A RANDOMISED CONTROLLED TRIAL COMPARING THE EFFECTS OF HONEY VERSUS SUCROSE AS AN ANALGESIA DURING ROUTINE VENEPUNCTURE IN NEWBORNS

BY

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Dissertation Submitted In Partial Fulfillment Of The Requirement For The Degree Of Master Of Medicine

(PAEDIATRICS)

UNIVERSITI SAINS MALAYSIA

2011

ACKNOWLEDGEMENT

First of all, many thanks to Allah for His blessings, without which this would not come true. My special thanks to Dr Nor Rosidah Ibrahim for her guidance, patience and perseverence in helping me to make what initially was impossible to become a reality. Thank you to all those involved in this study namely, Assoc. Prof Noraida Ramli, Prof Hans Amin Van Rostenberghe, Dr Fahisham Taib, all staff of the Neonatal Intensive Care Unit and Special Care Nursery, HUSM. Finally, to my mother, Pn. Hajjah Puteri Hajar, my husband, Ahmad Rom and my bundle of joys, Al Qari, Khairina, Al Qais and Khadeeja, thanks for the love and support throughout this whole journey.

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LIST OF ABBREVIATIONS

PIPP : Premature Infant Pain Profile

EMLA : Eutectic Mixture of Local anaesthetics

SPSS : Statistical Package for the Social Sciences

ICC : Intraclass Coefficient

CI : Confidence Interval

SD : Standard Deviation

ABSTRACT

TITLE

A Randomised Control Trial comparing the effects of Honey versus Sucrose as analgesia during routine venepuncture in newborn

OBJECTIVE

To determine the effectiveness and short term side effects of honey as analgesia in comparison to sucrose during routine venepuncture in newborn.

METHODS

A total of 78 term neonates were recruited from the Neonatal Intensive Care Unit and Special Care Nursery of Hospital Universiti Sains Malaysia. These neonates were randomized into two equal sized group receiving either 2 ml of oral 24% sucrose or 2 ml of Tualang honey 2 minutes prior to venepuncture. The whole procedure was videotaped. The degree of pain score using PIPP and duration of crying time were determined twice by two independent observer. The Mann Whitney U test was used to compare the pain scores and duration of cry between the study groups while the Wilcoxon sign rank test was used to compare differences within each group.

RESULTS

The result showed no significant differences in the demographic characteristics of the neonates. The median values of PIPP at 30 seconds and 150 seconds were comparable (p value = 0.871) between both groups (median PIPP sucrose = 5, 3 median PIPP for honey = 5, 2 respectively). The median PIPP score within each group was significantly higher (p value = 0.00) at 30 seconds (median =5) compared to at 150 seconds (median = 2.5). The duration of audible cry after venepuncture was not statistically significant (p=0.803) in neonates receiving honey (median= 5.5 seconds) compared to neonates receiving 24% sucrose (median = 4 seconds). No neonates developed hyperglycemia, diarrhea or glycosuria in this study.

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CONCLUSION

In conclusion, this study strongly suggests that Tualang honey is not more effective than sucrose for procedure related analgesia in neonates. The absence of adverse effects following the administration of small amounts of honey to neonates may facilitate further studies using different doses or different types of honey.

ABSTRAK

TAJUK

Kajian perbandingan secara rawak buta mengenai madu dan sukrosa sebagai ubat penahan sakit semasa pengambilan darah di kalangan bayi baru lahir.

OBJEKTIF

Untuk menilai keberkesanan dan kesan sampingan madu sebagai ubat penahan sakit dan membandingkannya dengan sukrosa ketika pengambilan darah di kalangan bayi baru lahir.

TATACARA

Sejumlah tujuh puluh lapan bayi yang dilahirkan cukup bulan telah dipilih dari wad intensif dan wad penjagaan khas bayi Hospital Universiti Sains Malaysia untuk kajian pengawalan secara rawak buta. Tiga puluh sembilan bayi telah diberi 2 ml air sukrosa 24% manakala tiga puluh sembilan bayi diberi 2 ml madu tualang, 2 minit sebelum pengambilan darah. Reaksi bayi dirakamkan didalam pita video sepanjang prosedur dijalankan. Skor tahap kesakitan bayi telah dinilai menggunakan Premature Infant Pain Profile(PIPP) dan julat masa tangisan bayi telah ditentukan dengan melihat pita rakaman prosedur oleh dua orang penyelidik secara rawak.

KEPUTUSAN

Keputusan dari kajian ini menunjukkan tiada perbezaan bererti bagi ciri-ciri demografik bayi di antara dua kumpulan tersebut. Nilai median PIPP pada 30 saat adalah sama di antara kumpulan iaitu 5 manakala nilai median PIPP pada 150 saat adalah 3 untuk kumpulan sukrosa dan 2 untuk kumpulan madu (p= 0.871). Perbandingan median PIPP di dalam kumpulan menunjukkan nilai median pada 30 saat adalah lebih tinggi berbanding dengan median pada 150 saat (p=0.00). Nilai median julat masa tangisan selepas venepunktur adalah sama (p=0.803) di antara bayi yang menerima madu (median 5.5 saat) dibandingkan bayi yang menerima 24% sukrosa (median = 4 saat). Tiada bayi di dalam kajian ini yang menunjukkan kesan sampingan seperti kandungan gula tinggi dalam darah, cirit birit atau kehadiran gula didalam air kencing .

KESIMPULAN

Kajian ini menunjukkan bahawa madu Tualang adalah tidak lebih berkesan daripada sukrosa sebagai ubat penahan sakit untuk prosedur di kalangan bayi. Ketiadaan kesan sampingan akibat penggunaan madu ini boleh membantu penyelidikan seterusnya menggunakan dos dan jenis madu yang berlainan.

1. INTRODUCTION

1. INTRODUCTION

Pain, which is the fifth vital sign, is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, according to the International Association for the Study of Pain (IASP) (McCaffery M 1999). Newborn infants are subjected to procedural pain like venepuncture and heel prick as part of routine medical procedure. The exposure to these noxious stimuli will engender the stress response which has specific negative physiological effects (Henry 2004). Basically, untreated procedural pain can lead to adverse effect such as hyperalgesia on subsequent procedure.

In realizing the importance of analgesia in the newborn, various methods have been employed for amelioration of pain during such procedure. To date, there are various modes of analgesia which can be categorized into non pharmacological and pharmacological methods. The use of local anesthetics such as EMLAS is an example of a pharmacological agent used in treating pain. Other interventions like non nutritive sucking with pacifier, breastfeeding, rocking and handling the newborn during venepuncture has been shown to decrease the pain response in the neonates (Henry 2004).

According to a recent Cochrane Review (Yamada 2010), oral sweet solution such as sucrose can significantly confer analgesic effects during minor procedure like venepuncture. Sucrose at a concentration more than 24% has been shown to be a safe and effective method of analgesia

(Yamada 2010). It is postulated that this effect takes place via the activation of the endogenous opiod system through taste (Blass 1999).

However, little is known regarding the analgesic effect of another naturally sweet substance-honey. This study aims to establish the analgesic effect of honey and to compare its effectiveness with sucrose as well as to delineate it's safety as an analgesia. Honey forms part of traditional medicine in many cultures, although it is widely used as a sweetener (Gomez-Carava 2006). It is composed of at least 181 components and is basically a solution supersaturated in sugars, namely fructose (38%) and glucose (31%). Its moisture content is about 17.7% with a total acidity of 0.08% and ashes content 0.18% (Nagai 2002).

In addition, there is a great variety of minor components, including phenolic acids and flavonoids, the enzyme glucose oxidase and catalase, ascorbic acid, carotenoids, organic acid, amino acid, protein and alpha tocopherol (Ferreres 1993). The actual composition of honey varies depending on many factors such as the pollen source, climate, environmental conditions and the processing it undergoes (Gheldof 2002).

Most of the functional and biological properties of honey are conferred by the phenolic compounds in the form of flavonoids as mentioned before. These properties include anti-oxidant, anti inflammatory, anti bacterial, anti viral, anti ulcerous and the capacity for the inhibition of enzymatic browning in fruits and vegetables (Viuda 2008). These biological properties of honey

especially the anti inflammatory and thus analgesic effects of honey will be established in this study using a locally derived Malaysian honey- the Tualang honey. This honey will be supplied by the Pharmacology Department, HUSM after undergoing a process of Gamma irradiation. This is done to eliminate all potential microorganisms including spore forming bacteria like *Clostridium botulinum* and yeast. To ensure the safety of honey which will be used in the neonatal period, stringent methods of precaution will be taken where samples of honey will be cultured prior and after undergoing radiation treatment.

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2. LITERATURE REVIEW

2. LITERATURE REVIEW

2.1 NEUROBIOLOGY AND NEUROANATOMY OF PAIN IN NEONATES

Neonatal analgesia is a recent issue: newborns were supposed to feel no pain until the late 1980's, but from that date many studies were performed to verify the extent of neonatal pain perception, ways to measure and overcome it. Neonatal care is advancing to levels where more neonates are being offered more invasive intervention and prolonged hospital stay. Needless to say, majority of these interventions are painful and a specific methods of analgesia need to be given and specific guidelines implemented to address this issue of neonatal pain.

During fetal development in utero, sensory fibers are abundant by 20 weeks; a functional spinal reflex is present by 19 weeks; connections to the thalamus by 20 weeks and connections to subplate neurons are present by 17 weeks with intensive differentiation by 25 weeks. These cells are important developmentally, but decline as a result of natural apoptosis (Lowery et al 2007). Neurobiological studies showed that from 30 weeks in utero, the anatomical and physiological system for pain transmission is already developed, with the establishment of mature thalamocortical projections from periphery to cortex (Goncalves 2010).

Pain requires both nociception and emotional reaction or interpretation. It is normally triggered by messages transmitted from specialized receptors (nociceptors) in the body to integrative centers in the spinal cord and brainstem and on to the brain, where it undergoes higher sensory and cognitive analysis, allowing the body to respond appropriately to the stimuli (Slater 2008).

Nociception causes physiologic stress with activation of the hypothalamus-pituitary-adrenal axis, autonomic nervous system and hemodynamic changes. The changes induced by strong nociceptive stimulation in newborn have important postnatal consequences since they affect future reactions to noxious stimuli (Taddio 2009). Central sensitization and immaturity of the pain inhibitory system are the main neurobiological explanation for increased pain in neonates (Goncalves 2010).

2.2 PHYSIOLOGY OF NOCICEPTION (PAIN SENSATION)

Nociception is related to the mechanisms elicited by stimuli threatening the integrity of the individual. At the peripheral level, unmyelinated C fibres (C polymodal nociceptores) or fine myelinated A delta fibres are excited by noxious stimulation, directly or indirectly by inflammatory processes. Nociceptive afferent fibres terminate in the superficial laminae of the dorsal horn of the spinal cord where informations are integrated and controlled. These first synapses are modulated by excitatory amino acids (glutamate and aspartate) and many peptides (substance P, CGRP, CCK, endogenous opiods). Majority of the ascending pathways involved in nociception are located in the ventrolateral contralateral quadrant of the cord (spinoreticular and spinothalamic tracts). Many supraspinal sites are activated following nociceptive stimuli, with relays in the reticular formation of the brain stem (including the subnucleus reticularis dorsalis), the ponto-mesencephalic regions (periaqueductal gray matter and parabrachial area) and thalamic sites. Amygdala and hypothamic targets could be involved in motivational reactions and neuroendocrine adaptations to a noxious event. The cingular, insular and somatosensory cortices also receive nociceptive informations. Nociceptive signals are modulated at all levels of their

transmission; the more extensively studied controls are located at the spinal level (Guirimand 1996). Spinal signals can also be inhibited following activation of bulbospinal descending inhibitor pathways and release of serotonin, norepinephrine and indirectly, endogenous opiods. Inhibitory controls triggered by noxious stimuli could facilitate the extraction of the nociceptive tone of informations having priority over other stimuli (Guirimand 1996).

2.3 NEUROCHEMICAL SYSTEMS ASSOCIATED WITH PAIN PERCEPTION

2.3.1 ENDOGENOUS OPIOD SYSTEM

A research has demonstrated that at 15 weeks of gestation, functionally mature endorphinergic cells have been observed in the human fetal pituitary gland (Li et al 1979). By twenty weeks of gestation, in vitro stimulation of these fetal pituitary cells by corticotrophin-releasing factor may result in secretion of the beta-endorphins (Gibbs et al 1982). Endogenous opiod are released in the human fetus at birth and in response to neonatal distress (Gautray et al 1977). A study by Wardlaw et al showed that umbilical cord plasma levels of beta-endorphins and beta-lipotropin from healthy full-term neonates delivered vaginally have been shown to be three to five times higher than plasma levels in the resting adults (Wardlaw et al 1979). In addition to that, neonates delivered vaginally by breech presentation or vacuum extraction had further increases in beta-endorphin levels, indicating beta-endorphin secretion in response to stress at birth (Puolakka et al 1982).

The elevated values of endogenous opiod may have been caused by the stress inflicted by the illness, the pain associated with the clinical conditions mentioned above or the invasive procedure that the fetus had to undergo. Nonetheless, these high levels of beta endorphin are unlikely to decrease the analgesic requirements. This is because the cerebrospinal fluid levels of beta endorphin required to produce analgesia in human adults have been found to be 10 000 times higher than the highest recorded level in neonates (Foley et al 1979). The high levels of beta endorphin and beta lipotropin in cord plasma reduces substantially by 24 hours after birth and reached adult levels by 5 days, whereas the levels in the cerebrospinal fluid fall to adult level by 24 hours (Facchinetti et al 1982).

2.3.2 TACHYKININ SYSTEM

The tachykinins are neurotransmitters which amplify pain perception from the periphery. Among the tachykinins, substance P has been widely investigated and shown to have a role in the transmission and control of pain impulses (Dickenson 1995). Neural elements containing substance P and its receptor appear in the dorsal root ganglia and dorsal horns of the spinal cord at 12 to 16 weeks of gestation (Charnay et al 1983). A high density of substance P fibres and cells have been observed in multiple areas of the fetal brain stem associated with the pathway for pain perception and control and the visceral reactions to pain (Del Fiacco 1984).

2.4 RATIONALE OF PROVIDING ANALGESIA TO NEONATES

The ability to communicate about pain allows an individual to seek strategies to ease the pain, such as taking analgesics. Unfortunately, neonates do not possess this ability, thus making them vulnerable to prolonged suffering during their stay in the neonatal intensive care unit. The difficulty in accurate measurement of pain in the newborn is a major impediment in providing effective analgesia for neonates undergoing routine procedure like heel lance and venepuncture. Ignored and untreated pain in infants has been shown to have immediate and long-term effects as a result of structural and physiological changes within the nervous system. For example, the body responds to untreated pain by increased release of stress hormones, which may be associated with increased morbidity and mortality in the short term (Slater 2008). Furthermore, the associated changes caused by untreated pain may result in decrease oxygenation, hemodynamic instability and increase in intracranial pressure (Kyoung 2010).

In a study by Bellieni et al, it is shown that even common routine procedure like heel prick can be potentially harmful for newborn if they provoke high level of pain (Bellieni et al 2009). In this study the generation of free radicals in the form of advanced oxidative protein product (AOPP) and total hydroperoxide (TH) was measured at the beginning and end of each heel prick and the level of pain was scored for every procedure. Significant increased in the free radicals was observed for those babies who showed highest pain intensity, thus stressing the need for any methods of analgesia to provide adequate pain relief during such procedure.

Further negative effects of untreated procedural pain was demonstrated by Taddio et al in her study on the effect of repeated painful procedure and development of hyperalgesia in the newborn. Hyperalgesia is defined as increase in response to a normally painful stimulus at a site distal from the site of injury. In this study, a total of 240 of both healthy infants and infants of diabetic mother were randomized into two groups and were subjected to venepuncture according to indications. It was found out that infants subjected to five or more venepuncture exhibit higher pain score and were prone to develop remote hyperalgesia (Taddio 2009). Finally, the long-term consequences of untreated pain may include altered pain perception, chronic pain syndromes, and somatic complaints such as sleep disturbances, feeding problems and inability to self-regulate in response to internal and external stressors. It has been proposed that attention deficit disorders, learning disorders and behavioral problems in later childhood may be linked to repetitive pain in preterm infants (Slater 2008).

2.5 METHODS OF PAIN ASSESSMENT FOR NEWBORN

In realizing that pain in the newborn is often underestimated and at times left untreated, various different pain scales have been developed and validated specifically for this population. To date, several validated and reliable pain measures exist to assess acute pain in term and preterm neonates (Abu-Saad 1998). Both behavioral indicators of pain (e.g. facial expression, body movements, crying) and physiological indicators of pain (e.g. heart rate, respiratory rate, blood pressure, oxygen saturation, vagal tone, palmar sweating and plasma cortisol or cathecolamine levels) can be used to assess and manage pain in neonates.

It is interesting to note that facial expression is widely used to judge pain in neonates. However, little is known about the relationship between intensity of stimulus and nature of expression in term neonates. In a recent study by Schiavenato et al, little difference is noted on the eye and eyebrow between pain intensities. The mouth will open wider (vertically) in neonates experiencing higher pain stimulus. Qualitative differences in neonates facial expression to pain intensity may exist and the mouth may be an area in which to detect them. Nevertheless, further study regarding the generalizability of these findings is needed (Schiavenato 2011).

Assessments that use multi-dimensional measures such as behavioral and physiological changes may result in more accurate assessment of neonatal pain (Stevens et al 1996). Composite measures of neonatal pain include the following: 1) the Neonatal Infant Pain Scale (NIPS) which assesses facial expression, cry, breathing patterns, movement of arms and legs and state of arousal (Lawrence et al 1993) 2) CRIES that assesses *C*rying, the *R*equirement for oxygen supplementation, *I*ncreases in heart rate and blood pressure, facial *E*xpression and *S*leeplessness (Krechel & Bildner 1995) 3) the Premature Infant Pain Profile (PIPP) that includes behavioral(brow bulge, eye squeeze and nasolabial furrow), physiological (change in heart rate and change in oxygen saturation) and contextual (gestational age and behavioral state before painful stimulus)(Yamada 2010). Based on a review from 1996 to 2009, The PIPP continues to be a reliable and valid measure of acute pain in infants with numerous positive validation studies. There is substantial support for the use of PIPP as an effective measure in pain intervention studies in infants (Stevens et al 2010).

The latest pain scale to be developed is the COVERS scale, which incorporates 6 physiological and behavioral measures for scoring. In a study by Hand et al, pain assessment was done on newborns during heel prick using indicators from three previously established scales (CRIES, the Premature Infant Pain Profile and the Neonatal Infant Pain Scale) as well as the COVERS scale, depending upon gestational age. For premature infant testing, similar results on pain assessment was obtained using the COVERS and PIPP scale while for full term infants, both the COVERS and NIPS scale resulted in similar pain assessment (Hand et al 2010). Another pain scale which is unidimensional in nature is the NFCS (Neonatal Facial Coding System). It is a valid and reliable coding system for quantifying facial actions associated with acute pain in infants (Grunau et al 1990).

2.6 METHODS OF ANALGESIA FOR NEONATES

2.6.1 PHARMACOLOGICAL METHODS OF ANALGESIA

2.6.1.1 Opiod Analgesia

Analgesia and sedation in Neonatal Intensive Care Unit (NICU) has been fraught with controversy because of concern over the safety of these drugs in the neonates, lack of adequate pharmacokinetic and pharmacodynamic data in this population, difficulty in pain assessment and lack of long term neurodevelopmental assessment of survivors for the pain experienced in the neonatal period (Hall 2009). According to a study by Kapellou, preterm or ill neonates may undergo 1-21 heel pricks or venepunctures a day. Heel prick comprise 61% to 87% and venepunctures comprise 8% to 13% of invasive procedures performed on ill infants. The study

further stated that analgesics are rarely given specifically for blood sampling procedures despite the alarming statistics mentioned above (Kapellou 2011).

MORPHINE

Morphine is the most frequently used opioid analgesic in all ages, and is the most commonly used drug for analgesia in ventilated neonates (Hall 2007). Morphine has a slow onset of analgesia with a mean onset of action in 5 minutes and peak action at 15 minutes. It is metabolized in the liver into two active compounds, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). The former is an opioid antagonist and the latter is a potent analgesic. Preterm infants mostly produce M3G, which explains why after 3–4 days of morphine therapy, the infant develops tolerance (Anand et al 2004). Side-effects of morphine include hypotension in neonates with pre-existing hypotension and gestational age less than 26 weeks, prolonged need for assisted ventilation and increased time to reach full feeds (Anand 2007). Others have suggested that morphine may have a specific effect on pulmonary mechanics, possibly due to some as yet undefined direct toxicity such as histamine release and/or bronchospasm (Levene 2005).

FENTANYL

Fentanyl is an opioid analgesic that is 50–100 times more potent than morphine. It is used frequently because of its ability to provide rapid analgesia. It may be used as a slow intravenous push every 2 to 4 hours or as a continuous infusion. Tolerance may develop and withdrawal

symptoms may occur after 5 days or more of continuous infusion. In a blinded randomized controlled trial, a single dose of fentanyl given to ventilated preterm newborns significantly reduced pain behaviors and changes in heart rate. It also increases growth hormone levels (Guinsburg 1998). In another study, fentanyl provided the same pain relief as morphine but with fewer side effects (Saarenmaa 1999). Side-effects of fentanyl include bradycardia, chest wall rigidity and opioid tolerance after prolonged therapy (Anand 2006).

2.6.1.2 Non Opiod Analgesia

MIDAZOLAM

The most commonly used benzodiazepine in the NICU is midazolam. When administered with morphine, it has been shown to provide better sedation than morphine alone in ventilated patients, without adverse effects. Intranasal midazolam has been shown to be effective for fundoscopic exams in older children, but this mode of delivery has not been tested in neonates. One recent review found no apparent clinical benefit of midazolam compared to opiates in mechanically ventilated neonates (Aranda 2005). In addition, midazolam was associated with worse short term adverse effects (death, severe intraventricular hemorrhage or periventricular leukomalacia) in the NOPAIN trial compared to morphine alone (Anand et al 1999). In summary, midazolam appears to provide sedative effects in mechanically ventilated neonates, but it should be used with caution because of reported adverse effects, particularly when used alone.

KETAMINE

Ketamine is a dissociative anesthetic used for anesthesia, analgesia and sedation. It causes bronchodilation and mild increase in blood pressure and heart rate (Betremieux 1993). Cerebral blood flow is relatively unaffected with ketamine, making it an attractive choice for some unstable hypotensive neonates requiring procedures such as cannulation for ECMO. Animal studies have raised concern over the neurodegenerative effects of ketamine; however it has been shown that ketamine in clinically relevant doses is neuroprotective in the presence of inflammatory pain (Anand 1999). Nevertheless, extrapolating animal to human data is problematic at best and there has been no credible evidence that ketamine is detrimental to the developing human brain in the presence of pain. Clearly, more study is needed to determine the safety and efficacy of this anesthetic.

2.6.1.3 Local Anaesthetics

Topical anesthetics [eutectic mixture of local anesthetic (EMLA)] have demonstrated effectiveness for certain types of procedural pain such as venipuncture, lumbar puncture or immunizations in children (Henry 2004). In order to obtain the maximum benefit of this drug, EMLA should be applied at least 60 minutes prior to the scheduled procedure. Unfortunately, Taddio and coworkers in their review on the use of EMLA found that it had little benefit when used for heel prick, because of increased skin thickness (Taddio et al 1998).

The possible complications surrounding the use of EMLA which limits its used in the neonatal period is regarding the potential for developing methemoglobinemia and transient skin rashes (Henry 2004). This is based on the postulation that there is decreased level of methemoglobin reductase in infants under three months and this concern is accentuated especially so for the premature infants (Essink et al 1999).

2.6.2 NON-PHARMACOLOGICAL METHODS OF ANALGESIA

To date, there are vast arrays of non pharmacological methods that can be employed as analgesia in the newborn infants. Apart from relatively free of side effects, they are easy to use, inexpensive and can be as effective if not superior to some of the pharmacological agents available (Walter-Nicolet et al 2010).

2.6.2.1 ORAL SWEET SOLUTIONS

The most common intervention studied in regards to ameliorating the pain of routine heel sticks, venipuncture and injections is the use of oral sweet solution shortly before the start of the procedure. The use of oral sucrose alone or in conjunction with other measures like carrying, simulated rocking or non-nutritive sucking decreases pain responses in both full term and preterm neonates. The exact mechanism, optimum concentration and method of administration will be mentioned under the headings of Sucrose as an analgesia. Apart from sucrose, oral dextrose and oral glucose have also been shown to confer the analgesic effect. In a study by Alen, oral glucose at varying concentration of 10 to 30% vs. placebo was given 2 minutes prior

to venepuncture. The pain assessment was done using the “Leuven Pain Scale”. It was found out that the group receiving 2ml of 30% glucose given orally 2 minutes prior to venepuncture showed the most effective pain reduction in the newborn (Alen 2010).

2.6.2.2 NON- NUTRITIVE SUCKING

Another intervention that appears to decrease the pain response in neonates is non nutritive sucking. Non nutritive sucking is analgesic when the infant sucks on a pacifier at a rate of at least 30 sucks per minute (Blass 1999). Sucking is effective in an additive manner when used in conjunction with sucrose solution, glucose solution or dextrose solution (American Academy of Pediatrics 2000).

2.6.2.3 BREASTFEEDING

Breastfeeding is also suggested as a mechanism to provide an analgesic effect in newborns undergoing venipuncture and heel stick. Mothers holding and breastfeeding their infants during venepuncture and the use of 30% glucose with pacifier were effective interventions for reducing a painful response in comparison to water or clothed mothers holding their infants. This finding is further supported by Okan et al, who found out in his study that the involvement of breast feeding and skin to skin contact can significantly reduce both physiological and behavioral pain response (Okan et al 2010).

2.6.2.4 ROCKING AND HOLDING

Johnston and coworkers studied simulated rocking and holding with and without the use of sucrose in relation to decreasing pain during heel stick. The use of sucrose 24% alone and sucrose 24% with simulated rocking significantly decreased Neonatal Facial Coding System scores in comparison to rocking alone and water (Grunau 1987). However, there were no significant difference between sucrose and sucrose and rocking. In contrast, holding and sucrose 24% were more effective than sucrose alone or holding alone in a study of healthy neonates undergoing heel lance (Johnston et al 1997). Alternatively, swaddling combined with positioning neonates upright during routine heel lance offers a nonpharmacological method of neonatal pain reduction during this procedure (Morrow 2010).

2.7 SUCROSE AS ANALGESIA

From the recent Cochrane Review, sucrose, a naturally occurring sweetener, has been shown to confer analgesic effects for newborn undergoing painful procedures like heel-lance, venepuncture, bladder catheterization, circumcision, ophthalmology examination and nasogastric tube insertion (Yamada 2010). It is postulated that the mechanism of action of sucrose is mediated by both the endogenous opiod system through taste and the non opiod system. Their underlying mechanisms of action may differ, however, they may act synergistically in conferring analgesia. Nevertheless, the exact mechanism of how sucrose activates the endogenous opiod system remains to be elucidated.

The greatest analgesic effect occurs when sucrose is administered approximately two minutes before the painful stimulus. This interval is thought to coincide with the release of endogenous opiod (Blass 1994). This is supported by the presence of opiod receptors on the tongue and animal studies demonstrating opiod-antagonist reversible analgesia during noxious stimulation (Shide 1989).

The exact concentration by which sucrose is effective as analgesia has not been fully established. From the recent Cochrane review, small doses of 24% sucrose (0.01 to 0.02g) are efficacious in very low birth weight infants while larger doses (0.24 to 0.50g) reduce the proportion of crying time in term infants. A dose range of sucrose for reducing procedural pain in neonates was identified as 0.012 to 0.12g (0.05ml to 0.5 ml of sucrose 24% solution). It is recommended that the sucrose solution be administered two minutes prior to the painful procedure, as the peak effects appears to occur at two minutes and lasts approximately four minutes.

Taddio et al, in his recent study has demonstrated the effectiveness and superiority of sucrose as analgesia when he compared this solution with another pharmacological agent, topical lidocaine during venepuncture in newborn (Taddio et al 2011). In this double blinded trial, 330 healthy term newborns were randomized into 3 groups: first group – received 1 g of topical liposomal lidocaine, second group – received 2 ml 24% sucrose 2 minutes prior to venepuncture, third group- received a combination of topical lidocaine and 24% sucrose. All infants were assessed using the facial grimacing score. The study concluded that 24% sucrose was more effective that

liposomal lidocaine for reducing pain during venepuncture in newborns. The addition of liposomal lidocaine to sucrose did not confer any additional benefit compared to sucrose alone.

The superiority of sucrose over other non pharmacological method of analgesia is further shown by Altun in his study comparing 12.5% sucrose, hindmilk and distilled water. Each newborn infant will be randomized into three groups and will receive 1ml of the test solution before, during and after the heel prick procedure. Assessment of pain was done using the Neonatal Facial Coding System (NFCS) and it was found out that sucrose is more superior than hindmilk in conferring analgesic effect in the newborn (Altun et al 2010).

2.8 HONEY AND ITS BIOLOGICAL PROPERTIES

Honey, a golden yellow viscous fluid containing sugars, results primarily from the transformation and concentration of nectars from flowers by two processes: interaction with the upper digestive tract secretion of the honey bee and concentration by water loss (>80%) in beehives (Biswa 2006). The content and composition of different types of honey vary with different floral sources as well as climatic and environmental condition (Gheldof 2002). As mentioned before, besides being supersaturated with sugars (mainly fructose and glucose), honey is also rich in carbohydrate, minerals, amino acids, protein and vitamins. Besides having these nutritional properties, honey is well known for its functional and biological properties which is conferred by the phenolic compound found in this solution (Viuda 2008). Chemically, phenolic compounds can be defined as substances that possess an aromatic ring bound with one or more hydrogenated substituents, including their functional derivatives (Marin 2001). The main group

of phenolic compounds present in plants is derivatives of cinnamic acid, cumarins and flavonoids (Manthey 2001). In honey, most of the phenolic compounds are in the form of flavonoids, which concentration depends on various factors including plant species used by the bees, health of the plant, season and other environmental factors (Kucuk 2007).

The functional properties of honey includes its capacity as an anti-oxidant, antibacterial, antiviral, anti-inflammatory, cardio-protective effects and prevention of enzymatic browning (Viuda 2008). These biological activity and therapeutic properties have been used for treatment of various diseases in many cultures dating back as far as during the era of Hippocrates, where it is used for the treatment of leg ulcers. In modern medicine, honey has been used successfully in the treatment of burns, graft donor sites, necrotizing fasciitis, neonatal post-op wound infection and skin ulcers. It has been observed both in clinical and experimental studies, that honey not only prevents infection around the wound, but also decreases inflammation and provides rapid tissue healing and epithelialization (Ozlugedik 2006). In addition, there are also well established studies using honey in the treatment of asthma, sore throat, cough and cold as well as prevention of radiation mucositis (Biswa 2006).

Different mechanisms of action have been proposed to account for the biological properties of honey. Its high sugar content and low pH hinders microbial growth. In addition, honey is hygroscopic, resulting in shrinking of bacteria with the aid of its hyperosmolar properties. Furthermore, it can generate hydrogen peroxide, when diluted, through the activation of enzyme glucose oxidase which oxidizes glucose to gluconic acid and hydrogen peroxide (Farrokhi 2011).

The anti-inflammatory and immune modulatory effect can reduce oedema and the amount of tissue exudates by down regulating the inflammatory process. It also reduces pain by reducing both sensitization following inflammation-mediated prostaglandin synthesis and pressure on tissue resulting from oedema (Farrokhi 2011). In another study, Van Den Berg et al showed that buckwheat honey was most effective in reducing reactive oxygen species, thus acting as anti-oxidant and this property is derived from its phenolic constituent (Van Den Berg 2008).

Honey also possess moderate anti tumor and pronounced anti-metastatic effect in five different strains of rat and mouse tumor as demonstrated by a recent study by Grubel and Pashiniski. Compound like caffeic acid, phenethyl ester and flavonoid have been proven to have anti-inhibitory effect on tumor cell proliferation and transformation by down regulation of many cellular enzymatic pathway (Ghandian 2011). Interestingly, in a study concerning medicinal properties of honey in Pakistan, it was demonstrated that the local honey showed anti-nociceptive, anti bacterial and anti-platelet activity. This observation pointed to the potential of honey as an analgesia and anti inflammatory agent (Kamran 2007).

This study was conducted in the hope to illustrate some of the analgesic and anti nociceptive properties of honey using a locally derived Tualang honey. This honey is a wild multi-floral honey found in the Rain Forest of Malaysia. The honey bee species is *Apis Dorsata* which built their hives high up in the Tualang tree (*Koompassia excelsa*) (Zaid S et al 2010). The Tualang honey was sterilized by Gamma irradiation at 25 kGy to eliminate all potential contamination especially botulinum spores. Studies have shown that radiation at 25 to 50 kGy do not affect the

quality of honey used (Yusof et al 2007). The honey was supplied by the Federal Agricultural Marketing Authority (FAMA), Malaysia.