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Research Article

Comparison of gum resin of Bombax malbaricum with Sucrose 24% for use in procedural pain in neonates

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Abstract:
Pain in neonates can be treated with pharmacological as well as non-pharmacological interventional approaches. Under the non-pharmacological pain relief strategies, like non-nutritive sucking, swading, facilitated tucking, oral administration of sucrose, breast feeding and skin to skin contact etc. are the convenient and inexpensive methods which can be adopted without physicians recommendations or prescriptions and are supposed to be well tolerated by infants. Whereas pharmacological methods of neonatal pain relief contains local anesthetics, pre-operative pain subsiding agents like opioids (Morphine) and opioid antagonists, sedatives or hypnotics, vapor anesthetics, NSAIDs and non-opioid analgesics like Acetaminophen. Non pharmacological interventions are better and feasible alternatives to pharmacological methods, concerned to its risk of adverse effects which is minimum. Sucrose and glucose, the most popular substances used for sweet-tasting solutions; as they are effective and easy to use, having no documented adverse effects; also, sucrose and glucose are as inert of pharmacologically neutral substances. The use of orally administered sweet tasting solutions in the management for neonatal pain in the clinical set up is widespread practice which is recommended in both national as well as international guidelines. Though there is no completely acceptable explanation on the pain-reducing effect of these sweet-tasting solutions, but certain mechanisms like activation of endogenous opioids is suggested as a possible mode of actions. Plenty of plant origin drugs are proven to have a analgesics effect in adults with no documented adverse reactions of any kind. These plant origin analgesics are in use since ages and recorded in ancient medical sciences like *Ayurveda*, *Unani* and Chinese Medicine. These plant origin analgesics are needed to be evaluated as a choice of drug in neonates during procedural pain stimulus. The particular study being discussed here has evaluated the pain perception and analgesic activity of *Mocharasa* (Gum resin of *Bombax malbaricum* or *Bombax ceiba*) in neonates and validated and established using pain assessment scales.

Keywords: *Mocharas*, *Bombax ceiba*, *Bombax malbaricum*, neonatal analgesia, procedural analgesia, 24% oral sucrose solution

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Significance Statement:
Procedural pain in neonates which is usually underestimated, is managed by giving Sucrose 24%. Herbal medicine, mentioned in ancient classical texts of Ayurveda and proved to be analgesic in adults can be used for the similar action effectively and safely in neonates.

Introduction and Background:
The fetus is capable of developing and mounting a stress response starting at approximately 23 weeks of gestation [American Academy of Pediatrics, 2016]. The autonomic responses and other markers of the stress response in the immature fetus or pre-term infant are less competent as compared to that of the more matured infant or a child.

Therefore, in immature infants, the common vital sign changes associated with pain or stress and behavioral cues both are non-reliable indicators of painful stimuli. Neonatal reactions to pain may lower the already compromised physiological state such as hypoxia, hypercarbia, acidosis, hyperglycemia or respiratory distress etc. various behavioral and neurological studies are suggestive of that preterm infants experiencing repeated painful procedures and noxious stimuli are having less response to painful stimuli at 18 months as corrected age [McPherson et.al., 2020].

The physiological effects of pain includes changes in signs indicated as variations in the heart rate, blood pressure, intra cranial pressure, respiratory rate, oxygen saturation, color changes or changes observed in muscle tone. Behavioral patterns identified as crying, facial expressions, movements and state changes of the body. Hormonal or Metabolic responses usually causes increase in epinephrine, nor epinephrine, growth hormone and endorphins, whereas it decreases the insulin secretion, secretion of cortisol, glucagon, and aldosterone, leading to increased serum glucose, lactate and ketones thereby developing to lactic acidosis [Sprague et.al., 2011]. Short durational effects of un-treated pain includes reduced tidal volume and volume capacity in the lungs, increase demand in cardio vascular system, hyper metabolism which results into neuroendocrine balances, increased oxygen consumption, hypoxemia, myocardial ischemia, mobilization of endocrine and metabolic resources resulting in variations in blood pressure (Intra Ventricular Hemorrhage), change in the skin color and temperature changes.

Pain in neonates could be treated with a pharmacological and non-pharmacological intervention [Koukou et. al., 2022]. The non-pharmacological pain-relieving strategies are considered to be more convenient, inexpensive, can be undertaken without any prescriptions from physicians which are also well tolerable by infants. Procedural pain in newborns is managed by non-pharmacological interventions like non-nutritive sucking (NNS), swading, facilitated tucking, and administration of oral sucrose, breast feeding and skin to skin contact of the infants. Pharmacological methods for neonatal pain relief usually include methods such as local anesthetics, pre-operative pain relief like opioids (morphine) and opioid antagonists, sedatives or hypnotics, vapor anesthetics, NSAIDs, fentanyl, remifentanyl and alfentanyl an non-opioid analgesics like Acetaminophen (paracetamol).

Pharmacological interventions are not used frequently for procedural pain [Maciel et. al., 2019] due to concerns about the side effects of the drugs and a lack of conviction that pain is important to the infant's present or future well-being. Non pharmacologic interventions are more feasible alternatives to pharmacological methods when concerned about the risk of adverse effects which are negligible or minimal. Various well-conducted research studies have proven the highly concentrated, sweet-tasting solutions when administered orally in infants before the intervention could reduce the pain in newborns [Harrison et. al., 2015] who are undergoing heel stick, venipuncture, or any other painful coetaneous procedures. Sucrose and glucose are the two widely used sweet-tasting solutions; as they are effective and easy to administer and have no documented adverse effects as such; and both sucrose and glucose are considered as an inert pharmacologically neutral substance. The orally administered sweet tasting solutions in the management of neonatal pain in the clinical set up is a widespread practice which is recommended under both the national as well as international guidelines. Though there is no completely acceptable explanation on the pain-reducing effect of sweet-tasting solutions, but certain mechanisms like activation of endogenous opioids is considered to be a possible mode of action.

In *Ayurveda*, the ancient life science of Indian origin has elaborated the *Vedanasthapak (anodynes)* and *Shonitasthapak (styptics)*, two separate divisions of drugs [Singh et. al., 2020] mentioned in *Charak Samhita*, which helps to eliminate the physical pain. *Mocharasa* (Gum resin of *Bombax malbaricum* or *Bombax ceiba*) is one of such drugs that is included in both these groups and is considered as a pain alleviating drug.

Materials and Methods (Study Design):

The present study was designed with the principle objective to assess the analgesic (pain alleviating) effect of *Mocharas* in neonates, comparing it with the standard neonatal analgesic currently prescribed and recommended by American Academy of Pediatrics (AAP). The study was an open ended, randomized, controlled, comparative, two arm clinical trial. The trial was carried out at the special care neonatal unit of Bharati Ayurved Hospital, Pune. A clearance was obtained from the ethics committee/IRB and a total of 100 neonates were studied, 50 neonates were allotted to each arm of the trial study. The subjects were randomly and equally allocated in two groups using the simple randomization method; where alternate neonates were assigned to the specific arms of the trial. The first arm was labelled as the Trial Arm and neonates assigned to this group were administered *Mocharasa* and the other arm was of the established drug, labelled as the Control Arm who were administered 24% sucrose solution. Only full-term neonates delivered vaginally or by caesarean section at Bharati Ayurved Hospital, Pune were included after obtaining a clear informed proxy consent from the respective parents. As per protocol of the study sight, a scheduled blood sampling was being done with the venous blood for routine investigations like blood grouping and a complete blood count, metabolic screening for hypothyroidism, and for estimation of bilirubin levels, after completion of 72 hours of life.

As per the recommended allowance by American Academy of Pediatrics (AAP), a dose of 0.2ml/kg of 24% sucrose solution [Chavan, 2016], was administered orally. The dose for *Mocharasa* usage for a neonate has not been clarified in *Ayurvedic* classics, and therefore, the trial drug was administered in a dose constant comparable to the control drug i.e. it was kept constant as that of 24% sucrose solution, in the form of a saturated suspension prepared in sterile water. This opened a new window to compare the potency and efficacy of a newer drug at the same dosage. The respective drugs were administered in a calculated dose, by a trained nursing staff who would assist the resident doctor for the venous blood collection, over a period of 30 seconds, two minutes prior to the painful prick, in the baby's mouth with a sterile syringe and a needle prick was taken on the dorsum of hand 2 minutes, for a scheduled blood sample collection, after the selected drug had been administered [Jatana, 2003].

Two pain scoring systems, the neonatal infant pain scoring (NIPS) and the pain assessment tool score (PATS) [Luo et. al., 2023, Gomarverdi et. al., 2019] were adopted to assess pain. The data was collected by observations and measurements (observation and scoring of subjective and parameters and measurement of objective measurable variables). The PATS system though contains few objective variables, the others are subjective parameters. The NIPS score was used for measuring pain which included facial expression, crying, and limb movements with breathing pattern. The heart rate (HR), respiratory rate (RR) and systolic neonatal infantile blood pressure (NIBP) were also monitored and recorded. Behavioral responses to pain were monitored by Neonatal Facial Coding System score. In terms of practicality, NIPS is the most acceptable scale. NIPS scale has a high inter-rater reliability as compared to other pain scales based on behavioral changes. It can be used in both full term as well as pre-term infants and is an established scale for the use in NICU. Considering its practical ease and feasibility NIPS pain scale was selected in the present study for assessment of pain. Neonatal Infant Pain Scale is composed of six indicators which use the behaviors that clinicians have described as being indicative of pain or distress in infants. HR and SPO_2 were monitored using pulse oxymeter. Pain response was assessed, by recording duration of crying, change in HR, change in SPO_2 and facial action score after the procedure. Heart Rate, Respiratory Rate, Blood Pressure and SpO_2 were recorded 30seconds before giving the stimulus and were again recorded at 2 minutes and 4 minutes after the stimulus. NIPS (neonatal infant pain scale) and PATS (Pain Assessment tool score) behavioral score was assessed 2-3 minutes after giving stimulus.

The data collected was analyzed by application of 'dependent-t test' for paired data and 'fisher's exact test' to determine if there are non-random associations between two categorical variables.

Observation Tables:

Table No. 01 Mean Weight of enrolled study subjects in both groups

Group	Number of Subjects	Weight (kg)		p Value
		Mean	SD	
Control Group	50	2.97	0.47	0.152
Trial Group	50	2.84	0.44	

Table No. 02 PATS and NIPS scoring on Facial Expressions

		Control Group	Trial Group	Total	p Value
Facial Expressions	**PATS**				
	No Expression	02	00	02	0.025
	Frown	19	31	50	
	Grimace	29	16	48	
	NIPS				
	Relaxed	09	25	34	< 0.001
	Grimace	41	25	66	

Table No. 03 PATS and NIPS scoring on Cry

		Control Group	Trial Group	Total	p Value
Cry	**PATS**				
	No Cry	02	08	10	0.092
	Cry	42	41	90	
	NIPS				
	No Cry	03	06	09	0.204
	Whimper	35	38	73	
	Vigorous Cry	12	06	18	

Table No. 04 PATS and NIPS scoring on Breathing Pattern.

		Control Group	Trial Group	Total	p Value
Breathing Pattern / Respiration	**PATS**				
	Normal	50	47	97	0.242
	Tachypnoea	00	03	03	
	NIPS				
	Relaxed	10	05	15	0.262
	Changed	40	45	85	

Table No. 05 PATS and NIPS scoring on State of Arousal/Sleep Pattern.

		Control Group	Trial Group	Total	p Value
Sleep Pattern / State of Arousal	**PATS**				
	Relaxed	07	25	32	< 0.001
	Agitated or Withdrawn	43	25	68	
	NIPS				
	Sleep/Awake	29	38	67	0.088
	Fussy	21	12	33	

Table No. 06 PATS and NIPS scoring on Posture.

		Control Group	Trial Group	Total	p Value
Posture	**PATS**				
	Extended	17	25	42	0.156
	Flexed	33	25	58	
	NIPS				
Posture of Arms	Relaxed/restrained	9	18	27	0.070
	Flexed/Extended	41	32	73	
Posture of Legs	Relaxed/restrained	14	21	35	0.208
	Flexed/Extended	36	29	65	

Table No. 07 PATS Scoring on Colour of Neonate

		Group		Total	p Value
		Control group	Trial group		
	Cry	48	42	90	
Colour	Pink	36	49	85	< 0.001
	Pale/Dusky/Flushed	14	1	15	

Table No. 08 PATS Scoring for Heart Rate

		Group		Total	p Value
		Control group	Trial group		
Heart Rate	Normal	40	27	67	0.013
	Tachycardia	1	2	3	
	Fluctuating	9	21	30	

Table No. 09 PATS Scoring for Peripheral Saturation of Oxygen

		Group		Total	p Value
		Control group	Trial group		
Saturation	Normal	50	49	99	0.999
	Desaturating	0	1	1	

Table No. 10 PATS Scoring on Blood Pressure

		Group		Total	p Value
		Control group	Trial group		
Blood Pressure	Normal	46	49	95	0.362
	Hypotension/Hypertension	4	1	5	

Table No. 11 Total of PATS and NIPS Score in all Patients.

Total PATS Score	Control group	Trial group	Total	p Value
≤10	44	50	94	0.027
> 10	6	0	6	
Total NIPS Score				
0 – 2	5	7	12	0.032
3 – 4	14	25	39	
> 4	31	18	49	

Table No. 12 Gender Wise PATS and NIPS Score

Total PATS SCORE	**Male**		**Female**	
	Control	**Trial**	**Control**	**Trial**
≤10	25	26	19	24
>10	2	0	4	0
SUM	27	26	23	24
Total NIPS SCORE				
0-2	4	3	1	4
3-O4	9	13	5	12
>4	14	10	17	8
SUM	27	26	23	24

Table No. 13 Effect of Drug on Heart Rate during Venous Sampling

Heart Rate	**Number of patients**	**Control group**		**Trial group**		**Inter group p Value**
		Mean	**SD**	**Mean**	**SD**	
Pre sampling	50	142.2	17.1	138.1	14.4	0.020
During sampling	50	151.6	17.0	144.4	13.0	0.001
Post sampling	50	146.1	19.5	134.3	14.5	0.003

Table No. 13-A Intra group analysis of Heart Rate

Intra group p Value	**Control group**	**Trial group**
Pre sampling to During sampling	< 0.001	0.186
Pre sampling to Post sampling	0.001	0.016

Table No. 14 Effect of Control and Trial Drug on Respiratory Rate

Respiratory Rate	**Number of patients**	**Control group**		**Trial group**		**Inter group p Value**
		Mean	**SD**	**Mean**	**SD**	
Pre sampling	50	32.8	1.2	33.7	1.6	0.003
During sampling	50	33.4	1.5	33.5	1.5	0.640
Post sampling	50	33.9	1.5	33.8	1.5	0.693

Table No. 14-A Intra group Analysis of Respiratory Rate

Intra group p Value	**Control group**	**Trial group**
Pre sampling to During sampling	0.003	0.551
Pre sampling to Post sampling	< 0.001	0.717

Table No. 15 Effect on Peripheral Saturation of Oxygen

SPO_2	**Number of patients**	**Control group**		**Trial group**		**Inter group p Value**
		Mean	**SD(±)**	**Mean**	**SD(±)**	
Pre sampling	50	96.3	2.5	97.1	2.1	0.115
During sampling	50	96.0	2.3	97.1	2.0	0.018
Post sampling	50	96.0	2.4	97.1	2.1	0.020

Table No. 15-A Intra group Analysis of Peripheral Saturation of Oxygen

Intra group p Value	**Control group**	**Trial group**
Pre sampling to During sampling	0.371	0.999
Pre sampling to Post sampling	0.462	0.906

Table No. 16 Effect on Systolic Blood Pressure

Systolic Blood Pressure	Number of patients	Control group		Trial group		Inter group p Value
		Mean	SD(±)	Mean	SD(±)	
Pre sampling	50	76.6	14.1	83.2	18.7	0.643
During sampling	50	83.6	16.0	84.9	18.7	0.983
Post sampling	50	80.1	12.1	75.2	13.8	0.068

Table No. 16-A Intra group Analysis of Systolic Blood Pressure

Intra group p Value	Control group	Trial group
Pre sampling to During sampling	0.014	0.627
Pre sampling to Post sampling	0.188	0.012

Table No. 17 Effect on Diastolic Blood Pressure

Diastolic Blood Pressure	Number of patients	Control group		Trial group		Inter group p Value
		Mean	SD(±)	Mean	SD(±)	
Pre sampling	50	43.4	11.3	42.3	13.1	0.697
During sampling	50	44.1	12.7	44.0	15.5	0.062
Post sampling	50	44.9	9.6	41.1	10.8	0.106

Table No. 17-A Intra group Analysis of Diastolic Blood Pressure

Intra group p Value	Control group	Trial group
Pre sampling to During sampling	0.742	0.485
Pre sampling to Post sampling	0.474	0.170

Table No. 18 Effect on Skin Temperature

Temperature	Number of patients	Control group		Trial group		Inter group p Value
		Mean	SD(±)	Mean	SD(±)	
Pre sampling	50	36.4	0.5	36.5	0.4	0.106
Post sampling	50	36.7	0.5	37.0	0.4	< 0.001

Results and Discussion:

The mean weight of registered subjects was 2.97 kg in the control group as compared to 2.84 kg of those registered in the trial group. The birth weight of the subjects of both the groups were comparable and statistically there was no significant difference as shown by the p value in Table 01. The p values for the analysis of facial expressions (Table 01), colour of the baby during the procedure (Table 07) and heart rate (Table 08), were significant on comparison and analysis of data, whereas, for all other parameters the p values derived were insignificant. The subjective parameters like facial expression, breathing pattern, tone and posture, cry, colour and sleep pattern were analyzed and p values were derived by using the Fisher's exact test whereas p values for objective parameters like the heart rate, blood pressure, peripheral saturation of oxygen etc. were derived by applying the 2 independent sample t-test. In another observation it was also observed that gender does not influence the PATS or NIPS score (Table 12) which disproves the general belief that females have a higher pain threshold as compared to males. The heart rate rose from the base line (pre sampling) during sampling but fell post sampling significantly. The mean heart fell below the baseline in the trial group showing a significant p value (Table 13, 13A). The p values were highly significant during and post sampling. There was no significant effect of control or trial drug on the respiratory rate pre, during and post venous sampling Table 14, 14A) and thus it did not influence the peripheral saturation of oxygen too; the effect was insignificant. The other parameters like the mean systolic and mean diastolic blood pressure, skin temperature, and peripheral saturation of oxygen showed comparable effect of the trial drug and the control drug as the p values derived on inter group correlation were insignificant thus depicting equitable activity of both the drugs (Table 15, 16, 17, 18).

Pain perception is classified into two major types viz. fast perception pain and the slow perception pain, both possessing different characters and having different pathways [McPherson et. al., 2020]. The pain receptors in the skin and tissues are free nerve endings. Nerve fibers usually respond to excessive mechanical stretch which is termed as mechanical pain receptors and those responding to excessive of hot or cold are termed as thermal pain receptors whereas others to specific chemicals in the tissues are the chemical pain receptors. Fast pain is induced by the mechanical and thermal types of receptors, whereas the slow pain can be evoked by all three types of receptors. Bradykinin, serotonin, histamine, potassium ions, acids, and acetylcholine and proteolytic enzymes stimulate chemical type of pains. [Rashmi et. al., 2019]. Prostaglandins increases the sensitivity of the pain endings but does not directly excite those [Meves, 2006]. The pain receptors do not acclimate to the stimulus [Yam et. al., 2018]. Bradykinin causes the pain and is considered to be the single agent which is responsible for causing the tissue damage type of pain [Mathivanan et. al., 2016].

Few mechanisms act to inhibit pain transmission of pain at the spinal cord level and via descending inhibition from higher centers. The periaqueductal grey (PAG) and rostral ventromedial medulla (RVM) are the two important areas of the brain which are involved in descending inhibitory modulation. Both these centers contain high concentrations of opioid receptors. Descending pathways are projected in the dorsal horn which inhibit pain transmission.

Various pharmacological and non-pharmacological therapies and protocols for intervention are adopted in the pain management for infants [Maciel et. al., 2019]. Pharmacological interventions used in procedural are of the concerns about adverse effects. Non-pharmacological pain relief methods on the other hand are convenient, inexpensive, which could be used without recommendation form physicians and are also well tolerable by infants. Non pharmacological interventions are feasible alternatives as compared to the risk of side effects which are eliminated and even if present are to its minimal and non-threatening. Procedural pain in newborn is managed through the non-pharmacological interventions, like nonnutritive sucking (NNS) using a pacifier dipped in sucrose to synergize sucrose analgesia [Liu et.al., 2017], or swaddling which is possible in certain infants of which the result depends on the procedure [Erkut et. al., 2018], or facilitated tucking [Ranjbaret.al., 2020], or oral sucrose administration [Chavan et. al., 2016, Liu et.al., 2017], breast feeding [Koukou et. al., 2022, Shah et. al., 2023] which is supposed to reduce pain and bring a significant difference in the duration of cry [Shalini et. al, 2005], and skin to skin contact by kangaroo care which is proved to be effective in preterm neonates as small as 28 weeks [Sharma et.al., 2022], sweet solutions like sucrose or glucose are also helpful in promoting calmness and reduce pain.

Sucrose, a disaccharide of glucose and laevulose, is supposed to limit the immediate absorption of carbohydrates in the gut. [Taylor et. al., 2019]. 24% Sucrose, when administered orally induces production of endogenous opioids providing analgesic effect for minor procedures [McPherson et. al., 2020, Manasi et.al. 2005]. 24% sucrose is contraindicated in following conditions in infants, i.e. who are at high risk of necrotizing enterocolitis (NEC) [Slaytor et. al., 2010, Krishnan, 2013], asphyxiated infants, the infants with congenital heart disease [Krishnan, 2013] infants not on established feeds [Stevens et. al., 2016], or infants with feeding intolerance [Stevens et. al., 2016], and post-operative infants who need to avoid excessive saliva production [Stevens et. al., 2016].

Behavioral and neurological studies have concluded about the preterm infants who are experiencing repeated painful procedures and noxious stimuli are less responsive to painful stimuli at 18 months of corrected age [McPherson et. al., 2020]. These studies are evidence that neonatal pain and stress are influencing factors for neuro-development and later on they affect the perceptions of painful stimuli and behavioral responses in infants. "The Neurological outcomes and Preemptive Analgesia in Neonates" (NEOPAIN) trial evaluated preemptive analgesia with morphine infusion up to 14 days among ventilated preterm infants which showed no overall difference in the primary composite outcome (neonatal death, severe intra-ventricular hemorrhage [IVH], or per ventricular leukomalacia [PVL]) in placebo and preemptive morphine-treated groups [Puia-Dumitrescu et. al., 2021]. Morphine infusions is to be used cautiously in extreme prematurity or preexisting hypotension. Analgesics or sedatives which have less cardiovascular effects, such as fentanyl or ketamine, can be a better substitute, if required in such neonates.

Newborn children have a functional nervous system, capable of perceiving pain. Infants often develop an enhancements in signs of discomfort with painful procedures, similarly the premature infants may have unpredictable responses to painful stimuli. Due to unmanaged pain in the neonates, long term developmental complications may arise. Painful stimulus can increase physiological effects like changes in normal responses such as variations in heart rate, blood pressure, increased intra cranial pressure, increased or decreased respiratory rate, decreased peripheral saturation of oxygen or increase in oxygen requirement, color changes (pale, poor perfusion or, increased perfusion), increased or decreased muscle tone; behavioral features like crying which may vary from high pitched, tense to soft moaning or whining, facial expressions like grimacing, quivering of chin, squeezing eyes shut, furrowed brow, body movements as like limb withdrawal, fist clenching, hyper tonicity or hypo tonicity, changes in sleep-wake cycles, changes in activity levels-increased fussiness or irritability; hormonal/metabolic responses viz. increased epinephrine and nor epinephrine, growth hormone, cortisol, glucagon, aldosterone and endorphins which may lead to raised plasma glucose, lactate and ketones, reduced insulin secretion finally affecting absorption of fat, protein and glucose.

Short duration effects of untreated pain may result into reduced tidal volume and volume capacity of the lungs, increased work demand of the cardio vascular system, hyper metabolism which results in neuroendocrine balances, increased oxygen consumption, hypoxemia, myocardial ischemia and mobilization of endocrine and metabolic resources resulting in changes in blood pressure, changes in skin color and temperature. The long duration or later effects of untreated pain are suggestive of generating abnormal pathways to be formed in the brain which result in impaired social or cognitive skills and specific patterns of self-destructive behavior, and developmental delays with emotional disorders.

The underlying mode of action of the analgesic effects of sweet tasting solutions is considered to be because of an orally mediated release of endogenous opioids [McPherson et. al., 2020, Manasi et. al., 2005]. Calming effects were seen due to the sweet taste, and not volume dependent, as small volumes of 0.2ml sucrose were equally as effective as larger volumes of 0.6ml and 1.0ml.The effect of sweet taste was peak at two minutes following administration and persisted for around five to eight minutes further [Krishnan, 2013] which is dependent on contact with the tongue, and not by sweet ingestion directly via a nasogastric tube [6, Lee et. al., 2017].

A gummy exudate from the branches and stem of Bombax, known as mochras, contains gallic and tannic acids, L-arbinose, D-galactose, D-galacturonic acid, D-galactopyranose and traces of rhamnose. Extracts testing has proved the presence of 6-O-β-D-galactopyranosyluronic acid-D-galactose. 2, 4, 6-tri-2, 6-di-O-methyl-D-galactose and 2, 3, 4-tri-O-methyl-D-galacturonic acid in equivalent amounts [Seema et. al., 2016]. The active ingredients have shown significant analgesic effect in acetic acid induced writhing and hot plate test in mice which was independent to opioid receptor. A study which evaluated the

membrane stabilizing property and the antioxidizing property of ethyl acetate soluble fraction of *Bombax ceiba* on human red blood cells and sheep red blood cells, also correlated it as a probable mode by which *Bombax ceiba* arbitrates its effects on inflammatory conditions. The result of the study proved the significant anti-inflammatory property in *Bombax ceiba* however, the extract did not show any membrane stabilizing property [Mohammed et. al., 2020]. The study also confirmed that, Methenol Extract of *Bombax Malbaricum* possess anti-inflammatory activity, mediated through inhibition of (NO) production [Mohammed et. al., 2020]. This could be a reason for the gum resin of *Bombax* depicted a procedural analgesic activity, similar to that of 24% sucrose solution in neonates.

Conclusion:

Oral use of Sucrose 24% is proved as an inert agent equally effective like other non-pharmacological methods to induce neonatal analgesia for procedural pain. Plant medicines are also equally effective against nociceptive stimuli showing an equal and comparable effect along with safety to that of Sucrose 24%. This opens a vast scope of research in understanding the plant drugs for the evaluation of their analgesic activity with safer outcomes.

Declaration Section:

Ethical Issues: As humans were involved in this study, ethical clearance/permission was obtained from the ethics committee/IRB of Bharati Vidyapeeth College of Ayurved, Institutional ethical committee.

Competing Interest: None.

Authors Contribution: Rahul Gujarathi, Yogita Chavan conducted the trial, prepared the article; Manish Arora framed the trial study; Shailesh Deshpande finalized the article and Akshar Kulkarni did the literature search and worked with the concepts

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Availability of Data: As per the permission granted by the IRB/Ethics committee the data of the patient cannot be shared as in the form of case sheet. However, if demanded, the master chart of the data would be shared if the committee permits.

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