average pain scores at different times ($P < 0.001$).

(3) The main effect of the intervention: The primary aim of this research is to examine this effect. The analysis of variance table results indicates a notable difference in average pain scores among the sucrose, distilled water, and control groups ($P < 0.001$).

As depicted in Figure 2, initially, the averages of all three groups were nearly identical. Subsequently, in the control group, the averages remained relatively consistent over time, showing no significant change. Contrastingly, in the intervention groups of sucrose and distilled water, which exhibited similar effects (as indicated by their overlapping linear graphs), the mean scores notably decreased over time. Furthermore, due to this reduction, the average scores significantly differed from those of the control group.

Given the significant interaction effect of time and intervention, the comparison of average pain scores among the three groups across different times is assessed as the intervention's impact. These results are succinctly summarized using Bonferroni's multiple comparison method in Table 5.

Average pain scores between three groups of sucrose, distilled water and control

According to findings from Table 5, before intervention, the average pain score difference between the sucrose and control groups was – 0.06 with a standard deviation of 0.17 (P value: 1.000). Similarly, the difference before intervention between the distilled water and control groups was – 0.18 with a standard deviation of 0.17 (P value: 0.903). The difference before intervention between the sucrose and distilled water groups was 0.12 with a standard deviation of 0.17 (P value: 1.000).

Two minutes after the intervention, the average pain score difference between the sucrose and control groups was – 1.76 with a standard deviation of 0.21 (P value: 0.000). Likewise, the difference 2 min after the intervention between the distilled water and control groups was – 1.90 with a standard deviation of 0.21 (P value: 0.000). The difference 2 min after the intervention between the sucrose and distilled water groups was 0.14 with a standard deviation of 0.21 (P value: 1.000).

Seven minutes after the intervention, the average pain score difference between the sucrose and control groups was – 1.70 with a standard deviation of 0.20 (P value: 0.000). Similarly, the difference 7 min after the intervention between the distilled water and control groups was – 1.64 with a standard deviation of 0.20 (P value: 0.000). The difference 7 min after the intervention between the sucrose and distilled water groups was 0.06 with a standard deviation of 0.20 (P value: 1.000).

The results n Table 5 revealed that prior to the intervention, the average pain scores did not significantly differ among the three groups ($P > 0.001$), suggesting similar pain levels across the groups before the study commenced. However, a notable contrast emerged in the average pain scores 2 and 7 min after the sucrose and distilled water interventions compared to the control group, indicating a reduction in pain scores following sucrose and distilled water administration ($P < 0.001$). Interestingly, no significant difference was observed between the pain scores of the sucrose and distilled water groups at these two time points, implying similar effects resulting from these interventions ($P > 0.001$).

Comparison of mean pain scores within groups

According to the data in Table 6, within the sucrose group, the average differences in pain scores before and 2 min after the intervention were 1.60 and 0.19 (P value: 0.000). These differences before and seven minutes after the intervention in the sucrose group were 1.76 and 0.19 (P value: 0.000). Additionally, the differences within the sucrose group between 2 and 7 min after the intervention were 0.16 and 0.13 (P value: 0.710).

Similarly, in the distilled water group, the average differences in pain scores before and two minutes after the intervention were 1.62 and 0.19 (P value: 0.000). The differences before and 7 min after the intervention within the distilled water group were 1.58 and 0.19 (P value: 0.000). The differences between 2 and 7 min after the intervention within the distilled water group were – 0.04 and 0.13 (P value: 1.000).

Within the control group, the average differences in pain scores before and two minutes after the intervention were – 0.10 and 0.19 (P value: 1.000). These differences before and 7 min after the intervention within the control group were 0.12 and 0.19 (P

Table 4

Analysis table of repeated measurement of pain scores in 3 time points between three groups

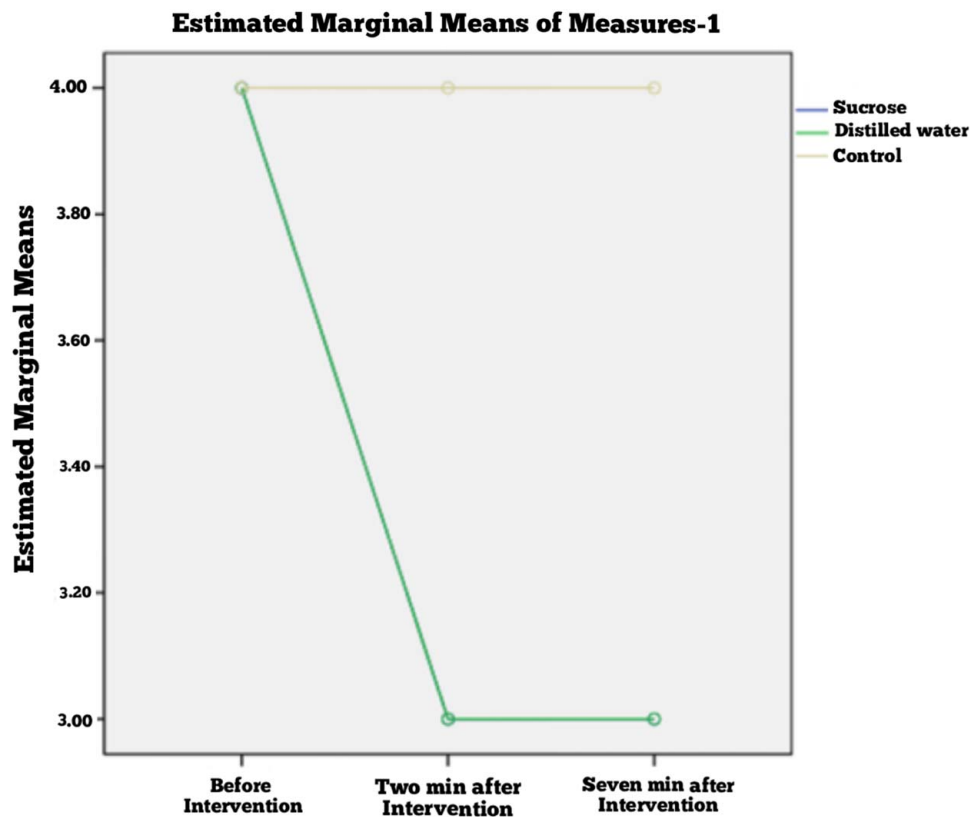| Partial eta squared	P	F	Mean squared error	Degrees of freedom	Sum of squared error	Pain score
0/426	001/ < 0p	109/20	99/76	1	99/76	Main effect (time)
0/195	001/ < 0p	22/13	40/44	1	40/44	Reciprocal effect (with intervention)
—	—	—	0/91	147	134/29	Error component (time)
0/972	001/ < 0p	51/89	72/96	2	145/93	Main effect (intervention)
—	—	—	1/40	147	206/68	Error component (interference)

Figure 2. Trend diagram of average pain scores in 3 time points between three groups of sucrose, distilled water and control.

value: 1.000). Additionally, the differences between 2 and 7 min after the intervention within the control group were 0.22 and 0.13 (P value: 0.313).

The results in Table 6 indicate a significant difference in the mean pain scores before, 2 min after, and 7 min after the intervention for both the sucrose and distilled water groups ($P < 0.001$). However, there was no significant difference observed between the pain scores at 2 and 7 min after the intervention ($P > 0.001$). Conversely, in the control group, the average pain scores before the intervention, at 2 min, and at 7 min post-intervention did not exhibit significant differences.

In essence, the pain scores in the sucrose and distilled water groups decreased significantly after 2 min, indicating the effectiveness of the intervention.

Discussion

Principal results

The research findings unequivocally establish that both sucrose 20% and distilled water are equally efficacious in mitigating pain experienced by premature infants. This discovery challenges traditional perceptions regarding pain management strategies in neonatal care, indicating that a simple and cost-effective solution such as distilled water can be as potent as sucrose 20% in alleviating discomfort during medical procedures for premature babies. The implications of this equivalence are profound, offering healthcare providers a valuable alternative that is not only effective but also easily accessible and economical. This study's results underscore the importance of exploring diverse

Table 5

Average pain scores between three groups of sucrose, distilled water and control according to different times

P	Standard deviation difference	Average difference	Group	Time
1/000	0/17	-0/06	Sucrose-control	Before intervention
0/903	0/17	-0/18	Distilled water-control	
1/000	0/17	0/12	Sucrose-distilled water	
0/000	0/21	-1/76	Sucrose-control	2 min after the intervention
0/000	0/21	-1/90	Distilled water-control	
1/000	0/21	0/14	Sucrose-distilled water	
0/000	0/20	-1/70	Sucrose-control	7 min after the intervention
0/000	0/20	-1/64	Distilled water-control	
1/000	0/20	-0/06	Sucrose-distilled water	

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Table 6

Comparison of average pain scores within groups in three groups of sucrose, distilled water and control

P	Average difference	Average difference	Time	Group
0/000	0/19	1/60	Before and 2 min after the intervention	Sucrose
0/000	0/19	1/76	Before and 7 min after the intervention	
0/710	0/13	0/16	2 min later with 7 min after the intervention	
0/000	0/19	1/62	Before and 2 min after the intervention	Distilled water
0/000	0/19	1/58	Before and 7 min after the intervention	
1/000	0/13	-0/04	2 min later with 7 min after the intervention	
1/000	0/19	-0/10	Before and 2 min after the intervention	Control
1/000	0/19	0/12	Before and 7 min after the intervention	
0/313	0/13	0/22	2 min later with 7 min after the intervention	

interventions in pain management for premature infants, emphasizing the need for further investigation and potential reevaluation of current clinical practices in neonatal care settings. By highlighting the comparable effectiveness of distilled water and sucrose 20%, this research contributes significantly to the discourse on optimizing pain relief strategies for vulnerable populations, paving the way for enhanced care practices and improved outcomes in neonatal healthcare.

Prior studies

After conducting a review of recent literature, it is evident that studies investigating the impact of sucrose on pain reduction during various procedures have yielded diverse and sometimes conflicting results. Nevertheless, in most studies, sucrose is recommended for minor procedures. For instance, a randomized clinical trial conducted by Moradi et al.[22] involving 60 infants revealed that 20% sucrose did not immediately reduce pain following intramuscular injection, but it did exhibit a soothing effect after 5 min ($P = 0.012$). Similarly, Giraldo et al.[23]'s 2009 study, using the infant pain scale tool, demonstrated that venous blood sampling in infants receiving oral sucrose solution was associated with less pain compared to the control group.

A study, conducted in February 2022 across various databases, assessed sucrose's efficacy in relieving neonatal heel lance pain with a focus on immediate and long-term outcomes. Inclusion criteria targeted randomized controlled trials involving term and/or preterm neonates receiving sucrose, comparing it to water, placebo, NNS, glucose, breastfeeding, breast milk, music therapy, acupuncture, facilitated tucking, and skin-to-skin care. Results indicated sucrose likely reduced PIPP scores at 30 and 60 s post-lances. However, uncertainty persisted in comparisons with NNS, breastfeeding, laser acupuncture, and the combined effect with NNS. Minimal differences were noted versus glucose, breast milk, and skin-to-skin care, prompting cautious use of combined interventions due to uncertain efficacy[24].

In 2020, Imani and colleagues undertook a three-blind trial study in Semnan involving 91 term infants to assess the impact of 30 and 50% sucrose on pain reduction post-hepatitis B vaccination. Utilizing the infant pain scale tool, their results highlighted the effectiveness of both sucrose concentrations in mitigating infant pain, with the 50% concentration exhibiting superior pain-relieving properties compared to the 30% concentration[25]. Contrastingly, in 2019, Rasha and colleagues conducted a randomized clinical trial in Egypt with 120 infants, aiming to compare various breastfeeding methods to sucrose and a control group in alleviating infant pain post-vaccination using the FLACC scale. Their study suggested that breastfeeding methods proved more efficacious in reducing infant pain than sucrose administration, prompting the need for further investigation in this area[26].

In various studies, including one by Gaspardo and colleagues in 2007 on premature babies and another by Taddio and colleagues in 2004 involving newborns, it was discovered that 25% and 24% sucrose, respectively, did not alleviate pain from medical procedures such as heel pricking and intramuscular injections of vitamin K. These studies utilized pain assessment tools like the premature infant pain profile (PIPP) and observed physiological changes to gauge pain intensity[13-27]. Similarly, Saeedi and colleagues's 2010 study in Iran on infants receiving intramuscular hepatitis B injections, and a 2010 clinical trial by Slater and colleagues involving painful procedures in infants, both found that 25% and 24% sucrose, respectively, did not effectively reduce pain. The infant pain scale tool and electroencephalography were utilized in these studies to measure pain responses, highlighting the limitations of sucrose in pain management for these specific procedures[28,29].

The variance observed in the outcomes of previous studies in comparison to the current research can be attributed to factors such as sample size discrepancies, potential random errors, variations in measurement tools, and the specific type of painful procedures administered to infants. Despite these differences, existing literature consistently highlights the significant efficacy of sucrose in mitigating mild pain, particularly within a short timeframe following procedures. Studies like Okan et al.[30]'s research have demonstrated that 20% sucrose can effectively reduce pain from heel pricking within minutes post-procedure, emphasizing sucrose's rapid pain-alleviating effects.

Hatfield et al.[31]'s 2008 study revealed a 24% reduction in vaccination pain intensity among 2–4 month-old infants who received a sucrose solution intervention, compared to the control group, just 5 minutes after administration. In the current study, the positive impact of a 20% sucrose intervention on premature infants' pain relief was notably observed within a 2-min timeframe. Additionally, while distilled water has shown promise as a pain-alleviating intervention post-venipuncture in premature infants in this study, limited research has explored its effects on pain intensity, with findings from studies like Pashib et al.[32] suggesting its potential as an effective pain-relieving alternative. Contrasting results from studies by Vakilian and colleagues and Martinsan and colleagues underscore the need for further investigation into the efficacy of distilled water, particularly in diverse pain management scenarios such as labor pain and back pain[33].

In addition, Previous research has shown that skin injections (subcutaneous and intradermal) of distilled water are effective in reducing pain caused by acute attacks of kidney stones, neck, shoulder, and back pain, as well as labor pain[34-35].

Given the disparity between previous studies and the current findings, the researchers recommend a separate trial with a larger sample size of infants to reevaluate the effect of distilled water in relieving pain in infants. As evidence in this area accumulates, it will be possible to make informed decisions about the advantages, disadvantages, effects, and mechanisms of this intervention in alleviating infant pain.

Limitation

Implementation challenges in this study involve parental reluctance to participate in research. To address this issue, we adjusted by increasing the number of samples in our study. We recommend that future studies should also consider a larger sample size to mitigate similar issues. Additionally, a short follow-up period in the research could constrain the comprehensive understanding of the long-term effectiveness and sustainability of pain management effects associated with both sucrose solution and distilled water beyond the immediate post-venipuncture phase. Moreover, the variation in infants' pain perception and their responses to pain management interventions, influenced by individual factors such as gestational age, health conditions, and prior exposure to painful procedures, could potentially impact study outcomes. Efforts were made to incorporate infants who closely matched these specific individual factors.

Conclusion

In conclusion, based on the findings outlined in this study, it is evident that both sucrose 20% and distilled water are equally effective in reducing the pain experienced by premature babies. These interventions have proven to be successful in alleviating discomfort, indicating the potential for their application in clinical settings. By reducing pain in these infants, healthcare professionals can improve the overall well-being of premature babies, promoting their development and ultimately enhancing their long-term outcomes. However, From an economical and practical standpoint, distilled water emerges as a preferred choice due to its simplicity and ease of preparation. By employing these cost-effective measures, healthcare providers can significantly enhance the comfort and well-being of premature babies.

Ethical approval

This study, identified by the code IRCT202002225046615N1, is a double-blind clinical trial that was conducted after acquiring the essential permits and approval from the research ethics committee (code: IR.UMSU.REC.1398.347) at Urmia University of Medical Sciences.

Consent

Written informed consent was obtained from the patient's parents/legal guardian for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

M.S.B., H.H.: study concept, data collection, writing the paper and making the revision of the manuscript following the reviewer's instructions. M.H.: study concept, reviewing and validating the manuscript's credibility. H.R.K.: statistic consultant, study concept, reviewing and validating the manuscript's credibility.

Conflicts of interest disclosure

We confirm that there are no conflicts of interest regarding the publication of this manuscript between all authors.

Research registration unique identifying number (UIN)

1. Name of the registry: Iranian Registry of Clinical Trials.
2. Unique identifying number or registration ID: IRCT202002225046615N1.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): irct.behdasht.gov.ir.

Guarantor

Maryam Salamat Bakhsh.

Data availability statement

The datasets generated during and/or analyzed during the current study are available upon reasonable request.

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