"ANALGESIC EFFECT OF 25% DEXTROSE VERSUS 25% DEXTROSE MIXED WITH EXPRESSED BREAST MILK (EBM) IN NEONATES DURING HEEL PRICK METHOD – AN OPEN LABELLED RANDOMISED COMPARATIVE CROSS SECTIONAL STUDY"

By Dr. J SANJANA



DISSERTATION SUBMITTED TO SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH TAMAKA KOLAR KARNATAKA

In partial fulfilment of the requirements for the degree of

DOCTOR OF MEDICINE IN PAEDIATRICS

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LIST OF ABBREVIATIONS

| GLOSSARY | ABBREVIATIONS |
|-----------------|---|
| wks | Weeks |
| kgs | Kilograms |
| gm% | Grams percentage |
| % | Percentage |
| Т | Thousand |
| mm ³ | Millimetre cube |
| mg | Milligram |
| dl | Decilitre |
| bpm | Beats per minute |
| mm | Millimetre |
| cpm | Cycles per minute |
| SpO2 | Saturation of oxygen |
| HR | Heart rate |
| EBM | Expressed breast milk |
| mOsm/L | Milliosmoles per litre |
| NIPS | Neonatal Infant Pain Scale |
| PIPP | Premature Infant Pain Profile |
| N-PASS | Neonatal Pain, Agitation and Sedation Score |
| DAN | DouleurAigüe du Nouveau-Né |

ABSTRACT

BACKGROUND

The experience of pain is a perplexing side effect of the human situation. As attitudes concerning pain have evolved over time, ways to relieve pain have been developed in conformity with scientific principles with the science and religious climate of the time ¹Pain is an important issue for people of all ages but failing to recognise and treat pain in new-borns has long-term consequences in later stages of development. Although neonates don't verbally communicate their distress, evidence shows they feel pain but lack the adaptive mechanisms to cope with unpleasant stimuli and hence fail to express it. They use specific behaviours to demonstrate their propensity to pain and stress, while also physiological and biochemical responses to the pain caused ². Pain can have both acute and chronic ramifications occur in infants, resulting in a range of neurological sequelae and affecting the baby's growth and development in early life. To reduce the acute and long - term repercussions of untreated pain in new-borns, there is a clear need for accurate intervention of pain and the challenges caused by pain. Multiple strategies have been suggested including pharmacological and non-pharmacological methods for pain relief treatments. Several concentrations of commercially available dextrose solutions were utilised ³. This study explores use of an orally administered quasi-biological fluid which is an acceptable method for to alleviate the procedural pain in the neonates.

MATERIALS AND METHODS

This study was a randomized comparative cross - sectional study done on 158 babies. By using block randomization method neonates were divided into 2 groups to receive Solution A (2 ml of 25% dextrose orally) in one group and Solution B (1 ml of 25% dextrose and 1ml of expressed breast milk) orally in the other group. NIPS (Neonatal Infant Pain Scale) scoring was used to monitor the neonates during heel prick procedures.

RESULTS

158 babies were considered in preparation for the evaluation process with 79 babies in the 25% dextrose taken as solution A group and 79 babies in the 25% dextrose and EBM (Expressed breast milk) in equal amounts taken as solution B group after block randomisation by computerised method. Different time periods for saturation between the study groups showed significant reduction in pain with 25 %dextrose and EBM solution merged at the conclusion of 1 min and 3 min i.e., 96.3 ± 2.55 and 97.71 ± 1.17 (p = 0.001). The overall NIPS score at 1, 3 and 5 min were significant with p value < 0.0001 for the solution B using 25 % dextrose and EBM.

CONCLUSION

Pain was significantly reduced in both solution A (25 percent dextrose) and solution B (25 percent dextrose mixed with EBM), though an equal mixture of 25 percent dextrose and EBM (expressed breast milk) proved to be a better pain alleviating mixture in neonates when assessed by NIPS score as compared to 25 percent dextrose alone to alleviate pain during the heel prick procedures in neonates.

INTRODUCTION

INTRODUCTION

Charles Darwin, in one of his writings "The Expression of the Emotions in Man and Animals" which was dated in the late 1800's wrote that even though new-borns exhibit pain reactions, these were only reflexive, and babies were incapable of experiencing and expressing true pain probably due to the lack of myelination in their nervous system ⁴.

This indicates that research investigating neonatal pain is a relatively ancient, yet rapidly evolving idea in the field of neonatal analgesia. Even though pain alleviation is regarded as a core precept of compassionate medicine, new-born pain continues to receive less attention and is treated with significantly less enthusiasm than that experienced by infants and older age children and adults.

"A distressing emotional along with sensory experience connected with, or resembling, actually occurring, or hypothetically occurring tissue injury," as per the definition of pain. ⁵ Pain is an excessively individualised experience that is influenced by biological, social, and psychological variables. When new-borns are hospitalised, they are more liable to experiencing from discomfort and develop the notion of pain during various operations. When undergoing any unpleasant operations, new-borns cannot convey their displeasure vocally, but they might

express it through their facial expressions or any autonomic irregularities ⁶

Many procedures in the NICU cause pain to the new-borns, but the type of procedure performed determines the severity of the pain the neonate will feel. Procedures range from non-invasive monitoring to central line insertion, which necessitates a tiered approach to what type of analgesia can be used in the neonates to relieve pain ⁷According to the many grading methods employed depending on the various gestational ages, pain in new-borns can be categorised as mild pain, moderate pain, or severe pain. 8 There are several approved scoring methods for analysing pain in neonates utilising diverse factors like as facial expressions, heart rate, and crying time, among others. Assessing new-born pain is often a subjective, time-consuming, and labour-intensive task. ⁹As just a consequence of neuronal maturity and abundance of myelination content in the pain-carrying fibres, preterm and late preterm new-borns are more likely to be in agony than term new-borns. Preterm and term babies both experience pain, according to research, but their perception of pain differs depending on their myelination levels and neural system development. Increased procedural pain exposure has been linked to poorer cognitive and behaviouraloutcomes¹⁰. Peripheral nerve density is higher in newand pain perception is underdeveloped. Immature pain borns,

appreciation pathway which tends to expose these neonates to greater the magnitude of agony during the first 2 months of life in comparison to children exposed to the same stimulation. Dextrose reveals to be a better analgesic than other non-pharmacological approaches for alleviating the tier 1 class of painful procedures throughout the last decade. Dextrose has the ability to pain in new-borns because it has a tends to cause the release of endogenous opioids that amplify the response to nociceptive at the level of the dorsal horn, which has been proven in studies to be essential in reducing the intensity of pain appreciation. ¹²

Various concentrations of dextrose have been explored and tested time and again to determine the ideal concentration analgesia. In the recent past, 25 percent dextrose has been shown to efficiently relieve pain in infants when compared to other non-pharmacological ways of pain relief for various operations. Despite being readily available and sterile, the concentration and hyperosmolality of 25 % dextrose has yet to be proven safe. ¹³ More research is needed to understand the various dosages and concentrations of dextrose solutions for new-born pain treatment. ¹⁴ It is thought that glucose and EBM (expressed breast milk) release endogenous opioids, lowering the pain threshold of new-borns. Solutions containing the sugar such as dextrose, tend to bind to the sweet taste

receptors and lead to an endogenous inundation of endorphins, lowering the sensation of pain and raising the pain threshold level. ¹⁵

In comparison to dextrose, expressed breast milk has also proven to be a very effective pain reliever, however with slightly less variety in results and efficacy than the commercially available dextrose solution. Although EBM has been shown to be more effective than 10% dextrose, swaddling, and tucking in relieving discomfort, it is still somewhat less effective than 25% dextrose. Despite the fact that EBM has less dextrose than 10 percent dextrose, it has been established to be a more effective pain reliever, with a concentration of dextrose in near equivalence to 25 percent dextrose. 16 with possible relations to factors like such as osmolarity, immunogenicity, biologically equating composition of the neonatal body which is readily acceptable and suitable. Tryptophan is an essential amino acid potentially required for effective new-born growth, as well as the formation and maintenance of proteins, muscles, enzymes, and neurotransmitters in the body. This amino acid is required for survival. ¹⁷ For exclusively breast-fed new-borns, breast milk is the sole supply of this important amino acid.

This study is critical in measuring the efficacy and feasibility of combining 25 percent dextrose and EBM, both of which are accessible without scarcity for pain alleviation in heel prick procedures in neonates.

NEED FOR STUDY

"To cure sometimes, to relieve often, to comfort always", is a 15th century French description of the treating doctor ¹⁸. Studies implicate that neonate exposed to procedural pains have adverse neurodevelopmental outcomes.

Dextrose solution in neonates is a useful, feasible and non-expensive method of analgesia for peripheral heel puncture. The glucose content in the expressed breast milk also has shown to considerably equate with the commercially available dextrose solutions to relieve the pain. Breast milk contents the naturally available glucose trying to mix it with the commercially available solutions would make it more acceptable, more feasible, non-expensive, and biologically much safer and immunologically greater in compared to ready-to-use dextrose solutions in terms of content. In our research, we looked at the possibility of biomolecular changes occurring when these two preparations were mixed in equal quantity.

EBM is selected for usage because it is physiologically, biochemically, and maieutically close to the sentient internal environment. We are yet to investigate the possibility of biomolecular changes occurring during mixing of the two solutions which occurred in our work. The goal of this research is to draw comparisons of the analgesic efficacy of

concentrations of 25% dextrose and 25% dextrose mixed with expressed breast milk following heel prick procedure in neonates.

AIMS AND OBJECTIVES OF THE STUDY

OBJECTIVES OF THE STUDY:

- To study the analgesic effect of pain alleviation after administration of 2ml of 25% dextrose (SOLUTION A) and 2ml i.e. 1ml 25% dextrose mixed with 1ml of expressed breast milk (EBM)
 (SOLUTION B) orally using Neonatal infant pain scale (NIPS)
- To compare the analgesic effect in neonates using solution A and solution
 B in neonates requiring heel prick procedures in postnatal wards and
 NICU using Neonatal infant pain scale (NIPS).

REVIEW OF LITERATURE

REVIEW OF LITERATURE

HISTORY OF PAIN

The assumption that newborns do not have appropriate pain response is not new.

Adults often describe their pain by vocal signals that evoke the type of pain, the region of the pain, if the pain is radiating, if the pain caused is severe or acceptable, and so on. It was thought that providing pain medication was unnecessary because the newborn would not remember the suffering. Even surgeries, including open-heart surgery, were once supposed to be performed by not using analgesics or anesthetics, as per an ancient school of thought ^{19.}

This was due to a view that newborn neural systems were so immature since they did not experience pain, and that this lack of myelination translated into a reduced or confusing reaction to the pain that was generated.

It has been revealed that newborns frequently produce ambiguous and inconsistent indications to the discomfort they are experiencing, which might be concealed by their underlying disease (such as a premature infant having an apneic episode in which pain may not be considered

primarily as the problem). Neonates cannot verbalize their pain and thus depend on others to recognize, assess and manage their pain.

An infant hospitalized to the Neonatal Intensive Care Unit (NICU), or Special Care Nursery (SCN) suffers an average of 14 unpleasant procedures every day, according to recent research. ^{19,29}

As time and technology has passed, it has grown increasingly crucial. to understand that every cell in the body, including those that form tissue components and are innervated by neuronal endings, has pain receptors, and that even minor changes in the environment can cause pain, which can manifest in a variety of ways, regardless of the neonate's age.

Neonates have a legal right to have management of the undergoing pain, that is both safe and effective. ²⁰

Definition of Pain

The International Association for the Study of Pain (IASP) definition of pain as, "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" 5

Need to understand Neonatal Pain

The American Academy of Pediatrics recommends that every health care facility needs to create a neonatal pain management programme²¹ which includes:

- To detect neonatal pain as a part of routine assessments
- Lesser painful procedures
- Preventing or alleviating acute pain produced by invasive bedside procedures
- Estimating and reducing postoperative pain following surgical procedures
- Avoiding prolonged or recurrent pain/stress when receiving NICU care

Impediments to identifying and managing pain in newborns

Because of the immaturity of the central nervous system in newborns, the relationship between noxious input and behavioral reaction is not predictable, making pain measurement and analgesia effectiveness evaluation difficult. ²². The absence of a vocabulary for expressing pain emphasizes the importance of age-appropriate physiological interventions. Furthermore, age-related alterations in analgesic drug metabolism might cause therapeutic effects to be muddled. Pain during infancy may have long-term repercussions due to the plasticity of the newborn's neurological activity. Appropriate identification and treatment are especially critical in this age group.

Physiology of Pain:

The fifth vital sign is pain and is a form of sensory deprivation. Despite its unpleasantness, it provides protective and survival effects, including:

Pain serves as a warning indicator when a problem or threat is there. It also raises injury awareness. It avoids future harm by prompting the body to retreat reflexively from the site of the injury. Pain compels the person to rest or limit their activity, allowing the afflicted portion to recover quickly. It also encourages the individual to seek therapy immediately to avoid serious consequences. ^{23,25}

Adults commonly describe their pain as sharp, pricking, electrical, dull aching, shooting, cutting, stabbing, and so on. In newborns, however, pain sensation is produced by crying and variations in facial expressions.

24,27

Components of Pain sensation

Pain sensation has two components:

- 1. Fast Pain
- 2. Slow Pain.

When a pain stimulus is administered, the first sensation is fast pain^{26,28}. It manifests itself as a bright, acute, and localized pain feeling. The fast pain is followed by the delayed pain, which feels dull, dispersed, and unpleasant.

Both pain components have the same receptors, which are found in the free nerve terminals of the heel and fingertips. Pain receptors are headquartered in the free nerve terminals found throughout the body. The A kind of nerve fibers transmit pain feelings quickly, whereas the C type of nerve fibers transmit pain sensations gradually.

Pathways of Pain sensation

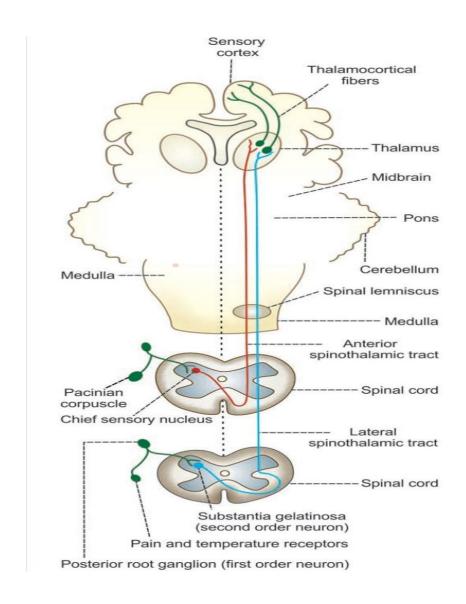
Different routes carry pain sensations from various regions of the body to the brain, including from the skin and deeper tissues, the face, and viscera.

Free nerve endings present throughout the body contain the pain receptors which act as neurons of first order ²⁹

First rank sensory neurons in the posterior nerve root ganglia that receive pain perception impulses from pain receptors via their dendrites. Such impulses are relayed to the spinal cord via the axons of these neurons.

A-type afferent axons carry the fast pain sensation component that connect with neurons from the marginal nucleus in the posterior grey horn. Slow pain component is carried by C type form of afferent fibers that connect with Rolando's substantia gelatinosa neurons in the posterior grey horn. (Fig. 1)

Fig - 1 Showing the sensory, first and second order neurons in pain pathway from the skin and tissues



Second order neurons are composed of neurons from Rolando's border nucleus and substantia gelatinosa. The lateral spinothalamic tract is made up of fibers from these neurons.

Fast Pain fibers

Neurons in the marginal nucleus produce rapid pain fibers. The fibers cross the midline via the anterior grey commissure, reach the lateral white column on the other side, and rise shortly after taking origin. In the lateral spinothalamic tract, these fibers become neospinothalamic fibers. These nerve fibers end in the thalamus's ventral posterolateral nucleus. Some of the fibers terminate in the brainstem's ascending reticular activating system.

Slow Pain fibers

Slow pain fibers, which originate in substantia gelatinosa neurons, cross the midline and travel alongside fast pain fibres as paleospinothalamic fibers in the lateral spinothalamic tract. 1/5 of these fibers end in the thalamus's ventral posterolateral nucleus.

The remaining fibers can be found in one of the following locations:

- i. Reticular formation nuclei in the brainstem
- ii. Tectum of the midbrain
- iii. The grey matter that surrounds the Sylvius aqueduct.

Neurons of third order of the pain pathway are found in the following areas:

- i. Thalamic nucleus
- ii. Reticular formation
- iii. Tectum
- iv. The grey matter that surrounds the Sylvius aqueduct.

The sensory region of the cerebral cortex receives axons from these neurons.

Center for Pain Sensation

The pain center is in the parietal cortex's postcentral gyrus. Arousal mechanisms are concerned with fibers reaching the hypothalamus because of a pain signal.

Neurotransmitters involved in Pain Sensation

Pain nerve endings release glutamate and substance P, which are neurotransmitters. Glutamate is produced by afferent neurons, which carry rapid pain impulses. Substance P is produced by C type fibers, which carry sluggish pain signals.

Analgesia system

The pain control system is what is called as the analgesia system. The human body has its own analgesia mechanism in the brain that gives temporary pain relief. Endogenous analgesic system is another name for

it. The analgesia system has its own channel through which it suppresses the synaptic transmission of pain feeling in the spinal cord, reducing pain perception. Opioid analgesics work through this mechanism to give regulated pain relief.

Analgesic pathway

The descending pain route is the analgesic pathway that interferes with pain transmission, whereas the ascending pain pathway is the afferent fibers that send pain experience to the brain. (Fig. 2).

Role of Analgesic Pathway in Inhibiting Pain Transmission 30,31

- 1. Analgesic pathway fibers emerge from the frontal lobe cortex of the cerebrum and the hypothalamus
- 2. These fibers end at the grey matter that surrounds the third ventricle and Sylvius aqueduct (periaqueductal grey matter)
- 3. Fibers from here descend to brainstem and terminate on:
- i. Nucleus raphe magnus, situated in reticular formation of lower pons and upper medulla
- ii. Nucleus reticularis, para gigantocellularis situated in medulla

4. Fibers from these reticular nuclei descend down the lateral white column of the spinal cord to synapses of neurons in the afferent pain pathway located in the anterior grey horn.

Synapses of the afferent pain pathway are between:

- i. A δ type afferent fibers and neurons of marginal nucleus
- ii. C type afferent fibers and neurons of substantia gelatinosa of Rolando.
- 5. At synaptic level, analgesic fibers release neurotransmitters and inhibit the pain transmission before being relayed to brain.

Neurotransmitters of Analgesic Pathway

Serotonin and opiate receptor chemicals, including as enkephalin, dynorphin, and endorphin, are neurotransmitters produced by analgesia route fibres.

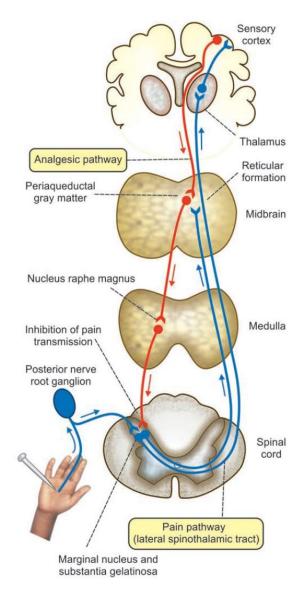


Fig - 2 Pain pathway and analgesic pathway

Mechanism of Gate Control at Spinal Level

When a pain stimulus is applied to any part of the body, it stimulates pain receptors as well as receptors for other sensations such as touch ³²When all of these impulses enter the spinal cord through the posterior nerve root (posterior column fibers) send collaterals to the neurons of the pain pathway, i.e., cells of the marginal nucleus and substantia gelatinosa.

Touch sensation impulses travelling via these collaterals limit glutamate and substance P release from pain fibers. This blocks the gate and prevents pain transmission.

Thus, gating of pain at the spinal level is analogous to presynaptic inhibition ^{33.} It serves as the foundation for pain management therapies such as rubbing, massage, cold packs, acupuncture, and electrical analgesia. All these methods alleviate pain by promoting the production of endogenous pain relievers (opioid peptides), which seal the gate and block pain signals.

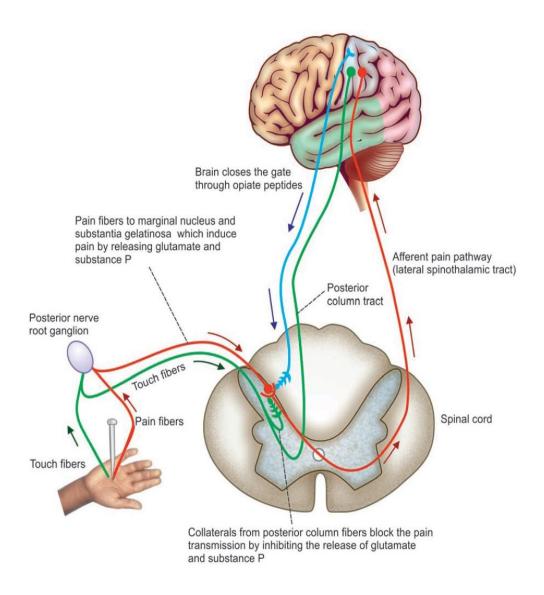


Fig - 3 Gate control system for pain

29

Anatomy of pain pathway in neonates

There is evidence of newborn pain expression and sensitivity to noxious stimuli, as well as discoveries indicating untreated pain has the potential to harm the evolving neurological system, which has persuaded many researchers of the need of pain management in this vulnerable patient population. ³⁴

Myelination in neonates is usually complete by the second to third trimester ^{28,32}.

A well-known fact is that that incomplete myelination in the newborns only leads to a slower conduction of pain, but not an absence of pain ³⁵

Responses to somatic stimuli start at a young age. Reflex responses to stimuli begin in the perioral skin approximately 7.5 weeks after conception and progress to the palms of the hands before reaching the limbs around 13 to 14 weeks.

Peripheral pain receptors are present in the body by roughly 20 weeks post-conception. Dendritic arborization occurs by 21 weeks. Nerve tracts from the spinal cord to the brain stem, also connections with thalamocortical fibers, are in situ approximately 22 weeks post conception. ³⁶

The descending, inhibitory fibers are not complete until roughly 32 weeks. These fibers contribute to the blunting of the complete pain response and sensation. As a result, a paucity of neurotransmitters in the descending tract reflects a lack of full neuromodulating mechanisms in the preterm and late preterm infant, making the infant more reactive to pain than older children and adults.

Nociception is the most prevalent pain route. Nociceptors are sensory receptors which are located in every part of the body that are readily triggered by physical, chemical, or thermal stimuli.

A stimulus is supplied, recognized by the nociceptors, and then transmitted down the spinal cord and into the brain for interpretation. ³⁷

These fibers are first-order neurons that initiate the pain-perception process. C-fibers are found largely in muscle, periosteum, and visceral organs, whereas A-delta fibers are located primarily in skin and muscle. Myelinated A-delta fibers provide quick acute, pricking, and piercing sensations.

This type of discomfort is generally localized. Whilst the C-fibers, are unmyelinated and can transmit temperature, chemical, or powerful physical impulses. These nonpainful sensations can either aid or hinder

pain management by adding to sensory overload or helping to inhibit painful messages. ³⁸

The impulses are subsequently sent to the spinal cord, the dorsal root ganglia, the dorsal horn, and the thalamus. The engagement of second-order neurons begins at this point. The spinothalamic tract connects the dorsal horn to the thalamus and is split into two pathways: the lateral neospinothalamic (NST) tract and the medial paleospinothalamic (PST) tract ³⁹ Similar to adults, these are responsible for these dorsal horn connections, which means that input from touch fibers can enter the different segmental spinal cordsections and synapse or communicate with cells carrying nociceptive input. This is an essential reason why procedures like massages, light touch, acupuncture/acupressure, and other alternative measures are used.

Neurotransmitters and neuropeptides are found in newborns. Neurotransmitters such as adrenaline, norepinephrine, acetylcholine, and dopamine function to either slow or speed up postsynaptic neuron activity. Neuromodulators are endogenous opiates that aid in pain alleviation. They are made up of big amino acid peptides like alphaendorphins, beta-endorphins, and enkephalins, which work similarly to morphine but with more power. Endorphins are synthesized in the

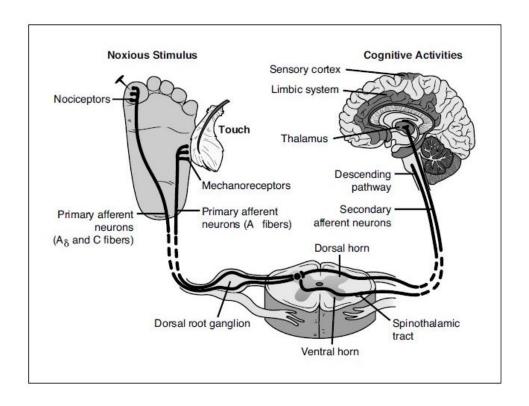
anterior pituitary gland and hypothalamus. Enkephalins are much extensively distributed throughout the rostral horn and brain 40.

When a pain signal enters the brain, it is processed at three levels: the thalamus, the midbrain, and the cortex. These regions collaborate to comprehend and respond to inputs. The thalamus transfers sensory information from the NST and PST tracts. The cortex differentiates and interprets stimuli. This illustrates that painful sensations must pass through various parts of the brain, including behavioral and emotional centers.

Almost all painful stimuli promote tissue damage (e.g., heel lancing, venipuncture, catheterization, difficult adhesive tape removal). ⁴¹This damage causes the production of substances such as noradrenaline, bradykinin, histamine, prostaglandins, purines, cytokines, 5-HT, leukotrienes, nerve growth factor, and neuropeptides, which sensitize the receptors. This sensitization occurs to make sure that the body is aware of the painful stimuli and can respond to halt the stimuli and begin mending.

In the upper extremities, neonates may have a higher pain threshold than in the lower extremities, resulting in enhanced sensitivity to pain in the lower limbs. The descending inhibitory fibers grow from the supraspinal brainstem nuclei, only reaching the cervical region of the spinal cord by 30 to 32 weeks; and do not reach the lumbar spine by 30 weeks, allowing for higher sensitivity to pain in the lower limbs. This is an essential clinical consideration when selecting between an intravenous catheter site versus a heel stick for blood sample. ⁴²

Fig – 4 Pain pathways in neonates



Adult and neonatal pain perception variation

In adults, uncomfortable or tissue-damaging stimuli, with the subsequent inflammatory and trophic chemical release ,activate and sensitize nociceptors at the injured area, creating a flood of nociceptive insertional inputs to the CNS.

Such processes activates the main spinal cord, brainstem, and nociceptive circuits, thalamus, and brain regions such as the somatosensory cortex, cingulate cortex, and amygdala, all of which lead to contribution of the "pain matrix."

For sensory inputs, very short Activity trains in peripheral nociceptors have the ability to cause long-term changes in CNS circuitry and extended episodes of hypersensitivity.

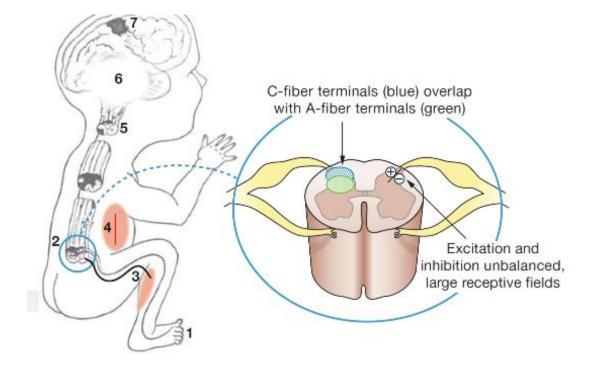
This 'central sensitization' leads to the amplification of noxious input and the spread of pain to locations other than the initial injured region (hyperalgesia), as well as the start of pain from typically harmless stimuli (allodynia).

Central sensitization is characterized by persistent increases in membrane excitability, strengthened excitatory synaptic inputs, and decreased inhibitory intraneuronal activity, all of which are impacted by expression of genes as well as the generation and exploitation of key

neurotransmitters, networks, and downstream neuronal signal transduction pathways.

Because of the newborn's immature synaptic connections and integrated circuits, the infant's pain experience is more diffuse and less spatially concentrated than that of adults, but it is also under less endogenous control.

Fig - 5 Sites of developmental transition in pain pathways in infants



Activity trains in peripheral nociceptors can cause chronic changes in CNS circuitry and protracted episodes of hypersensitivity which gradually get pruned throughout the postnatal period. The separation of the two types of sensory terminals is not complete until the rats are 3–4 weeks old; before that time, discriminating between noxious and non-noxious stimuli is less effective. Immature ion channel kinetics lead sensory and motor neurons in the CNS to react at longer and more variable latencies, resulting in less-synchronized responses to peripheral input.

Individual spinal sensory neurons' cutaneous receptive fields are bigger at a younger gestational age and gradually become smaller and more ordered as the child grows older. Contralateral inhibitory receptive fields, which mimic excitatory fields in adults, are missing in newborn spinal cords.

Because of these characteristics, painful cutaneous stimulation can excite many more neurons in preterm newborns than it can in older neonates, but this excitation may be poorly integrated both geographically and temporally, making the final output in terms of motor activity less dependable.

The brain mechanisms that cause sensitization and hyperalgesia are active in newborns but differ from those in adults. Central sensitization

can develop, and newborn children who have had numerous painful operations respond more during a painful process than those who have not had repeated painful experiences.

Although both cyclo-oxygenase 1 activity and extracellular signalregulated kinase phosphorylation are known to be developmentally modulated.

A hazardous stimulus or trauma not only stimulates neural networks but also activates local inhibitory circuits and changes the balance of brainstem descending inhibitory and excitatory activity, contributing to a homeostatic feedback regulation mechanism.

These descending and endogenous pain-modulatory pathway controls are the processes through which factors such as attention and distraction, suggestion and expectation, stress and anxiety, context, and prior experience impact pain responses.

A lack of balance between inhibitory and excitatory supraspinal controls may suggest that babies are less capable than adults of establishing robust endogenous control over unpleasant stimuli.

According to anatomical studies, neural connections to the cortex establish relatively late in gestation, at about 22 weeks, implying that

higher pain processing may be limited throughout infancy despite the presence of a behavioral response.

Pain processing in neonates

When nociceptors are subjected to a noxious stimulus, this is known as transduction ⁴³

Transmission in the path of the stimulus from the transduction point to the dorsal horn of the spinal cord, then to the brain stem, and eventually to higher regions of the brain.

Modulation based on the path to perception, neurotransmitters can suppress or increase painful sensations.

Pain signals arrive at their final destination in the brain and are processed.

Physiologic, Behavioral, Biochemical responses to pain

When adults encounter severe pain, their sympathetic nervous system responds with a rise in heart rate, blood pressure, respiration, anxiety, hormone fluctuation, and inflammation. Similarly, newborns feel distinct sorts of discomfort.

Physiologic Response

- Heart rate increase or fluctuation
- Blood pressure increase or fluctuation
- Increased PO2 (partial pressure of oxygen), SaO2 (oxygen saturation; initially)
- Decreased PO2, SaO2 (prolonged stress)
- Increased work of breathing
- Apnea
- Hypercapnia
- V/Q mismatch
- Increase in intracranial pressure
- Vomiting

Behavioral Response

- Intense or high-pitched cry
- Difficult to console
- Constant need to be consoled
- Frowning, grimacing, brow furrow
- Eye closure or aversion
- Disorganized or frantic body movements
- Increased tone
- Decreased activity, "shutting down" (prolonged stress)
- Tremors

- Hyperalert state
- Erratic sleep pattern
- Feeding difficulties or increased feeds, which may result in
- Vomiting

Long-Term Response

- Increased length of stay in the hospital
- Higher mortality
- Increased sensitivity to pain

Types of pain in neonates

The effect of anguish and suffering can have both short-term (physiological and behavioral) and long-term implications (increased or decreased behavioral responses to pain) 44

There are two forms of pain in neonates:

- 1. Acute procedural pain: the outcome of a specific painful process or event; it is self-limiting, for example, a heel prick.
- 2. Chronic or chronic pain: a condition that remains after tissue healing, generally for more than three months, e.g., endotracheal intubation, central line

Commonly Performed Painful Procedures on Neonates 45:

Table - 1 Painful procedures in NICU

Diagnostic
Heel stick
Venipuncture
Arterial puncture
Bronchoscopy
Endoscopy
Lumbar puncture
Retinopathy of
prematurity exam

Therapeutic
Bladder catheterization
Central line insertion/removal
Chest physiotherapy
Umbilical vessel catheterization
Dressing change
Gavage tube insertion
Intramuscular injection

Peripheral venous catheterization Mechanical ventilation Postural drainage Removal of adhesive tape Suture removal

Tracheal intubation/extubation

Tracheal suctioning Ventricular tap Surgical
Circumcision
Cardiac surgery
Congenital
anomaly repairs
Minimally invasive
surgeries
(laparoscopy,
thoracoscopy)

Neonatal Pain Assessment

The use of qualitative or subjective approaches for assessing newborn pain rather than measurable data leads to errors and inconsistency in analysesic administration.

Adopting an objective pain assessment strategy improves the quality of pain treatment in NICUs and elsewhere by preventing untreated pain or excessive analgesia.

Pain assessment approaches should be intended to limit nursing burden, the side effects of under- or over-dosing analgesics, clinical practise diversity within and among NICUs, and problems such as tolerance, withdrawal, or delayed recovery from analgesia/sedation (46)

These tools are based on indications that may be easily examined at the bedside, such as changes in heart rate, breathing pattern, blood pressure, or oxygen saturation. Crying, changes in face expressions, and bodily movements are all examples of behavioural reactions. Total facial activity and a cluster of particular facial features (brow bulge, eye squeeze, nasolabial furrow, open mouth) were linked to severe discomfort during vein puncture operations.

Facial expressions are the most specific and sensitive markers of pain, and they are included in the majority of newborn pain assessment measures.

For acute pain (procedural, post-operative):

- Premature Infant Pain Profile (PIPP)
- Neonatal Infant Pain Scale (NIPS)
- Douleur Aigüe du Nouveau-Né (DAN)
- Crying, Requires oxygen, Increased vital signs, Expression, Sleepless (CRIES)

For chronic pain:

• Neonatal Pain, Agitation and Sedation Score (N-PASS)

| Measure | Variables Included | Type of Pain | Psychometric Testing |
|---|---|---|---|
| PIPP (Premature Infant Pain Profile) ¹⁵⁸ | Heart rate, oxygen saturation, facial actions; takes state and gestational age into account | Procedural, postoperative (minor) | Reliability, validity, clinical utility well established |
| NIPS (Neonatal Infant Pain Score) ¹⁵⁹ | Facial expression, crying, breathing patterns, arm and leg movements, arousal | Procedural | Reliability, validity |
| NFCS (Neonatal Facial Coding System) ¹⁶⁰ | Facial actions | Procedural | Reliability, validity, clinical utility, high degree of sensitivity to analgesia |
| N-PASS (Neonatal Pain, Agitation, and Sedation Scale) ¹⁶¹ | Crying, irritability, behavioral state, facial expression, extremity tone, vital signs | Postoperative, procedural, ventilated | Reliability, validity, includes sedation end of scale, does not distinguish pain from agitation |
| CRIES (Cry, Requires oxygen, Increased vital signs, Expression, Sleeplessness) ¹⁶² | Crying, facial expression, sleeplessness, requires oxygen to stay at >95% saturation, increased vital signs | Postoperative | Reliability, validity |
| COMFORT Scale ^{92,163–165} | Movement, calmness, facial tension, alertness, respiration rate, muscle tone, heart rate, blood pressure | Postoperative, critical care, developed for sedation, recently validated for postoperative pain in 0- to 3-year- old infants ⁹⁹ | Reliability, validity, clinical utility |

Limitations of the pain assessment methods include

A lot of techniques were developed for infants experiencing acute discomfort (e.g., venipuncture, heel stick).

Many of the indications employed in these assessment methods need subjective judgement by observers. As a result, there is high interobserver heterogeneity in the appraisal of behavioral responses.

Some measurements, such as heart rate variability or palmar skin conductance, need the use of specialist equipment that is not readily available at the bedside.

Other indicators, such as salivary cortisol or other biomarkers, are not accessible in real-time to be therapeutically helpful.

Behavioral pain responses may be altered in neurologically damaged infants and nonexistent in those who get neuromuscular inhibition.

Increased procedural pain exposure has been linked to worse cognitive and motor scores, growth deficits, decreased white matter and subcortical grey matter maturation, and altered corticospinal tract anatomy.

Adults ordered sugars in the same order as newborns, with sucrose preferred over fructose, which is preferred over glucose, which is preferred over lactose ⁴⁷

Sucrose is digested into glucose and fructose by the intestinal epithelium by 26 weeks of gestation.

0.24 g sucrose (2 ml of 12 percent w/v sucrose) is effective for heel lances when the length of cry is employed as a measure of pain.

Other parameters connected to the intervention's delivery, such as dosage and concentration, may change the amplitude of pain responses, yet they are improbable to be responsible for modulating the endogenous opioid response.

Assessing the long-term impact of infant pain

There is evidence that in many newborns who have been exposed to a painful stimulus, long-term alterations in pain sensitivity occur.

In a double-blind, randomized study, neonatal circumcision was related with an enhanced behavioral reaction to vaccination many months later, which was mitigated by local anesthetic during the first likely insult.

Retrospective cohort studies of newborn intensive care children demonstrate that areas that have received multiple operations might have flexion reflex hypersensitivity for at least a year later, and that the thenar and occipital regions have increased perceptual sensitization to a prolonged heat stimulation. These claims of hypersensitivity to painful stimuli are followed by evidence of underlying hyposensitivity to normal, physiological levels of sensory stimulation in children exposed to early tissue injury and pain; sensory threshold testing of neonatal-surgery groups at 9–12 years has indicated long-term thermal and mechanical hypoalgesia next to the surgical site.

Children exposed to early tissue damage and pain exhibit universal reductions in temperature sensitivity, indicating centrally mediated changes in regulation of C-fiber nociceptive pathways.

Understanding the long-term impact of early pain

Many postnatal developmental alterations in nociceptive processing are dependent on a proper balance of brain sensory activity and do not occur if the patterns of activity are altered.

Nociceptive processes remain immature in neonates with consistently blocked spinal NMDA receptors because the CaMKII enzyme does not auto phosphorylate. 48

Posterior horn nociceptive circuits are not permanent or programmed at birth, but rather in a flexible or transitory state, responding to sensory input. Early tissue injury might change somatosensory processing and pain signals, potentially impacting future analgesic response. The developmental regulation of the expression, distribution, and function of antinociceptive transmitters and receptors has a massive effect on the improved pharmacokinetic profile of analgesics during postnatal development, and knowledge of these processes can inform and improve the development of future clinical trials.

Neonatal exposure to pain-unrelated stress may also result in a different general pattern of alterations in future pain sensitivity than neonatal exposure to local noxious stimulus.

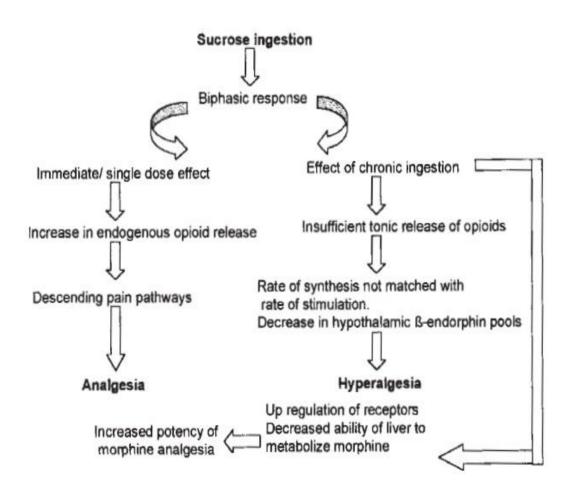
Dextrose in pain relieving

The sweeteners fructose, glucose, maltose, and lactose are 1.7, 0.75, 0.33, and 0.6 times sweeter than sucrose, respectively.⁴⁸

The administration of sucrose has been the most extensively researched non pharmacological strategy for the alleviation of procedural pain in newborn newborns. Sucrose has shown to induce soothing behaviors and lessen acute procedure unpleasantness in preterm and full-term neonates. Dextrose has an antinociceptive effect, which might be favored. Although the effectiveness of sweet tastes appears to promote opioid-mediated analgesia.

The sweet flavoring of is thought to induce analgesia by activating endogenous opioids that reduce nociceptive information.

Fig – 6 Mechanism of sucrose



Dose of sucrose that should be administered

The dose that can be given is 1-2ml in late preterm and 0.5-1 ml in 32 weeks based on the concentration of sucrose that may be delivered (24 percent / 25 percent). Sucrose/dextrose is given orally with a syringe 2-3 minutes prior to the procedure. ⁴⁹

Dextrose intragastric injection shows to have no analgesic effect in infants.

Osmolality of the milk and dextrose

Osmolality is a measure of a solution's concentration in terms of osmoles of solute per kilogramme of solvent. Expressed in milliosmole/kg. Osmolarity is a measure of a solution's concentration in units of osmoles of solute per litre of solution. mOsm/L is the unit of measurement. High feed osmolality is frequently connected to adverse outcomes, notably gastrointestinal dysfunctions and necrotising enterocolitis (NEC)⁵⁰, which occur more frequently in preterm new-borns than term babies. Mammalian/human milk has an osmolality of about 300 mOsm/kg.⁵¹ In new-borns, hyperosmolar oral products have been linked to the development of gastrointestinal problems such as feeding intolerance, delayed gastric emptying, and necrotizing enterocolitis.

Expressed breast milk (EBM)

Expressed breast milk (EBM) is a disaccharide glucose that is regarded an alternate intervention to sweet solutions, albeit there is less clear data about its analgesic efficacy.

Milk and its components are considered to alter newborn pain sensitivity.

The analgesic effect of breast milk may be connected to its sweetness due to the presence of lactose or a greater content of tryptophan, a precursor of melatonin that raises the concentration of beta endorphins. ⁵²

Potential mechanisms of action of breast milk and impact on development

Multiple pathways interact to provide pain signals to the brain and to reduce the consequences of pain. The mesolimbic dopaminergic and cholinergic systems share common linkages with central sugar processing, pain regulation, attention, and motor development (53).

Dopamine is crucial in the downward regulation of pain. During phasic (acute) pain, dopamine is released in sufficient amounts to excite postsynaptic receptors, resulting in fast reactions to a stimulus.

Acetylcholine plays an important part in many physiological processes. Increases in acetylcholine levels tend to reduce the release of glutamate (excitatory amino acid) and increase the release of aminobutyric acid when acting on muscarinic receptors in the spinal cord and supraspinal on

nicotinic receptors in the thalamic periaqueductal grey region (inhibitory amino acid).

Tryptophan, a precursor to melatonin, is found in breast milk. Melatonin boosts the beta-endorphin levels, which is a mechanism for nociception blockage in breast milk ⁵⁴

The aroma of breast milk has been likened to that of vanilla, and breast milk has been proven to have a substantial effect on heart and oxygen saturation before and after venipuncture, as well as to reduce premature newborn heart rate variability and saturation. Breast milk and lavender scents both avoided an increase in pulse rate, a drop in Neonatal Infant Discomfort Scale (NIPS) score, a decrease in oxygen saturation, and a decrease in pain during the neonatal procedure.

Because milk stimulation has been shown in clinical research to be effective as an antinociceptive, we hypothesized that human milk may be a viable substitute for sucrose ^{53,55}

Sweet taste is hypothesized to have analgesic properties by activating Oro-gustatory receptors and causing the release of endogenous opioids. Regardless of carbohydrate quantity, sweet flavor is essential for pain alleviation. It enables the mother to feed her kids largely independently of the supply of her own food, depending on her own stockpiles of energy,

macronutrients, and micronutrients. Milk includes a wide range of potential signaling components, including nutrients, growth factors, hormones, microbes, cells, and micro-RNA. ⁵⁶Milk flavor, like sweet taste, may be mediated by an opioid route. ⁵⁷

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MATERIALS AND METHODS

MATERIALS AND METHODS

Source of Data: Study group will be term and late preterm newborn

babies born and admitted at RL Jalappa Hospital & Research Center

irrespective of the method of delivery after taking consent from the

parents

Study design: An open labelled randomized comparative cross-sectional

study

Study period: January 2020 to December 2020

55

METHOD OF COLLECTION OF DATA:

Inclusion Criteria:

- **Term-** Babies requiring heel prick procedure (Term gestation being defined as a gestational age of more than 259 days (37weeks to 41 weeks 6 days of any weight)
- Late-preterm Babies requiring heel prick procedures (late preterm being defined as 34weeks of gestation to 36weeks +6 days of any weight is being included in this study)
- Post term- Babies requiring heel prick procedure (Post term being defined as 40 weeks of gestation to 41weeks +6 days of any weight is being included in this study)

Exclusion Criteria:

- Any condition where oral feeds are contraindicated in neonates
- Any babies requiring supplementary oxygen
- Babies on ventilators, seizures disorders, babies on anticonvulsants
- Babies with birth injury i.e., Forceps delivery leading to facial nerve palsies.
- Infants whose mothers on methadone
- Doppler studies showing uteroplacental insufficiency
- Birth asphyxiated babies

Sample size:

The sample size was chosen based on baseline demographics and NIPS questionnaire variables 18 , which have been compared between research groups using the paired T- Test and the Chi-squared test as suitable. The confidence interval was set at 95%, and statistical significance was set at P=0.05

Hence the following sample sizes derived were

- 1. Sample Size of Group 1 79
- 2. Sample Size of Group 2 79
- 3. Total Sample Size 158

The subjects will be randomly assigned to two groups by using block randomization technique with block size of 2.

METHODOLOGY:

- Study tool: NEONATAL INFANT PAIN SCALE (NIPS)designed and developed in Canada, adapted by CHEOPS⁵⁸
- All residents and nurses posted in postnatal ward, NICU were trained regarding the use of NIPS SCALE.
- All neonates fulfilling the criteria were included in this study.
- At the time of enrollment, an informed consent was obtained from parents.
- The Institutional Ethical Review Board approved the study.
- Employing computer generated random numbers, the eligible neonates were categorized into two parts: expressed breast milk group (EBM) and 25 percent dextrose group (25D) and 25 percent dextrose group (25D). Allocation concealment was accomplished by employing sequentially numbered opaque sealed envelopes holding the intervention codes (EBM for expressed breast milk, 25D for 25% dextrose). The envelopes were solely accessible to the primary investigator⁵⁹
- The nurses were unaware of the study's goal. NIPS CHART will be included in the files of the newborns undergoing the heel prick procedure.
- Equipment such as sterile gloves, Antiseptic (betadine/saline / alcohol swab), Heel lancing device, 2 ml 25% dextrose, 1 ml Expressed breast milk and 1 ml 25% dextrose, 2ml sterile syringe.

- Heel prick procedure: Heel blood sampling is a simple, minimally invasive approach that is simple to learn. A minute before the heel prick, before administering the test solutions. Oral administration using a 2mL sterile syringe containing test solutions. Because intragastric delivery has no analgesic effects, the oral route was chosen.
- Location of heel prick: Unlike vaccinations, which are considered deep tissue damaging activities, heel prick is a superficial harm process. In term newborns, the space between the epidermis and the calcaneal perichondrium is 3mm⁶⁰

Hands must be washed, and gloves must be used. A betadine/saline/alcohol swab should be used to clean the puncture site.

Prick the heel by positioning the lancet perpendicular to the site of prick

with the lancet at the apex of the angle formed by thumb and forefinger, with fingers sliding along the sole of the foot. Apply pressure on the calf with the thumb acting as a counterweight. While the operation is being performed, do not press the heel; instead, examine the NIPS SCALE and

provide a score. The assessed score must be entered into the proforma provided.

- The neonates requiring venepuncture were taken to a quiet room. It was ensured that time interval between the procedure and previous breast milk intake was at least one hour. The neonates were ensured that they were assessed usually 6 hours after birth as neonates would accustom to the external environment and be relived of the stress⁶¹
- All venepunctures were done with 23-gauge needle 2 minutes after the administering 2 ml of the test solution.
- During the sample period, two observers have been present. One observer video graphed the baby's face for subsequent study, while the other was in charge of recording the HR, SpO2, and venepuncture time. The observers were veiled to the test solution since they entered the room after it had been delivered. HR and SpO2 were measured at baseline, 1, 3, and 5 minutes after venepuncture (to exclude any stress variables produced by adjusting to the external environment).
- Crying time was defined as the whole duration of audible crying captured
 on camera. However, in our study, we did not consider the timing of
 weeping, but rather the type of cry seen, such as whimpering or forceful
 sobbing was taken into account ⁶²

- Sampling time was defined as the time gap between the times of insertion of needle for venepuncture to the time the needle was removed from the baby.
 - A single observer recorded and studied the facial reaction to discomfort (brow bulge, eye squeeze, nasolabial furrow) during this period.

The NIP score was the study's primary endpoint.

- The NIP score is a pain measure that incorporates contextual (behavioural state and gestational age), behavioural (brow bulging, eye squeezing, and nasolabial furrowing), and physiologic (heart rate and oxygen saturation) pain signs. Each indication is graded on a four-point scale (0-3). A pain score of 6 or less indicates that there is no or very little discomfort.
- The NIP score was not calculated if evaluating the facial response from the videos proved problematic hence excluded.

STATISTICAL ANALYSIS:

Descriptive analysis was performed using mean and standard deviation for quantitative data and frequency and percentage for categorical variables. The quantitative variables were not normally distributed, then were summarized by median and interquartile range (IQR). Data was also represented using appropriate diagrams like bar diagram, pie diagram and box plots.

All Quantitative variables were checked for normal distribution within each category of explanatory variable by using visual inspection of histograms and normality Q-Q plots. Shapiro wilk test was also conducted to assess normal distribution. Shapiro wilk test p value of >0.05 was considered as normal distribution.

For normally distributed Quantitative parameters the mean values were compared between study groups using independent sample t-test (2 groups).

Categorical outcomes were compared between study groups using Chi square test /Fisher's Exact test (If the overall sample size was < 20 or if the expected number in any one of the cells is < 5, Fisher's exact test was used.)

P value < 0.05 was considered statistically significant. Data will be analysed by using coGuide software, V.1.03. (1)

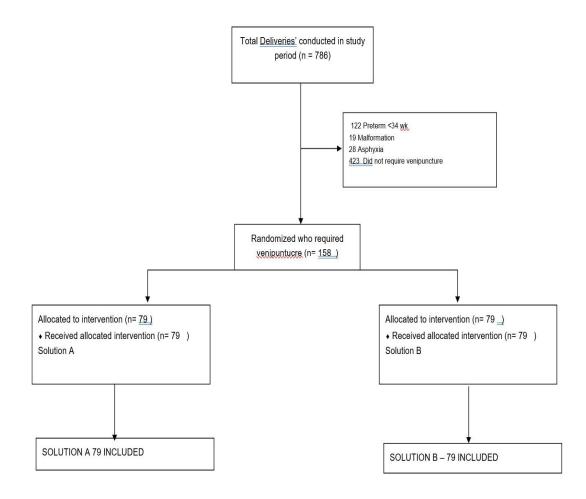
ADSS Corp. Released 2020. coGuide Statistics software, Version 1.0, India: ADSS corp.

RESULT ANALYSIS

RESULT ANALYSIS

A total of 158 babies were taken into the sample size after computerised random allocation in blocks of 2 using Quiccalussoftware .

CONSORT ANALYSIS: Fig -7

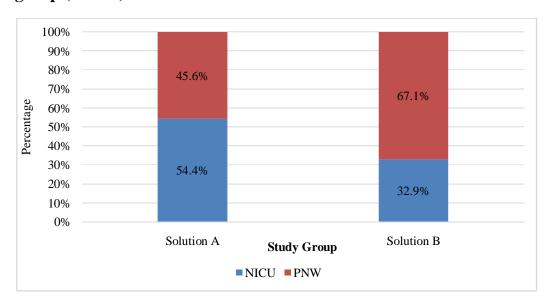


In solution A group, 43 (54.43%) were admitted in NICU and remaining 36 (45.57%) were admitted PNW. In solution B group, 26 (32.91%) admitted in NICU and remaining 53 (67.09%) were admitted PNW. The difference in the proportion of place between the research group was statically important (P value 0.006).

Table 3 : Comparison of place between study group (N=158)

| | Study Group | | | |
|-------|-------------------|-------------------|------------|---------|
| Place | Solution A (N=79) | Solution B (N=79) | Chi square | P value |
| NICU | 43 (54.43%) | 26 (32.91%) | 7.426 | 0.006 |
| PNW | 36 (45.57%) | 53 (67.09%) | 7.436 | 0.000 |

Figure - 8 : Staked bar chart of comparison of place between study group (N=158)



The mean gestational age of solution A group was 37.52 ± 1.19 (in weeks) and solution B group was 37.42 ± 1.33 (in weeks), and the mean difference between two groups was statistically not significant (P value 0.608). (Table 4 and Figure-9)

Table 4: Comparison of mean of gestational age (in weeks) between study group (N=158)

| Parameter | Study group | P | |
|----------------------------|-------------------|-------------------|-------|
| rarameter | Solution A (N=79) | Solution B (N=79) | value |
| Gestational age (in weeks) | 37.52 ± 1.19 | 37.42 ± 1.33 | 0.608 |

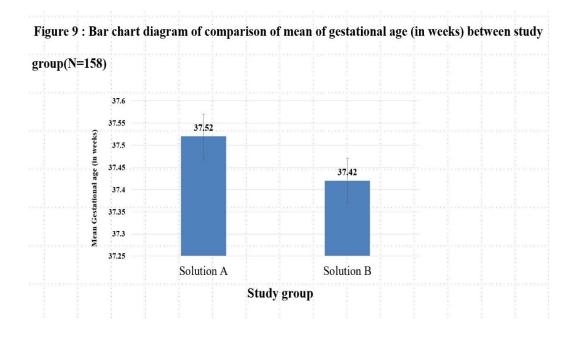
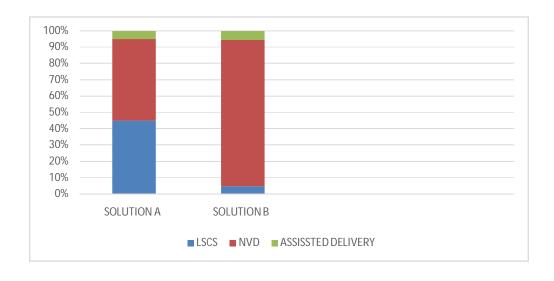


Table 5: Comparison of mode of delivery between study group (N=158)

| M. I. G.I.Y. | Study Group | | |
|------------------|-------------------|-------------------|--|
| Mode of delivery | Solution A (N=79) | Solution B (N=79) | |
| LSCS | 36 (44.56%) | 28 (35.44%) | |
| NVD | 40 (50.64%) | 48 (60.76%) | |
| Vacuum | 4 (3.9%) | 3 (3.8%) | |

Fig-10: Bar Staked Diagram comparing mode of delivery between two study groups



The average birth weight of solution A batch was 2.67 ± 0.46 (kg) and solution B group was 2.75 ± 0.44 (kg), and the mean difference between two groups was statistically not significant (P value 0.264) (Table 6 , Fig-:11)

Table 6: Comparison of mean of birth weight between study group (N=158)

| Parameter | Study group (Mean± SD) | | P value |
|--------------|--------------------------|--------------------------|---------|
| rarameter | Solution A (N=79) | Solution B (N=79) | r value |
| Birth Weight | 2.67 ± 0.46 | 2.75 ± 0.44 | 0.264 |

Fig -11 : Bar chart diagram of mean of birth weight between study group

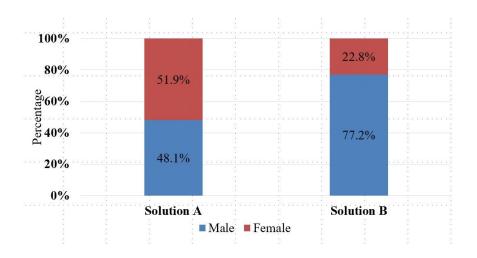


In solution A group, 38 (48.1%) were male and remaining 41 (51.9%) were female. In solution B group, 61 (77.22%) participants were male and remaining 53 (67.09%) were admitted PNW. The difference in the proportion of place between study group was statistically significant (P value 0.006). (Table 7 and Fig 12)

Table 7: Comparison of gender between study group (N=158)

| | Study Group | | | P | |
|--------|----------------------|----------------------|------------|---------|--|
| Gender | Solution A (N=79) | Solution B (N=79) | Chi square | value | |
| Male | 38 (48.1%) | 61 (77.22%) | 14.310 | < 0.001 | |
| Female | 41 (51.9%) | 18 (22.78%) | 14.310 | <0.001 | |

Fig -12: Staked bar diagram comparing the gender between the study groups



In solution A group in people with risk factors, 6 (7.59%) participants had IDM and only 1 (1.27%) participant had Maternal - hypertension NDDM diet Preeclampsia for each respectively

Table 8: Descriptive analysis of risk factors among solution A group (N=79)

| Risk Factors | Frequency | Percentages |
|---------------------|-----------|-------------|
| NIL | 70 | 88.61% |
| IDM | 6 | 7.59% |
| Maternal - | | |
| hypertension on | 1 | 1.27% |
| medications | | |
| Preeclampsia not on | 1 | 1.27% |
| medications | 1 | 1.2770 |

Fig-13 Bar Chart of risk factors among of solution A (N=79)

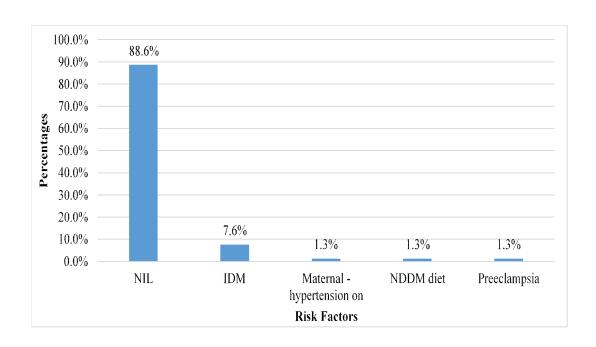


Table 9: Descriptive analysis of risk factors among the solution B group (N=79)

| Risk Factors | Frequency | Percentages |
|--|-----------|-------------|
| NIL | 64 | 81.01% |
| IDM | 11 | 13.9% |
| Maternal - hypertension on medications | 2 | 2.57% |
| Preeclampsia not on medications | 2 | 2.57% |

Fig - 14 Bar Chart of risk factors among solution B (N=79)

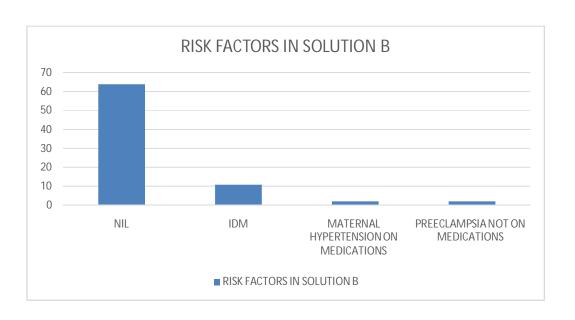


Table 10: Comparison of medications between study group (N=158)

| 25.11.41 | Study Group | | |
|---------------------|-------------------|----------------------|--|
| Medications | Solution A (N=79) | Solution B (N=79) | |
| Nil | 72 (91.14%) | 68 (86.08%) | |
| Metformin | 4 (5.06%) | 4 (5.06%) | |
| Labetalol | 2(2.53%) | 2 (1.27%) | |
| Nutritional Therapy | 0 (0%) | 1 (1.27%) | |

The average heart rate at baseline of solution A group was 140.86 ± 10.27 and solution B group was 140.32 ± 9.77 , and the mean difference between two groups was not statistically significant (P value 0.733).

The mean heart rate at 1 min of solution A group was 142.1 ± 10.21 and solution B group was 141.29 ± 10.05 , and the mean difference between two groups was not statistically significant (P value 0.616).

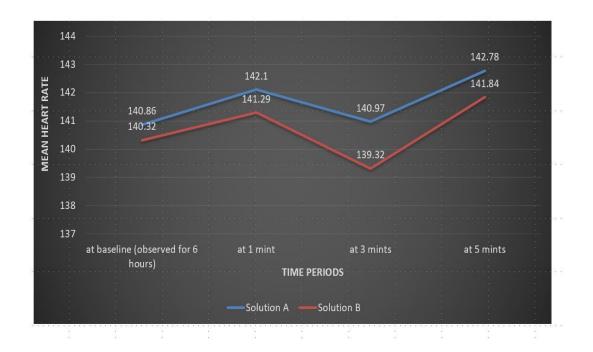
The mean heart rate at 3 min of solution A group was 140.97 ± 10.36 and solution B group was 139.32 ± 9.17 , and the mean difference between two groups was not statistically significant (P value 0.288).

The mean heart rate at 5 min of solution A group was 142.78 ± 10.86 and solution B group was 141.84 ± 9.35 , and the mean difference between two groups was not statistically significant (P value 0.557).

Table 11 : Comparison of mean heart rate at different time periods between the study groups (N=158)

| D | Study group (Mean± SD) | | Danalara |
|--|------------------------|--------------------|----------|
| Parameter | Solution A (N=79) | Solution B (N=79) | P value |
| Heart rate baseline (observed for 6 hours) | 140.86 ± 10.27 | 140.32 ± 9.77 | 0.733 |
| HR-1 MIN | 142.1 ± 10.21 | 141.29 ± 10.05 | 0.616 |
| HR 3 MIN | 140.97 ± 10.36 | 139.32 ± 9.17 | 0.288 |
| HR 5 MIN | 142.78 ± 10.86 | 141.84 ± 9.35 | 0.557 |

Fig-15: Line diagram of comparison of mean of heart rate at different time periods between the study groups (N=158)

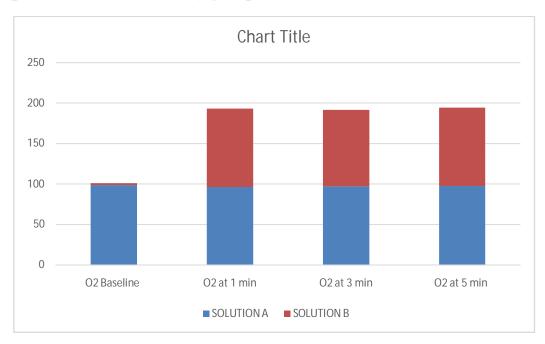


- The mean 0₂saturation at 1 min of solution A group was 96.3 ± 2.55 and solution B group was 97.71 ± 1.17, and the mean difference between two groups was statistically significant (P value <0.001).
- The mean $\mathbf{0}_2$ saturation at 3 min of solution A group was 96.75 ± 1.83 and solution B group was 95.41 ± 2.71 , and the mean difference between two groups was statistically significant (P value <0.001).
- The mean $\mathbf{0}_2$ saturation at 5 min of solution A group was 97.32 ± 1.33 and solution B group was 97.05 ± 2.05 , and the mean difference between two groups was statistically not significant (P value 0.335).

Table 12: Comparison of mean of 0_2 sat at different time periods between the study groups (N=158)

| Parameter | Study group | P value | |
|--------------------------------|-------------------|-------------------|---------------|
| Parameter | Solution A (N=79) | Solution B (N=79) | P value |
| 0 ₂ Baseline | 98.7 ± 0.01 | 96 ± 0.01 | 98 ± 0.01 |
| 0 ₂ at 1 min | 96.3 ± 2.55 | 97.71 ± 1.17 | < 0.001 |
| 0 ₂ at 3 min | 96.75 ± 1.83 | 95.41 ± 2.71 | < 0.001 |
| 0 ₂ at 5 min | 97.32 ± 1.33 | 97.05 ± 2.05 | 0.335 |

Fig - 16: Bar staked chart of mean of θ_2 saturation at different time periods between the study groups

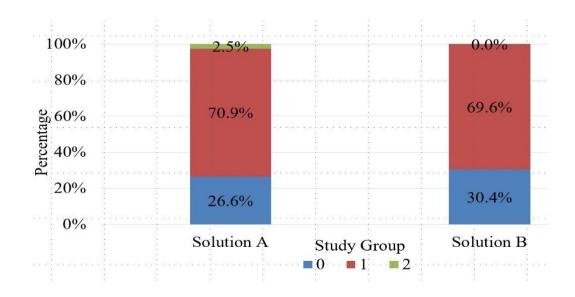


In solution A group people with NIPS score at 1 min, 21 (26.58%) participants were score 0, 56 (70.89%) participants were score 1 and 2 (2.53%) participants were score 2. In solution B group people withNIPS score at 1 min, 24 (30.38%) participants were score 0 and 55 (69.62) participants were score 1.

Table 13: Comparison of NIPS score 1 min between study group (N=158)

| NIDC Coope 1 Min | Study Group | |
|------------------|-------------------|-------------------|
| NIPS Score 1 Min | Solution A (N=79) | Solution B (N=79) |
| 0 | 21 (26.58%) | 24 (30.38%) |
| 1 | 56 (70.89%) | 55 (69.62%) |
| 2 | 2 (2.53%) | 0 (0%) |

Fig - 17: Staked bar chart of comparison of NIPS score 1 min between study group (N=158)



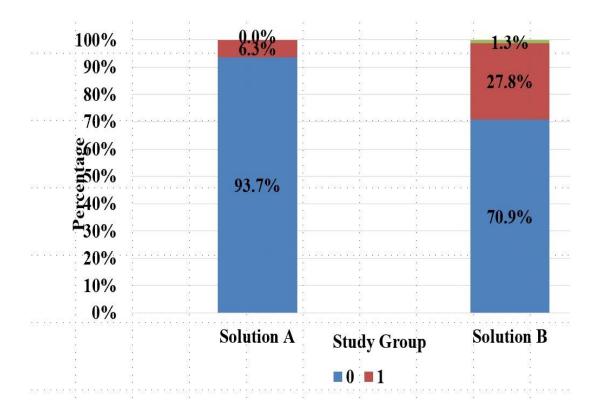
Comparison of NIPS score at 3 min between study group (N=158)

In solution A group people with NIPS score at 3 min, 74 (93.67%) participants were score 0 and 5 (6.33%) participants were score 1. In solution B group people with NIPS score at 3 min, 56 (70.89%) participants were score 0, 22 (27.85%) participants were score 1 and only 1 (1.27%) participant was score 2.

Table 14: Comparison of NIPS $\,$ score at 3 min between study group (N=158)

| NIPS Score at 3 Mins | Study Group | | |
|----------------------|-------------------|-------------------|--|
| | Solution A (N=79) | Solution B (N=79) | |
| 0 | 74 (93.67%) | 56 (70.89%) | |
| 1 | 5 (6.33%) | 22 (27.85%) | |
| 2 | 0 (0%) | 1 (1.27%) | |

Fig - 18 : Staked bar chart of comparison of NIPS score at 3 min between study group (N=158)



In solution A group people with NIPS score at 5 min, 68 (86.08%) participants were score 0 and 11 (13.92%) participants were score 1.

In solution B group people with NIPS score at 5 min, 40 (50.63%) participants were score 0 and 39 (49.37%) participants were score 1.

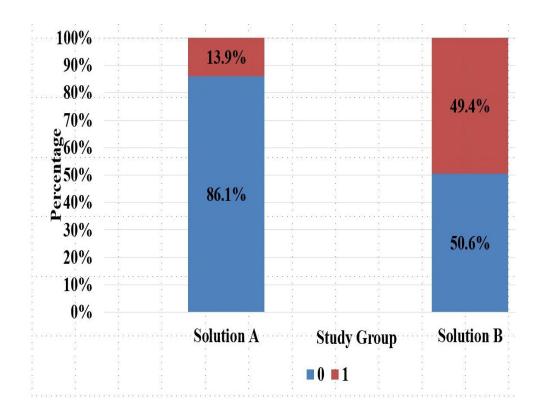
The difference in the proportion of NIPS score at 5 min between study

The difference in the proportion of NIPS score at 5 min between study group was statistically significant (P value <0.001).

Table 15: Comparison of NIPS score 5 min between study group (N=158)

| NIPS Score 5 Min | Study Group | | Chi square | P |
|------------------|----------------------|----------------------|------------|--------|
| | Solution A (N=79) | Solution B (N=79) | 1 | value |
| 0 | 68 (86.08%) | 40 (50.63%) | 22.939 | <0.001 |
| 1 | 11 (13.92%) | 39 (49.37%) | | |

Fig - 19 : Staked Bar Chart Of Comparison of NIPS Score 5 Min Between Study Group (N=158)



DISCUSSION

DISCUSSION

Scientific evidence for persistent Changes in sensory processing and/or responsiveness to future pain because of childhood pain and injury are more prevalent. Hence the need to reduce pain is radically important^{63,69} This can happen when the pain is identified briefly and tried to reduce chances the long-term behavioural responses are also influenced by child coping style, and family and social context⁵³

Diffusion tension imaging and fractional anisotropy improve resolution of structural changes in white matter, axonal development, and structural connectivity; and the degree of white matter damage at term has been shown to be predictive of neurocognitive outcome at pre-schoolers. ⁶⁴

While several research have demonstrated the analgesic impact of sucrose and breast milk, few investigations have compared the effectiveness of glucose and sucrose in alleviating the pain in preterm during regular procedures as well .^{59,62}

Our study compares the effectiveness of 25% glucose (dextrose) and combined admixture of EBM and 25% dextrose which is a novelty in the field of research.

Future studies are commonly used in reference to prospective cohort studies wherein a group of comparable individuals is followed up on

throughout time. Cross-sectional studies take measurements at a particular instant. 63,64

Our study perspectives on the point that a cross sectional study is more apt than any prospective cohort studies as conducted by H. N. Yashwanth Raju et al⁶⁴

Randomization in clinical studies is the technique of randomly assigning patients to groups that receive different treatments. The experimental group receives the novel treatment, while the control group receives normal care in the most basic study design. Bias can be minimized by randomization.⁶⁵

Our study conducted was an open labelled randomised double blinded trail whilst the study conducted by Aurimery Gomes Chermont et al ^{66,67}was A prospective, randomized, partially blinded, clinical trial. In another study by Jagadish Sahoo⁶⁸ the study conducted was Prospective, double blind, randomized controlled trial.

Block randomization is a strategy often employed in clinical trial design to eliminate bias and create balance in the allocation of participants to treatment arms, particularly when the sample size is small. By arranging participant assignments in blocks, this strategy enhances the likelihood that each arm will have an equal number of people.⁶⁹ A simple random

allocation strategy is a method in which each participant has an equal chance of being assigned to the treatment or referent groups. However, an uneven number of subjects may be randomly allocated to each arm of the research, reducing the power to detect statistically significant changes between groups.

Method of randomisation chosen in our study and the study conducted by Jagadish Sahoo were using computer generated random numbers⁶⁸.

The study of pain in neonates and the ways to reduce them was started way back in 1860's to study the effect of pain on the babies till this new era the process of finding newer methods is dynamic.

In our study the total sample size was 158 out of whom 99 babies were male and 69 babies were female. According to a research done by Rudrappa Sudha et al ^{64,71}100 neonates who were enrolled in the study were divided into dextrose(cases) and non-dextrose group(controls). Among 50 cases 28 were males and 22 were females. It was thus concluded that males had a better predilection for pain relief.

In our study out of 158 babies in sample size, the mean gestational age was 37.52 ± 1.19 in solution A and 37.42 ± 1.33 in solution B while the study conducted by Rudrappa Sudha et al^{64,69} mean gestational age of cases (dextrose group) which are included in this study was 37.5 weeks

and in controls (non-dextrose group) was 38.4 weeks. Hence concluded that term babies respond better to the pain alleviation than late preterm.

In our study, out of 158 babies 43 babies were delivered through vaginal route 36 babies were extracted by caesarean route in solution A whilst 51 babies were extracted by caesarean and 28 babies delivered by vaginal route in solution B. Although the mode of delivery did not affect the result in the study.

In our study the mean time of mean postnatal age were ranging from 6 hours to 12 hours of life done after the initial brief adaption after stress to the environment whilst in the study conducted when compared to study done by Mundol TH et al ⁷²mean postnatal age among cases in the present study was 3.61days and in controls was 4.35 days.

In our study out of 158 babies in the sample size, the mean weight in each group 2.67 ± 0.46 in solution A and 2.75 ± 0.44 in solution B whilst in a study conducted by Siti Yuyun Rahayu Fitri et al 2.465 to $2.123.06^{71}$ probably stating that lower weight birth weight babies require a higher concentration of dextrose content to ease the pain as they are more prone to hypoglycaemia .

In our study out of 158 babies 16 babies were born to mothers with risk factors such as GDM, preeclampsia, hypothyroid and on medications

which could have also affected the time lapse period for relief in pain using solution B as compared to 6 babies who had mothers with risk factors. No studies have shown the effects of maternal risk factors which could affect the physiology in relieving pain of the neonates.

In our study we used NIPSS scoring for the babies whilst compared to Hudson-Barr⁷⁴which uses the PIPS scoring system for the assessment of pain in neonates.

Our study focused on superficial tissue damage procedures such as heel stick prick in neonates as opposed to immunisation at the deltoid / anterolateral part of the thigh, which is a deeper tissue injury in the study conducted by Rudrappa Sudha et al ^{64,75}which could explain why a higher concentration of dextrose was required to relieve the pain because pain gating for such procedures probably requires higher concentrations of dextrose to release endogenous

In our study the mean heart rate value among solution A at baseline 6 hours , HR at 1 min , 3 min and 5 min were 140.86 \pm 10.27, 142.1 \pm 10.21, 140.97 \pm 10.36 , 142.78 \pm 10.86 in solution A and 140.32 \pm 9.77 , 141.29 \pm 10.05 , 139.32 \pm 9.17 , 141.84 \pm 9.35 respectively as compared to a study conducted by Ramar, et al ⁷³ where EBM and 25% dextrose was used the Baseline HR (per min) 141.8 \pm 4.8 and 138.2 \pm 5.2 , probably due to the fact that the neonates were randomised and were not strictly

confined to the NICU as there were distributed in the neonatal wards as well. Also according to the NIPS scale the time frame was for at 1 min, 3 min and 5 min as compared to first minute only, so the prolonged effects of the solutions also were studied and taken account into. Heart rates for both solution was not statistically significant.

The osmolality of 25% dextrose is 1389 mOsm/L on an average and the combination of the 25% dextrose and EBM is approximately 920 mOsm/L, which could also affect the component of pain relieving in neonates, which is not studied in any studies. ⁶¹ Because high osmolality substances cannot relieve pain

In our study the mean SpO2 value among solution A at baseline at 1 min, 3 min and 5 min were 96.3 ± 2.55 , 96.75 ± 1.83 , 97.32 ± 1.33 and 97.71 ± 1.17 , 95.41 ± 2.71 were statistically significant but not significant at the 5 min 97.05 ± 2.05 respectively as compared to a study conducted by Soroosh Soltani1, 63 where EBM and 25% dextrose was used and no statistical difference in the SpO2 was noted using the NIPS scoring system .

In our study the overall NIPS score among solution B at 1 min, 3 min and 5 min was statistically significant as compared to the NIPS score for solution A at the end of 5 min.

Although the content of dextrose in 25% dextrose is more as compared to expressed breast milk, and when admixture together the total content was lower than 25% dextrose alone the overall relieving pain could be due to the other immunomodulating effects in breast milk and the tryptophan levels which is obviously lacking in the artificially prepared dextrose levels.

There could be a possibility that the admixture of the concentration of dextrose in 25% dextrose along with the tryptophan levels and the capacity to release endogenous opioids by expressed breast milk would alleviate pain much better and be a quasi-biological product as compared to using 25% alone or using EBM alone in alleviating pain in neonates.

From the above discussion 25% dextrose and EBM mixture is comparatively a better analgesic than when 25% dextrose is used alone.

LIMITATIONS

Limitations

- The sample size is small to determine the various other effects of pain alleviating components of EBM and 25 % dextrose mixed together.
- The effects of maternal drugs such as antihypertensives, oral
 hypoglycaemics, antithyroid medications having any effect on the
 neonatal pain relief is yet to be understood extensively
- Follow up of the neonates for studying of the long-term effects of the neonatal pain was not done.
- Multiple dosage trial of the EBM and 25 % mixture to compare the time frame the period from solution administration to relieving pain was not tested although it does not affect the osmolality of the neonate's osmolality
- Need to research on how the admixture of EBM and 25% dextrose could change the immunomodulatory functioning effects of EBM alone could be studied.
- Need to study the osmolality of the EBM and 25 % dextrose admixture adjunction to the relieving in the pain is needed.

CONCLUSION

CONCLUSION

In recent years, considerable advancements have been achieved in the treatment of pain in new-borns.

- All NICU patients will require an emphasis on pain prevention, repetitive pain evaluations, and evidence-based pain management regimens that include both non-pharmacologic and therapeutic approaches treatment options due to the significant immediate and long-term dire effects of pain, as well as for humanitarian grounds.
- The admixture of EBM and dextrose used has a near normal osmolality as compared to the neonatal required osmolality which also could help in relieving pain for superficial tissue damages like heel prick.
- Expressed breast milk is nearly as good as the internal milieu of the neonatal bodily composition, easily available, having more immunomodulatory substances, the naturally available amino acids that could also possibly aid in relieving pain in neonates as compared to commercially prepared solutions which are still artificial to the neonatal system.
- Regardless of the fact that pain management strategies continue to fall short, future research should concentrate on systems-based exercise and knowledge transfer programs to improve pain management in NICUs, how to best assess pain, especially prolonged or chronic pain, and how to

incorporate the many variables affecting pain found in modern neonatology, such as light, sound, touch, parental separation, thermal stress, and extrauterine malnutrition.

 Maintaining an emphasis on new-born pain management research may help to mitigate some of the unfavourable foetal brain development observed in neonates.

BIBLOGRAPHY

<u>REFERENCES</u>

- 1. Unruh AM. Voices from the past: ancient views of pain in childhood. Clin J Pain. 1992 Sep 1;8(3):247-54.
- 2. Anand KJ, Hickey PR. Pain and its effects in the human neonate and fetus. N Engl J Med. 1987 Nov 19;317(21):1321-9.
- 3. Leng HY, Zheng XL, Yan L, Zhang XH, He HY, Xiang M. Effects of different types and concentration of oral sweet solution on reducing neonatal pain during heel lance procedures. Zhonghua Er Ke Za Zhi. 2013 Sep 1;51(9):654-8.
- 4. Gross DM. Defending the humanities with Charles Darwin's The Expression of the Emotions in Man and Animals (1872). Crit Inq. 2010 Sep;37(1):34-59.
- 5. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, Keefe FJ, Mogil JS, Ringkamp M, Sluka KA, Song XJ, Stevens B, Sullivan MD, Tutelman PR, Ushida T, Vader K. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020 Sep 1;161(9):1976-82.
- 6. Hatfield LA. Neonatal pain: what's age got to do with it? Surg Neurol Int. 2014;5(Suppl 13);Suppl 13:S479-89.
- 7. Khurana S, Hall RW, Anand KJS. Treatment of pain and stress in the neonate: when and how. NeoReviews. 2005 Feb 1;6(2):76-86.

- 8. Laudiano-Dray MP, Pillai Riddell RP, Jones L, Iyer R, Whitehead K, Fitzgerald M, Fabrizi L, Meek J. Quantification of neonatal procedural pain severity: a platform for estimating total pain burden in individual infants. Pain. 2020 Jun 1;161(6):1270-7.
- 9. Hudson-Barr D, Capper-Michel B, Lambert S, Palermo TM, Morbeto K, Lombardo S. Validation of the pain assessment in neonates (PAIN) scale with the neonatal infant pain scale (NIPS). Neonatal Network. 2002 Oct 1;21(6):15-21.
- 10. Hall RW, Anand KJS. Physiology of pain and stress in the newborn. NeoReviews. 2005 Feb 1;6(2):61-8.
- 11. Vanhatalo S, van Nieuwenhuizen O. Fetal pain? Brain Dev. 2000 May 24;22(3):145-50.
- 12. Bauer K, Ketteler J, Hellwig M, Laurenz M, Versmold H. Oral glucose before venepuncture relieves neonates of pain, but stress is still evidenced by increase in oxygen consumption, energy expenditure, and heart rate. Pediatr Res. 2004 Apr;55(4):695-700.
- 13. Fox TP, Godavitarne C. What really causes necrotising enterocolitis? ISRN Gastroenterol. 2012;2012:628317.
- 14. Walter-Nicolet E, Calvel L, Gazzo G, Poisbeau P, Kuhn P. Neonatal pain, still searching for the optimal approach. Curr Pharm Des. 2017 Oct 1;23(38):5861-78.

- 15. Blass EM, Ciaramitaro V, Barr RG. A new look at some old mechanisms in human newborns: taste and tactile determinants of state, affect, and action. Monogr Soc Res Child Dev. 1994 Jan 1;59(1):i-101.
- 16. Goswami G, Upadhyay A, Gupta NK, Chaudhry R, Chawla D, Sreenivas V. Comparison of analgesic effect of direct breastfeeding, oral 25% dextrose solution and placebo during 1 st DPT vaccination in healthy term infants: a randomized, placebo controlled trial. Indian Pediatr. 2013 Jul;50(7):649-53
- 17. Aroke EN, Powell-Roach KL, Jaime-Lara RB, Tesfaye M, Roy A, Jackson P, Joseph PV. Taste the pain: the role of TRP channels in pain and taste perception. Int J Mol Sci. 2020 Jan;21(16):5929.
- 18. Schneiderman LJ, Faber-Langendoen K, Jecker NS. Beyond futility to an ethic of care. Am J Med. 1994 Feb 1;96(2):110-4.
- 19. Motta Gde C, Schardosim JM, Cunha ML. Neonatal infant pain scale: cross-cultural adaptation and validation in Brazil. J Pain Symptom Manage. 2015 Sep 1;50(3):394-401.
- 20. Als H. A synactive model of neonatal behavioralorganization: framework for the assessment of neurobehavioral development in the premature infant and for support of infants and parents in the neonatal intensive care environment. Phys Occup Ther Pediatr. 1986 Jan 1;6(3-4):3-53.

- 21. Noureldein M, Gowda H. Question 2: is it safe to use the centre of the heel for obtaining capillary blood samples in neonates? Arch Dis Child. 2018 Apr 1;103(4):401-4.
- 22. Cope DK. Neonatal pain: the evolution of an idea. The American Association of anesthesiologists. Newsletter. 1998 Sep:6-8.
- 23. Craig KD. The social communication model of pain. Can Psychol Psychol Canadienne. 2009 Feb;50(1):22-32.
- 24. Butler DS, Moseley GL, Pain E. 2nd ed. Noigroup publications; 2013.
- 25. Franck LS, Greenberg CS, Stevens B. Pain assessment in infants and children. Pediatr Clin North Am. 2000 Jun 1;47(3):487-512.
- 26. Franck LS, Oulton K, Bruce E. Parental involvement in neonatal pain management: an empirical and conceptual update. J Nurs Scholarsh. 2012 Mar;44(1):45-54.
- 27. Kol E, Erdogan A, Karslı B, Erbil N. Evaluation of the outcomes for the control of pain. Pain Manag Nurs. 2013 Mar 1;14(1):29-35
- 28. Ploner M, Gross J, Timmermann L, Schnitzler A. Cortical representation of first and second pain sensation in humans. Proc Natl Acad Sci U S A. 2002 Sep 17;99(19):12444-8.
- 29. Yam MF, Loh YC, Tan CS, Khadijah Adam S, Abdul Manan N, Basir R. General pathways of pain sensation and the major neurotransmitters involved in pain regulation. Int J Mol Sci. 2018 Aug;19(8):2164.

- 30. Lau BK, Winters BL, Vaughan CW. Opioid presynaptic disinhibition of the midbrain periaqueductal grey descending analgesic pathway. Br J Pharmacol. 2020 May;177(10):2320-32.
- 31. Melzack R, Katz J. The gate control theory: reaching for the brain. Pain. Psychol Perspect. 2004 Jan 27:13-34.
- 32. McGrath PJ, Unruh AM. The social context of neonatal pain. Clin Perinatol. 2002 Sep 1;29(3):555-72
- 33. Borsani E, Della Vedova AM, Rezzani R, Rodella LF, Cristini C. Correlation between human nervous system development and acquisition of fetal skills: an overview. Brain Dev. 2019 Mar 1;41(3):225-33.
- 34. Anand KJ, Hickey PR. Pain and its effects in the human neonate and fetus. J Prenat Perinat Psychol Health. 1988;3(2):103.
- 35. Harrison D, Loughnan P, Johnston L. Pain assessment and procedural pain management practices in neonatal units in Australia. J Paediatr Child Health. 2006 Jan;42(1-2):6-9.
- 36. Bouza H. The impact of pain in the immature brain. J Matern Fetal Neonatal Med. 2009 Sep 1;22(9):722-32.
- 37. Greenspan JD, McGillis SL. Stimulus features relevant to the perception of sharpness and mechanically evoked cutaneous pain. Somatosens Mot Res. 1991 Jan 1;8(2):137-47.
- 38. Marko T, Dickerson M. Clinical handbook of neonatal pain management for nurses. Springer Publishing Company; 2016 Sep 12.

- 39. Almeida TF, Roizenblatt S, Tufik S. Afferent pain pathways: a neuroanatomical review. Brain Res. 2004 Mar 12;1000(1-2):40-56.
- 40. Watson SJ, Khachaturian H, Akil H, Coy DH, Goldstein A. Comparison of the distribution of dynorphin systems and enkephalin systems in brain. Science. 1982 Dec 10;218(4577):1134-6.
- 41. GARDNER SL, ENZMAN-HINES MA, AGARWAL R. Pain and pain relief; 2006.
- 42. Bouza H. The impact of pain in the immature brain. J Matern Fetal Neonatal Med. 2009 Sep 1;22(9):722-32.
- 43. Johnston CC, Fernandes AM, Campbell-Yeo M. Pain in neonates is different. Pain. 2011 Mar 1;152(3);Suppl:65-73.
- 44. Carbajal R, Rousset A, Danan C, Coquery S, Nolent P, Ducrocq S, Saizou C, Lapillonne A, Granier M, Durand P, Lenclen R, Coursol A, Hubert P, de Saint Blanquat L, Boëlle PY, Annequin D, Cimerman P, Anand KJ, Bréart G. Epidemiology and treatment of painful procedures in neonates in intensive care units. JAMA. 2008 Jul 2;300(1):60-70.
- 45. Anand KJ. Pharmacological approaches to the management of pain in the neonatal intensive care unit. J Perinatol. 2007 May;27(1);Suppl 1:4-11
- 46. Kizza IB, Muliira JK. Nurses' pain assessment practices with critically ill adult patients. Int Nurs Rev. 2015 Dec;62(4):573-82.

- 47. Fitzgerald M, Walker SM. Infant pain management: a developmental neurobiological approach. Nat Clin Pract Neurol. 2009 Jan;5(1):35-50.
- 48. Jayasinghe SN, Kruger R, Walsh DCI, Cao G, Rivers S, Richter M, Breier BH. Is sweet taste perception associated with sweet food liking and intake? Nutrients. 2017 Jul;9(7):750.
- 49. Nayak R, Nagaraj KN, Gururaj G. Prevention of pain during screening for retinopathy of prematurity: A randomized control trial comparing breast milk, 10% dextrose and sterile water. Indian J Pediatr. 2020 May;87(5):353-8.
- 50. Senterre T. Practice of enteral nutrition in very low birth weight and extremely low birth weight infants. World Rev Nutr Diet. 2014;110:201-14.
- 51. Yalçin SS. Breast-feeding for the management of painful procedures. Journal of pediatrichematology/oncology. 2012 May 1;34(4):322-3
- 52. Ellis ZM, Tan HSG, Embleton ND, Sangild PT, van Elburg RM. Milk feed osmolality and adverse events in newborn infants and animals: a systematic review. Arch Dis Child Fetal Neonatal Ed. 2019 May 1;104(3):333-40
- 53. Maller O, Turner RE. Taste in acceptance of sugars by human infants.

 J Comp Physiol Psychol. 1973 Sep;84(3):496-501
- 54. Erbi I, Ciantelli M, Farinella R, Tuoni C, Gentiluomo M, Moscuzza F, Rizzato C, Bedini A, Faraoni M, Giusfredi S, Tavanti A, Ghirri P,

- Campa D. Role of OPRM1, clinical and anthropometric variants in neonatal pain reduction. Sci Rep. 2020 Apr 27;10(1):7091.
- 55. Fitri SYR, Lusmilasari L, Juffrie M, Bellieni CV. Modified sensory stimulation using breastmilk for reducing pain intensity in neonates in Indonesia: A randomized controlled trial. Journal of pediatricnursing. 2020 Jul 1;53:199-203.
- 56. Verduci E, Banderali G, Barberi S, Radaelli G, Lops A, Betti F, Riva E, Giovannini M. Epigenetic effects of human breast milk. Nutrients. 2014 Apr;6(4):1711-24.
- 57. Örs R, Özek E, Baysoy G, Cebeci Dİ, Bilgen HÜ, Türküner M, Başaran M. Comparison of sucrose and human milk on pain response in newborns. Eur J Pediatr. 1999 Jan;158(1):63-6.
- 58. Fitri SYR, Lusmilasari L, Juffrie M, Bellieni CV. Modified sensory stimulation using breastmilk for reducing pain intensity in neonates in Indonesia: A randomized controlled trial. Journal of pediatricnursing. 2020 Jul 1;53:199-203.
- 59. Sahoo JP, Rao S, Nesargi S, Ranjit T, Ashok C, Bhat S. Expressed breast milk vs 25% dextrose in procedural pain in neonates: a double blind randomized controlled trial. Indian Pediatr. 2013 Feb 1;50(2):203-7. 60. Blass EM. Milk-induced hypoalgesia in human newborns. Pediatrics. 1997 Jun 1;99(6):825-9.

- 61. Johnston CC, Strada ME. Acute pain response in infants: a multidimensional description. Pain. 1986 Mar 1;24(3):373-82.
- 62. Rochow N, Fusch G, Choi A, Chessell L, Elliott L, McDonald K, Kuiper E, Purcha M, Turner S, Chan E, Xia MY, Fusch C. Target fortification of breast milk with fat, protein, and carbohydrates for preterm infants. J Pediatr. 2013;163(4):1001-7.
- 63. Ernst JA, Williams JM, Glick MR, Lemons JA. Osmolality of substances used in the intensive care nursery. Pediatrics. 1983;72(3):347-52.
- 64. Isani MA, Delaplain PT, Grishin A, Ford HR. Evolving understanding of neonatal necrotizing enterocolitis. Curr Opin Pediatr. 2018;30(3):417-23.
- 65. Soltani S, Zohoori D, Adineh M. Comparison the effectiveness of breastfeeding, oral 25% dextrose, kangaroo-mother care method, and EMLA cream on pain score level following heal pick sampling in newborns: a randomized clinical trial. Electron Physician. 2018 May;10(5):6741-8.
- 66. Raju HNY, Sudha R, N. SB. Effect of oral 25% dextrose on pain relief in newborn infants undergoing venepuncture. Int J Contemp Pediatr;7(4).
- 67. Pocock SJ. Allocation of patients to treatment in clinical trials. Biometrics. 1979 Mar 1;35(1):183-97.

- 68. Mann CJ. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. Emerg Med J. 2003 Jan 1;20(1):54-60
- 69. Chermont AG, Falcão LF, de Souza Silva EH, Balda RD, Guinsburg R. Skin-to-skin contact and/or oral 25% dextrose for procedural pain relief for term newborninfants. Pediatrics. 2009 Dec 1;124(6):1101-7.
- 70. Sahoo JP, Rao S, Nesargi S, Ranjit T, Ashok C, Bhat S. Expressed breast milk vs 25% dextrose in procedural pain in neonates: a double blind randomized controlled trial. Indian Pediatr. 2013 Feb 1;50(2):203-7.
- 71. Egbewale BE. Random allocation in controlled clinical trials: a review. J Pharm Pharm Sci. 2014 Jun 7;17(2):248-53.
- 72. Mundol TH, Prabhu AS, Saldanha PRM. 25% oral dextrose as analgesia during neonatal immunisation with BCG. Int J Contemp Pediatr. 2018 Mar;5(2):416-9
- 73. Fitri SYR, Lusmilasari L, Juffrie M, Bellieni CV. Modified sensory stimulation using breastmilk for reducing pain intensity in neonates in Indonesia: A randomized controlled trial. Journal of pediatricnursing. 2020 Jul 1; 53:199-203.
- 74. Hudson-Barr D, Capper-Michel B, Lambert S, Palermo TM, Morbeto K, Lombardo S. Validation of the pain assessment in neonates (PAIN) scale with the neonatal infant pain scale (NIPS). Neonatal Network. 2002 Oct 1;21(6):15-21.

75. Ramar P, Vinayagam P, Seeralar A. Effectiveness of oral glucose as analgesic for neonates undergoing retinopathy of prematurity screening—A randomized pilot study for a parallel randomized control trial. J Clin Neonatol. 2019 Oct 1;8(4):238

ANNEXURES

ANNEXURES-1

PART A - PROFORMA

NAME OF BABY:

- 1. DATE OF BIRTH:
- 2. TIME OF BIRTH:
- 3. GESTATIONAL AGE:
- 4. UHID NUMBER:
- 5. PHONE NUMBER:
- 6. MODE OF DELIVERY:
- 7. RISKFACTORS:
- 8. BIRTH WEIGHT:
- 9. MATERNAL HISTORY:
- 10. MEDICATIONS: (yes/no), if yes specify:
 - a) sedatives
 - b) analgesics
 - c) antibiotics
 - d) inotropes
- 11. PROVISIONAL DIAGNOSIS
- 12. TIME BETWEEN LAST FEED AND HEEL PRICK
- 13. TIME ADMINISTRATION OFTEST SOLUTION:

Test solution A:

Test solution B:

- 14. TIME OF HEEL PRICK:
- 15. SCORE ON NIPS SCALE:

PART B - PROFORMA

Clinical parameters:

| PARAMETER | BEFORE HEEL PRICK | AFTER HEEL PRICK AND ADMINISTRATION OF SOLUTION A | AFTER HEEL PRICK AND ADMINISTRATION OF SOLUTION B |
|----------------------|-------------------------|--|--|
| HEART RATE | | | |
| BREATHING PATTERN | | | |
| CRY | | | |
| O2 SATURATION | | | |
| ARMS MOVEMENTS | | | |
| LEG MOVEMENTS | | | |
| STATE OF AROUSAL | | | |
| FACIAL EXPRESSION | | | |
| SCORE | | | |

NEONATAL INFANT PAIN SCALE

| Variable | Finding | |
|---------------------------|---|---|
| Facial expression | Relaxed (Restful face, neutral expression) | |
| | Grimace (Tight facial muscles, furrowed brow, chin, jaw) | 1 |
| Cry | No cry (Quiet, not crying) | |
| | Whimper (Mild moaning, intermittent) | |
| | Vigorous crying (Loud scream, shrill, continuous). If | 2 |
| | infant is intubated, score silent cry based on facial movement. | |
| Breathing pattern | Relaxed (Usual pattern for this infant) | |
| | Change in breathing (Irregular, faster than usual, gagging, breath holding) | 1 |
| Arms | Relaxed (No muscular rigidity, occasional random movements of arms) | |
| | Flexed/extended (Tense, straight arms, rigid and/or rapid extension, flexion) | 1 |
| Legs | Relaxed (No muscular rigidity, occasional random leg movements) | 0 |
| | Flexed/Extended (Tense, straight legs, rigid and/or rapid extension, flexion) | 1 |
| State of Arousal | Sleeping/Awake (Quiet, peaceful, sleeping or alert and settled) | |
| | Fussy (Alert, restless and thrashing) | 1 |
| Heart Rate | Within 10% of baseline | 0 |
| | 11-20% of baseline | 1 |
| | >20% of baseline | 2 |
| O ₂ Saturation | No additional O ₂ needed to maintain O ₂ saturation | 0 |
| | Additional O2 required to maintain O2 saturation | 1 |

| Pain Level | Intervention | |
|-----------------------|---|--|
| 0-2 = mild to no pain | None | |
| 3-4 = mild to | Non-pharmacological intervention | |
| moderate pain | with a reassessment in 30 minutes | |
| >4 = severe pain | Non-pharmacological intervention and possibly a pharmacological intervention with reassessment in 30 minutes | |



ANNEXURES-2

PATIENT INFORMATION SHEET

Study: "TO DETERMINE THE EFFECT OF 25% DEXTROSE VERSUS 25% DEXTROSE AND EXPRESSED BREAST MILK TO RELEIVE PAIN IN NEONATES DURING HEEL PRICK PROCEDURES USING MODIFIED NEONATAL INFANT PAIN SCALE"

Principal investigator: Dr J SANJANA/ DR K.N.V PRASAD/ DR BHUVANA K

Study location: NICU and Postnatal ward at R L JALAPPA HOSPITAL AND RESEARCH CENTRE attached to SRI DEVARAJ URS MEDICAL COLLEGE, TAMAKA, KOLAR.

Details - All neonates admitted to NICU and POSTNATAL WARD, undergoing minor procedures such as heel prick will be included in this study. I DR. J SANJANA Post graduate student in Department of Paediatrics at SRI DEVRAJ URS COLLEGE, will be conducting a study title 'to determine the effect of 25% dextrose versus 25% dextrose and expressed breast milk to relieve pain in neonates during heel prick procedures using modified neonatal infant pain scale ', for my dissertation under the guidance of DR K.N.V PRASAD Professor Department of Paediatrics . The participants of this study i.e. neonate will be included in a randomized control study where the effect of 25% dextrose versus 25% dextrose and expressed breast milk to relieve pain in neonates during heel prick procedures using modified neonatal infant pain scale "You will not be paid any financial compensation for the participation of your child in this research project. All data will be kept confidential and will be used only for research purpose by this institution. You are free to provide consent for the

participation of your child in this study. You can also withdraw your child in this study at any point of time without giving reasons whatsoever. Your refusal to participate will not prejudice you to any present or future care at this institution.

Name and signature of principal investigator date

ರೋಗಿಯ ಮಾಹಿತಿ ಹಾಳೆ

ಅಧ್ಯಯನ: "25% ಡೆಕ್ಸ್ಫೋಸ್ಮತ್ತು 25% ಡೆಕ್ಸ್ಫೋಸ್ನ ಪರಿಣಾಮವನ್ನು ನಿರ್ಧರಿಸಲು ಮತ್ತು ವ್ಯಕ್ತಪಡಿಸಿದ ಎದೆ ಹಾಲು ನವಜಾತ ಶಿಶುಗಳಲ್ಲಿ ಹೀಲ್ಪ್ರೈಕ್ವಿಧಾನಗಳ ಸಮಯದಲ್ಲಿ ಹೀಲ್ಪ್ರೈಕ್ವಿಧಾನಗಳನ್ನು ಬಳಸಿ "ಮಾರ್ಪಡಿಸಲಾಗಿದೆ.

ಪ್ರಧಾನ ತನಿಖಾಧಿಕಾರಿ: ಡಾ ಜೆ ಸಂಜನಾ/ ಡಾ ಕೆ ಎನ್ ವಿ ಪ್ರಸಾದ್/ ಡಾ ಭುವನ ಕೆ ಅಧ್ಯಯನಸ್ಥಳ: ಎನ್ಐಸಿಯು ಮತ್ತು ಪ್ರಸವಪೂರ್ವವಾರ್ಡ್ ಆರ್ಎಲ್ಜಾಲಪ್ಪ ಆಸ್ಪತ್ರೆ ಮತ್ತು ಸಂಶೋಧನಾ ಕೇಂದ್ರಕ್ಕೆ ಲಗತ್ತಿಸಲಾದ ಶ್ರೀ ದೇವರಾಜು ಆರಸು ವೈದ್ಯಕೀಯ ಕಾಲೇಜು ತಮಕ, ಕೋಲಾರ.

ವಿವರಗಳು- NICU ಮತ್ತು POSTNATAL ವಾರ್ಡಿಗೆ ದಾಖಲಾದ ಎಲ್ಲಾ ನವಜಾತ ಶಿಶುಗಳು, ಹೀಲ್ಚುಚ್ಚುವಿಕೆಯಂತ ಹಸಣ್ಣ ಕಾರ್ಯ ವಿಧಾನಗಳಿಗೆ ಒಳಗಾಗುತ್ತಾರೆ ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಸೇರಿಸಲಾಗುತ್ತದೆ.

ನಾನು DR. J SANJANA ಶ್ರೀ ದೇವರಾಜು ಆರಸು ಕಾಲೇಜಿನಲ್ಲಿ ಪೀಡಿಯಾಟ್ರಿಕ್ಸ್ನಿ ಭಾಗದ ಸ್ನಾತಕೋತ್ತರ ವಿದ್ಯಾರ್ಥಿನಿ ಡಾ ಜೆ ಸಂಜನಾ ಅವರು 25% ಡೆಕ್ಸ್ಪೋಸ್ಮತ್ತು 25% ಡೆಕ್ಸ್ಪೋಸ್ನ ಪರಿಣಾಮವನ್ನು ನಿರ್ಧರಿಸಲು ಮತ್ತು ಹೀಲ್ಚುಚ್ಚುವ ವಿಧಾನಗಳನ್ನು ಬಳಸಿಕೊಂಡು ನವಜಾತ ಶಿಶುಗಳಲ್ಲಿನ ನೋವನ್ನು ನಿವಾರಿಸಲು ಎದೆ ಹಾಲಿನ ಪರಿಣಾಮವನ್ನು ನಿರ್ಧರಿಸಲು ..." ಎಂಬ ಅಧ್ಯಯನವನ್ನು ನಡೆಸುತ್ತಿದ್ದಾರೆ. ಮಾರ್ಪಡಿಸಿದ ನವ ಜಾತ ಶಿಶುಗಳ ನೋವಿನಮಾಪಕ", DR .ಕೆ ಎನ್ ವಿ ಪ್ರಸಾದ್ ಅವರ ಮಾರ್ಗದರ್ಶನದಲ್ಲಿ ನನ್ನ ಪ್ರಬಂಧಕ್ಕಾಗಿ ವಿಭಾಗದ ಪ್ರಾಧ್ಯಾಪಕ ಪೀಡಿಯಾಟ್ರಿಕ್ಸ್. ಹೀಗೆ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವವರು ಅಂದರೆ. ನವಜಾತ ಶಿಶುವನ್ನು ಯಾದೃಚ್ಛಿಕ ನಿಯಂತ್ರಣ ಅಧ್ಯಯನದಲ್ಲಿ ಸೇರಿಸಲಾಗುವುದು, ಅಲ್ಲಿ 25% ಡೆಕ್ಸ್ಪೋಸ್ಮತ್ತು 25% ಡೆಕ್ಸ್ಪೋಸ್ನ ಪರಿಣಾಮ ಮತ್ತು ಹೀಲ್ಬುಚ್ಚುವಿಕೆಯ ಪ್ರಕ್ರಿಯೆಯಲ್ಲಿ ನವಜಾತ ಶಿಶುಗಳಲ್ಲಿನ ನೋವನ್ನು ನಿವಾರಿಸಲು ಎದೆ ಹಾಲು ವ್ಯಕ್ತಪಡಿಸಲಾಗುತ್ತದೆ, ಮಾರ್ಪಡಿಸಿದ ನವಜಾತ ಶಿಶುವಿನ ನೋವಿನ ಪ್ರಮಾಣವನ್ನು ಬಳಸಿಕೊಂಡು ನಿಮಗೆ ಯಾವುದೇ ಹಣಕಾಸಿನ ಪರಿಹಾರವನ್ನು ನೀಡಲಾಗುವುದಿಲ್ಲ. ಈ ಸಂಶೋಧನಾ ಯೋಜನೆಯಲ್ಲಿ ನಿಮ್ಮ ಮಗುವಿನ ಭಾಗವಹಿಸುವಿಕೆ. ಎಲ್ಲಾ ಡೇಟಾವನ್ನು ಗೌಪ್ಯವಾಗಿ ಇರಿಸಲಾಗುತ್ತದೆ ಮತ್ತು ಈ ಸಂಸ್ಥೆಯಿಂದ ಸಂಶೋಧನಾ ಉದ್ದೇಶಕ್ಕಾಗಿ ಮಾತ್ರ ಬಳಸಲಾಗುತ್ತದೆ. ಈ ಅಧ್ಯಯನದಲ್ಲಿ ನಿಮ್ಮ ಮಗುವಿನ ಭಾಗವಹಿಸುವಿಕೆಗೆ ಒಪ್ಪಿಗೆ ನೀಡಲು ನೀವು ಸ್ವತಂತ್ರರಾಗಿದ್ದೀರಿ. ಯಾವುದೇ ಕಾರಣಗಳನ್ನು ನೀಡದೆಯೇ ನೀವು ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ಈ ಅಧ್ಯಯನದಲ್ಲಿ ನಿಮ್ಮ ಮಗುವನ್ನು ಹಿಂಪಡೆಯ ಬಹುದು. ಭಾಗವಹಿಸಲು ನಿಮ್ಮ ನಿರಾಕರಣೆಯು ಈ ಸಂಸ್ಥೆಯಲ್ಲಿ ಯಾವುದೇ ಪ್ರಸ್ತುತ ಅಥವಾ ಭವಿಷ್ಯದ ಕಾಳಜಿಗೆ ನಿಮ್ಮನ್ನು ಪೂರ್ವಾ ಗ್ರಹಮಾಡುವುದಿಲ್ಲ.

ಮುಖ್ಯ ತನಿಖಾಧಿಕಾರಿಯ ಹೆಸರು ಮತ್ತು ಸಹಿ-ದಿನಾಂಕ - **ANNEXURES - 3**

INFORMED CONSENT FORM

I, MR/MRS___, have been explained in my own vernacular language that my child will

be included in this study, Effect of 25% Dextrose versus 25% Dextrose and

expressed breast milk to relieve pain in neonates during heel prick procedures

using NEONATAL INFANT PAIN SCALE, hereby give my valid written informed

consent without any force or prejudice for recording the observations of clinical

parameters. The nature and risks involved have been explained to me, to my

satisfaction. I have been explained in detail about the study being conducted. I have

read the patient information sheet and I have had the opportunity to ask any question.

Any question that I have asked has been answered to my satisfaction. I provide

consent voluntarily to allow my child as a participant in this research. I hereby give

consent to provide history, undergo investigations, undergo procedure and provide its

results and documents etc to the doctor/ institute etc. For academic and scientific

purpose the procedure maybe video graphed or photographed. All the data maybe

published or used for any academic purpose. I will not hold the doctors / institute etc

responsible for any untoward consequences during the procedure / study.

(Signature & Name of patient attendant)

(Signature/ Thumb impression & name of patient / guardian) Relation with patient:

Witness:

(Signature& name of Research person / Doctor)

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ANNEXURES - 4

MASTER CHARTS

KEY TO MASTER CHART

25% D – 25 percent Dextrose

EBM – Expressed breast milk

NICU – Neonatal Intensive care unit

PNW – Postnatal ward

NVD - Normal Vaginal Delivery

ELSCS – Elective Lower segment caesarean section

LBW – Low birth weight

IUGR – Intra uterine Growth Retardation

SGA – Small for gestational age

AGA- Appropriate for gestational age

HR – Heart rate

O₂SPO2 – Oxygen saturation

NIPS – Neonatal Infant Pain Scale

Min – Minutes

KG- Kilogram

MASTER CHART - 25 % DEXTROSE (SOLUTION A)

MASTER CHART - 25 % DEXTROSE AND EXPRESSED BREAST MILK (EBM) (SOLUTION B)