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Benefits and limitations of the use of glucose for the treatment of pain in neonates: a literature review

Benefícios e limitações da utilização da glicose no tratamento da dor em neonatos: revisão da literatura

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ABSTRACT

This article aims to review the main studies evaluating glucose as a therapeutic alternative during mildly to moderately painful procedures in neonatology, highlighting its benefits and limitations.

During their stay in neonatal intensive care units, neonates are constantly subjected to a number of painful procedures without proper therapeutic management, although the medical literature emphatically recommends this type of management, highlighting the deleterious neurological consequences of pain. Most of these interventions are frequently necessary in neonatal intensive care units to maintain clinical stability in these children; the use of systemic analgesia, however, is not considered to be a good option.

The administration of oral glucose solution is apparently effective and safe for pain control during procedures causing mild-to-moderate pain in neonate intensive care units, with rare adverse effects; however, its mode of action has not yet been described clearly in the literature.

The administration of oral glucose solution is well described for use in venous punctures; it is apparently effective also for heel punctures, especially when associated with nonnutritive sucking, with most studies showing favorable results.

Keywords: Pain/therapy; Infant, newborn; Glucose/therapeutic use

INTRODUCTION

Prematurely delivered children often require therapeutic interventions to maintain their clinical stability. Because of the plasticity and immaturity of their central nervous systems, some interventions, including tactile stimuli, are perceived as painful.[1]

It is estimated that a preterm newborn is exposed to between two and 14 painful procedures daily within the first two weeks of life and may be exposed to more than 100 procedures before hospital discharge.[2] It is also known that from as early as 24 weeks of pregnancy, the neuroanatomical and neurochemical structures necessary for pain recognition are already developed. Therefore, untreated painful interventions during this time may change the brain architecture with both immediate and late effects that may affect the individual's biopsychosocial development.[3]

Painful experiences in newborns have to be evaluated indirectly, by observing changes to physiological and behavioral parameters during the interventions.[4] These physiological changes include the following: heart rate, respiratory rate, blood pressure, saturation of oxygen and hormonal changes. Pain behavioral parameters include facial mimicry,

motor patterns and crying.

Several pharmacological and non-pharmacological therapeutic strategies have been developed and proposed to prevent or reduce pain in the neonate. Restricted and gentle handling, appropriate positioning, music therapy, acupuncture, massage, nonnutritive sucking, sweet solutions and drug therapy are the most often discussed therapeutic alternatives.[5-8]

Oral glucose solution (OGS) has been used for the treatment of pain with favorable results during procedures causing mild-to-moderate pain, or as adjuvant therapy for severe pain.[9-29] The adverse effects of systemic analgesics discourage their routine use in pain control.[30,31] However, in the long term, these untreated painful experiences may result in both physiological and behavioral changes.

The need for neonatal pain control is well described in the literature. Most of the neonatal intensive care units (NICUs) use pain control strategies for procedures causing severe pain. However, procedures causing mild-to-moderate pain are more frequent in NICUs, requiring interventions appropriate for the level of pain intensity. Clinical practice suggests that these procedures are often performed with no analgesic considerations. The use of OGS during procedures causing mild-to-moderate pain is a pain control strategy worthy of consideration.

This article aims to present a literature review concerning the use of oral glucose solution in clinical practice, highlighting the different opinions regarding dosage, concentration, safety and possible induction of tolerance following consecutive administrations. It also aims to point out both the benefits and limitations of this treatment strategy.

Mode of action of oral glucose as an analgesic and potential tolerance induction

The mode of action of oral glucose solution for pain control is not fully understood; however, its effectiveness is well accepted by the scientific community. Two mechanisms are apparently involved in this process, and their combination is believed to provide the analgesia described in the literature.

The first of these mechanisms is the sweet sense stimulation of taste- and pleasure-differentiated cortical areas, a process which promotes both physiologic and sensorial effects.[32] Endogenous opioids are apparently released acting through their receptors (mainly μ receptors), modulating the painful experience.[33,34] The benefits are increased when some type of oral stimulation is provided just before the intervention, such as sucking a pacifier.[9,28] The administration should be made over the tongue, where the sweet sensation receptors are located. By comparison, administration at the lateral portion of the mouth or by nasogastric tube failed to show benefit.[35] Beneficial effects are more frequently observed in newborns and infants less than 12 months of age.[36]

The binding of endogenous opioids to nociceptors thereby modulating neuronal transmission of painful stimuli has been the central hypothesis for the mode of action of oral glucose. This mechanism has been detailed in animal models, where antagonist administration has inhibited this effect.[37] However, Gradin and Schollin[21] conducted a trial in neonates in which naloxone (an antagonist opioid) was given intravenously before OGS administration; the results showed that the analgesic effects were not reduced for the group receiving the antagonist as compared with the control group. These results illustrate that the mode of action of glucose for pain control is not yet fully understood.

Regarding the question of tolerance, this process is known to occur rapidly with opioids, commonly after 72 hours of continuous or intermittent therapy.[38] Because the hypothesized mode of action of oral glucose would be the release of endorphins (endogenous opioids), successive glucose administrations could be thought to result in tolerance and consequent reduction of the anticipated analgesic effects. Therefore, the benefits would be clearer during the early days of hospitalization. The role of tolerance is relevant because glucose has been used intensively in neonatal units, with no relevant considerations regarding concentration, dosage and indications.

The hypothesis of tolerance has been tested only in animal models, not in human studies.[19,37] Four studies evaluated recurrent sucrose dosing, with analgesic effects identified consistently in each study.[39-42]

OGS concentration and dose

Oral glucose dosage and concentration for painful procedures in routine neonatal units care have not been defined. In the available studies, the concentrations have ranged between 10% and 30%, with an administered volume between 0.05 and 2

mL. A 2010 Cochrane review concluded that the data on appropriate glucose doses are inconclusive, and consequently, an optimized dose could not be suggested.[24,43]

Clinical conditions in which OGS is recommended

Despite the advances in neonatal pain control in recent years, procedures causing mild-to-moderate pain tend to be disregarded and consequently, undertreated. Glucose is one of the primary indicated resources for these conditions. Procedures in which OGS has been used include the following: venous and arterial puncture, heel puncture, lumbar puncture, percutaneous catheter installation, venous dissections, subcutaneous and intramuscular injections, removal of skin patches and tapes and removal of drains. When associated with nonnutritive sucking, the paired interventions may result in more effective control of indirect signs of pain.[44,45]

This intervention can be used in association with a pacifier as long as the oral route is not contraindicated, as it is in intubated patients. Continued positive airway pressure (nasal CPAP) does not contraindicate the use of OGS because the volume given is usually not above 2 mL. OGS limitations include oral route contraindications and procedures which require severe pain control measures.

Complications related to analgesic oral glucose are rare and include nausea, vomiting, abdominal distension and sporadic oxygen saturation drops. No study has shown significant contraindications to OGS, except for necrotizing enterocolitis.[45] For this condition, other alternative pain therapies should be considered, both because of the severe pain associated with the procedure (for which glucose therapy would be insufficient) and the absolute oral route contraindication. Wills et al.[46] suggest an association between the frequency of sucrose administration and necrotizing enterocolitis; this association, however, has not been confirmed in clinical practice.

Johnston et al.[39] have indicated that excessive doses of sucrose (≥ 10) as analgesia in newborns at less than 31 weeks of gestacional age could result in impairments in motor development, energy, alertness and orientation at 36 weeks. These are not clinically significant findings, but were additionally investigated. These preliminary finds however need more investigation.

Charts 1, 2 and 3 describe the available clinical trials using oral glucose as pain control therapy in neonates, categorized according to the procedures evaluated: venous puncture, heel puncture and other procedures, respectively.

Chart 1 – Studies using oral glucose solution during venous puncture

Study	Study design	Gestacional age (GA)	N	Dose and concentration	Variables	Results
Carbajal et al. (1999)[9]	Prospective, randomized	Term newborn	150	2 mL glucose 30%.	DAN scale	Sucrose, glucose and pacifier showed analgesic effects; the pacifier was more effective than sweet solutions. Other authors recommend associating sweet solutions with a pacifier.
Eriksson, Gradin, Schollin (1999)[10]	Randomized, controlled, double-dummy	Term newborn	120	1 mL glucose 30%.	Duration of crying, PIPP, heart rate and oxygen saturation	The expression of pain was similar during heel puncture and venous puncture for the groups receiving OGS, and venous puncture was shown to be less painful than heel puncture when glucose was not administered. The heart rate increased in the group receiving glucose (more vigorous sucking and sucking effort) as compared with the group receiving placebo.

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Chart 1 – Continued

Study	Study design	Gestacional age (GA)	N	Dose and concentration	Variables	Results
Deshmukh, Udani (2002)[11]	Randomized, controlled, double-dummy	PA between 28 and 37 weeks, post-natal age 2-7 days	60	2 mL glucose 10% - 25%.	Respiratory rate, heart rate, oxygen saturation, time to first cry	There was no difference regarding heart rate, respiratory rate and hemoglobin oxygen saturation. The first cry duration was reduced in the group receiving glucose as compared with those receiving placebo.
Bauer et al. (2003)[12]	Randomized, controlled, double-dummy	PA between 31 and 42 weeks and post-natal age 1-7 days	58	2 mL or 0.4 mL glucose 30%.	PIPP, crying time, indirect calorimetry, heart rate and oxygen consumption (VO_2)	2 mL glucose 30% is effective for pain control during venous puncture, and the stress caused by the handling required for the puncture results in increased VO_2 and energy expenditure. The authors recommend considering minimal manipulation and combined nonnutritive sucking.
Gradin, Finnstrom, Shollin (2004)[13]	Randomized, controlled, double-dummy	Term newborn	120	1 mL glucose 30%.	PIPP, crying time, VAS (completed by the parents about their child's pain)	Glucose reduces pain during venous puncture in term newborn children. According to the authors, breastfeeding just before the intervention should be recommended.
Gradin (2005)	Randomized, controlled, double-dummy	PA between 36 and 42 weeks	70	1 mL glucose 30%.	Heart rate	Heart rate was increased in the group receiving glucose when compared to the group receiving placebo.
Saththasivam et al (2009)[15]	Clinical trial	Term newborn	66	2 mL dextrose 25%.	NFCS, duration of first cry, total crying time and procedure time	Heel puncture was the most indicated method to evaluate blood glucose, compared to venous puncture when only one puncture was used.
Liu et al. (2009)[16]	Randomized clinical trial	Above 32 weeks	105	2 mL glucose 25%.	NIPS	Nonnutritive sucking and glucose provided statistically significant reduction of the pain score during venous puncture when compared to the control group. Nonnutritive sucking was shown to be more effective than glucose.
Dilen, Elseviers (2010)[17]	Double-dummy clinical trial	Above 32 weeks	246	Glucose 10%, 20%, 30% and placebo.	Leuven Pain Scale and heart rate	2 mL oral glucose 30% before venous puncture was more effective for pain control than the other concentrations and placebo.

DAN - *Douleur Aiguë Du Nouveau-né* (newborn acute pain scale); PIPP - premature infant pain profile; VAS - visual analogue scale.

Chart 2 – Clinical trials using oral glucose solution for heel puncture

Study	Study design	Gestacional age (GA)	N	Dose and concentration	Variables	Results
Eriksson, Gradin, Schollin (1999)[10]	Randomized, controlled, double-dummy	Term newborn	120	1 mL glucose 30%	Crying time, PIPP, heart rate and oxygen saturation	The manifestation of pain was similar during both heel and venous puncture with OGS and venous puncture shown to be less painful than heel puncture when glucose was not administered. The heart rate was increased for the group receiving glucose (more vigorous sucking) as compared with those receiving placebo.
Isik et al. (2002)[18]	Randomized, placebo controlled	Term newborn	113	2 mL glucose 10% or 30%	Crying time, return to baseline, maximal heart rate, and heart rate changes in the 1st, 2nd and 3rd minutes	Sucrose, glucose and placebo were compared. Sucrose controlled pain more effectively than glucose as measured by the crying time.
Akçam, Ormeci (2004)[19]	Randomized, controlled, double-dummy	PA between 37 and 42 weeks	60	0.5 mL glucose 30%	DAN	A 0.5 mL glucose 30% dose was effective for pain control when given as a spray or with a syringe when compared with placebo.
Eriksson, Finnstrom (2004)[20]	Randomized, controlled, double-dummy	Term newborn	57	1 mL glucose 30%	Crying time, PIPP and heart rate	Repeated 1 mL glucose 30% doses for 3 days before heel puncture did not reduce analgesic effects during the procedure in term newborns when compared to the group receiving placebo (sterile water).
Gradin, Schollin (2005)[21]	Prospective, randomized, placebo controlled	Term newborn	30	1 mL glucose 30%	PIPP, mean crying time and heart rate	Administration of an opioid antagonist failed to reduce the analgesic effects of oral glucose during heel puncture.
Gradin (2005)[14]	Randomized, controlled, double-dummy	PA between 36 and 42 weeks	70	1 mL glucose 30%	Heart rate	Heart rate was increased in the group receiving glucose as compared to the group receiving placebo.
Okan et al. (2007)[22]	Randomized, controlled, double-dummy	Less than 37 weeks	31	2 mL glucose 20%	NFCS, crying time, heart rate, respiratory rate and hemoglobin oxygen saturation	Heart rate was increased on the group receiving placebo when compared with the group receiving either glucose or sucrose; no respiratory rate or hemoglobin oxygen saturation differences were found between the groups; the NFCS score was higher and crying time was longer for the placebo group.

Continue...

Chart 2 – Continued

Study	Study design	Gestacional age (GA)	N	Dose and concentration	Variables	Results
Freire, Garcia, Lamy (2008)[23]	Randomized, single-dummy	PA between 28 and 36 weeks	95	1 mL glucose 25%	Heart rate, oxygen saturation, PIPP, facial mimic changes time	Glucose and kangaroo care were compared. Little change was found for relative heart rate, hemoglobin oxygen saturation, duration of facial mimicry and pain scores, which were lower for the group receiving kangaroo care when compared with oral glucose.
Bonetto et al. (2008)[24]	Randomized, double-dummy	Above 36 weeks	76	1 mL glucose 25%	NIPS and PIPP	Glucose, EMLA® and paracetamol were compared during heel puncture. The group receiving glucose had lower pain scores. Paracetamol and EMLA® were not effective for pain control.
Axelin, Salantera, Kirjavainen (2009)[25]	Prospective, randomized, placebo controlled	Premature between 28 and 32 weeks	20	0.2 mL glucose 24%	PIPP	Compared parental contact, glucose, opioid and placebo in preterm newborns. Mean PIPP score was lower for the group receiving glucose and parental contact as compared with placebo. Opioid was similar to placebo for both procedures. Parental contact should be considered as a pain control strategy.
Saththasivam et al.(2009) [15]	Clinical trial	Term newborn	66	2 mL dextrose 25%	NFCS, first cry time, total crying time and procedure time	Heel puncture was the most indicated method to evaluate blood glucose, compared to venous puncture when only one puncture was used.
Weissman et al. (2009)[26]	Prospective clinical trial	Term newborn	180	2 mL glucose 30%	NFCS and heart rate	Sucking and breastfeeding during heel puncture was shown to be more effective for pain control when compared with oral glucose solution.
Slater et al (2010)[27]	Randomized, double-dummy, placebo controlled	Between 37 and 43 weeks	44	0.5 mL Sucrose 24%	PIPP and NIRS	The behavioral score PIPP was significantly lower for the group receiving glucose when compared to the control group. However, no statistically significant difference was found for the magnitude or latency of the spinal nociceptive reflex, suggesting that glucose does not affect brain activity or nociceptive circuits in newborns, and may be ineffective as an analgesic strategy.

PIPP - premature infant pain profile; DAN - *Douleur Aiguë Du Nouveau-né* (newborn acute pain scale); NFCS - neonatal facial coding system; NIPS - neonatal infant pain scale; NIRS – infrared spectroscopy

Chart 3 – Clinical trials using oral glucose solution for other painful interventions

Study	Procedure	Study Design	Gestacional age (GA)	N	Dose and concentration	Variables	Results
Carbajal et al. (2002)[28]	Subcutaneous injection	Prospective, randomized	PA ≤ 32 weeks, and less than 48 hours life	40	0.3 mL glucose 30%	DAN scale	A 0.3 mL oral glucose solution 30% is effective for pain control, and the scores trended to be lower for the group receiving glucose in association with a pacifier.
Axelin, Salantera, Kirjavainen (2009)[25]	Heel puncture and pharyngeal suction	Prospective, randomized, placebo controlled	PA between 28 and 32 weeks	20	0.2 mL glucose 24%	PIPP	Compared parental contact, glucose, opioid and placebo in premature newborns. Mean PIPP score was lower for the group receiving glucose and parental contact when compared with placebo for both procedures. Parental contact should be considered as a pain control strategy.
Chermont, Falcão, de Souza Silva, et al (2009)[29]	Intramuscular injection of hepatitis B vaccine	Prospective, randomized, partially masked	Healthy term newborns	640	1 mL dextrose 25%	NIPS, PIPP and NFCS	Oral dextrose was compared to skin-skin contact. The use of an oral dextrose 25% solution reduced the duration of the painful procedures for the studied population. Skin-skin contact reduced pain intensity and duration. The combination of both interventions was more effective than each of them alone in healthy term newborns.

DAN - *Douleur Aiguë Du Nouveau-né* (newborn acute pain scale); VAS - visual analogue scale; PIPP - premature infant pain profile.

COMMENTS

The first study proposed to evaluate the effectiveness of glucose for pain control was published in 1991[47], and 298 articles were published through 2010. After the first Cochrane review in 2010, 50 studies have investigated the use of oral glucose as a pain control strategy;[36] from these, only 3 were conducted in Brazil. The most studied procedures were heel puncture and venous puncture, followed by intramuscular injection.

The results of these studies indicate that oral glucose is effective for pain control during venous puncture in neonates, along with the recommended complementary interventions of nonnutritive sucking and kangaroo care.

The use of OGS during heel puncture apparently mitigates pain as compared to placebo or topical analgesics. However, heel puncture is comparatively more painful than venous puncture, and mild-to-moderate pain control strategies are apparently less effective for this procedure.

For other procedures causing mild-to-moderate pain, more studies are necessary to confirm OGS effectiveness for pain control; however, some studies suggest that this intervention is effective during subcutaneous and intramuscular injections and pharyngeal suction.

The data is insufficient to describe the effects of oral glucose solution for prolonged procedures, such as ophthalmologic examinations and urinary bladder catheterization, as well as during the immunization of children older than 12 months.

A study by Slater et al.[27] used infrared spectroscopy (NIRS) to evaluate the correlation between behavioral changes and cortical activation during painful

interventions when oral glucose solution was used as a therapeutic strategy; the results showed that even with a statistically significant reduction of the behavioral score (premature infant pain profile - PIPP), cortical activation was observed even in the group receiving oral glucose solution, suggesting that it was ineffective for pain control. However, more studies are necessary to confirm this conclusion.

CLOSING REMARKS

OGS administration is apparently effective and safe for pain control during mildly to moderately painful procedures in neonatal intensive care units. Adverse effects are rare, and the mode of action is still incompletely described in the literature. The indication for OGS during venous punctures is well described; for heel punctures, it is apparently the most effective method of pain control, especially when associated with nonnutritive sucking, showing favorable results in most studies. Both the 2001 consensus on pain management in newborns and the 2009 guideline for painful procedures in newborns recommended using sucrose as adjuvant therapy during arterial punctures, lumbar punctures and the insertion of percutaneous catheters in association with other methods such as topical and systemic analgesics.

The use of infrared spectroscopy will assist in the confirmation of behavioral strategies for the evaluation of pain and in the development of appropriate therapeutic strategies for each painful procedure.

RESUMO

Esta revisão se propõe analisar os estudos que utilizaram a glicose como recurso terapêutico em neonatologia durante procedimentos que resultam em dor de intensidade leve a moderada apontando os benefícios e limitações de sua utilização.

Os recém-nascidos internados em unidades neonatais são submetidos a inúmeros procedimentos dolorosos sem abordagem terapêutica adequada, apesar de a literatura recomendar de maneira enfática a necessidade de tratamento e ressaltar as repercussões neurológicas deletérias para esses pacientes. A maior parte destas intervenções constitui procedimentos frequentemente realizados nas unidades e necessários à manutenção da estabilidade clínica, nos quais a analgesia sistêmica não está indicada.

A administração de solução oral de glicose parece ser eficaz e segura no controle da dor durante procedimentos que geram dor de intensidade leve a moderada nas unidades de terapia intensiva neonatais, os efeitos adversos são raros e o mecanismo de ação ainda não está descrito de maneira consistente na literatura. A indicação da solução oral de glicose durante punções venosas é bem descrita e durante punções de calcanhar parece ser o método mais eficaz de controle da dor especialmente quando associado à sucção não nutritiva, com resultados favoráveis na maior parte dos estudos.

Descritores: Dor/terapia; Recém-nascido; Glucose/ uso terapêutico

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