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Topical anesthesia in preterm neonate: a reflection on the underutilization in clinical practice

Anestesia tópica em recém nascidos prematuros: uma reflexão acerca da subutilização deste recurso na prática clínica

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ABSTRACT

Premature neonates are customarily submitted to invasive painful procedures necessary to maintain clinically stability during their stay in NICUs. Topical anesthesia is a good option to be considered for interventions causing mild to moderate pain, with the advantage of not having systemic effects. In Brazil the most known topical anesthetic available is the eutectic mixture of local anesthetics (EMLA[®] cream). Its efficacy for skin painful procedures is well established both in children and adults. Its use in neonates has been investigated also due to the increased risk of methemoglobinemia. The

procedures where topical anesthesia would be better indicated are those related with mild to moderate pain such as arterial and venous puncture, heel puncture, lumbar puncture and percutaneous central line installation. The studies in the literature have so far lead to controversial conclusions, mainly depending on the type of procedure and also on very different methodologies. Direct pain evaluation could decrease methodological bias, leading to more accurate topical anesthesia efficacy evaluation also allowing comparisons of the indirect pain measures used so far.

Keywords: Anesthesia, local; Pain; Infant, newborn; Infant, premature

INTRODUCTION

Preterm neonates are exposed to a range of painful interventions, particularly during their first week of life. Respiratory, neurological and immunological immaturities require these interventions, needed for life support. It is estimated that a preterm newborn is exposed to between 2 and 14 painful procedures daily during their first two weeks of life, eventually reaching up to 100 procedures before hospital discharge.⁽¹⁾

The newborn feels pain, as neuroanatomic and neuroendocrine pathways, needed for noxious stimuli transmission are fully developed by the 30th week of pregnancy.⁽²⁾ Currently is a big challenge creating prevention and therapy strategies for procedures causing mild to moderate pain, as those leading to severe pain are more frequently approached. These procedures include most of the interventions, and there is a trend to underestimate their pain, resulting in inappropriate therapeutic approach. Untreated pain may affect children's physiological stability and behavioral adaptation generating emotional and learning disorders changing the newborn's final brain architecture, then in the synap-

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genic phase.^(3,4) This distress could be prevented if evaluation and treatment suitable for each intervention level protocols were developed.

Among the most common procedures in newborns are the venous, arterial, lumbar and heel punctures. Pain control measures during these procedures range from environmental adaptation (light and noise reduction), comfortable positioning, oral glucose or breast milk either or not associated with pacifiers, until drug therapy with either topical or systemic analgesia. Regarding oral glucose, Stevens et al.⁽⁵⁾ concluded that its administration is effective for pain control and should be used two minutes before the intervention, being the adverse effects mild and basically limited to mild saturations drops, not requiring important interventions. Regarding breast feeding and breast milk, Shah et al.⁽⁶⁾ concluded that both can be used for pain control and were effective strategies. Breast milk administration had similar results to glucose/sucrose administration.

This article main purpose is to review and discuss the use of topical analgesia as main or adjuvant therapy for mild to moderate pain control, specifically in preterm newborns.

General comments on topical anesthesia

Topical anesthesia is used for acute pain prevention and therapy, and its main advantage is providing local analgesia with no systemic effects.⁽⁷⁾ Topical anesthetics prevent nervous impulse transmission, promoting skin analgesia by acting on the free dermal terminations. They act blocking the nervous impulse conduction by sodium influx inhibition, resulting in increased threshold for nerve excitation until losing the ability of action potential generation.⁽⁸⁾ Topical anesthesia may be divided in two categories: physical and chemical.⁽⁹⁾ Among the physical methods are iontophoresis and phonophoresis, used to increase anesthetic agents absorption. Cryotherapy can be also included among physical methods, however the mucosal cold transference mechanism and its effects are disputable.⁽¹⁰⁾

Regarding chemical methods, we can mention: 1) conventional methods, with a saline solution formation, dissolution in organic solvent, and oil in water emulsion synthesis; 2) eutectic mixture; 3) incorporation of the anesthetic agent into a patch or peeling method; and 4) anesthetic involvement in liposomal membrane.⁽⁹⁾

The corneal layer is the main barrier to the topical anesthetic applied over intact skin distribution.⁽¹¹⁾ The skin preferably absorbs molecules soluble in lipids in aqueous base, because the keratin layer is composed also by water.^(8,12,13)

The skin has two absorption ways: cutaneous and percutaneous.⁽¹⁴⁾ Cutaneous absorption refers to the drug entry within the several layers, while percutaneous regards the entry through the skin into the vessels. The optimal situation is the local anesthetic effectively entering the corneal layer, acting on the nervous terminations, without diffusing into the blood stream.⁽¹⁵⁾

One of the most important limitations for topical anesthesia use is that is necessary to allow time of drug contact with skin to allow absorption, making this strategy only suitable for elective procedures. In urgent situations, other therapeutic strategies should be considered.

In the last two decades, many topical anesthetic brands were developed for use over intact skin: eutectic lidocaine/prilocaine (EMLA[®], AstraZeneca), 0.4% tetracaine gel (Ametop[®], Smith & Nephew) and 4% liposomal lidocaine (LMX4[®], Dermomax Ferndale Labs). Several international trials have used as topical analgesic in preterm newborns Ametop[®] compared with EMLA[®].^(7,16,17) In Brazil, the available topical drugs are EMLA[®] and more recently Dermomax[®], with the advantage of needing less contact time.⁽¹⁸⁾ However, the most used in clinical practice and investigated topical anesthetic is the lidocaine/prilocaine eutectic mixture, EMLA[®].⁽¹⁷⁾

EMLA[®] in preterm newborns pain control - use and adverse effects

EMLA[®] is a 5% local anesthetics eutectic mixture (lidocaine 2.5% and prilocaine 2.5%) marketed as a cream, recommended for pain therapy in children older than 3 months and adults. The generally used dose is one to two grams over the intact skin, occluded with a manufacturer's recommended hypoallergenic tape.⁽¹⁷⁾

EMLA[®] effectiveness during skin procedures is well established both in children and adults, and the side effects are limited to local skin reactions (contact dermatitis) and a local vasoconstrictive effect⁽¹⁷⁾ which could difficult venous puncture. However, the efficacy has been tested in newborns, and the studies lead to different conclusions.⁽¹⁹⁻²¹⁾ In addition, the risk of side effects in this age group is

increased, due to the increased risk of methemoglobinemia (MetHb).⁽¹⁷⁾

Prilocaine has a toxic metabolite, o-toluidine, that can lead to methemoglobinemia by direct hemoglobin oxidation. Three factors may increase methemoglobinemia risk: (1) low levels of Met-Hb reductase,⁽²²⁾ enzyme responsible for reducing Met-Hb oxidation; (2) increased absorption, due to skin immaturity, particularly during the first week of life; and (3) a larger body surface area exposed to the cream.⁽²³⁾ Some drugs may act as methemoglobinemia inducers when associated with EMLA[®], due to hemoglobin oxidation augmentation. The main inducer drugs, which should not be concomitantly given with local anesthesia are: sulfonamides, acetaminophen, sodium nitroprussiate, valproic acid and phenytoin.⁽²⁴⁾

Methemoglobinemia is a clinical syndrome caused by increased blood methemoglobin concentration.⁽²⁵⁾ Methemoglobinemia's main feature is central cyanosis, without saturation drop (as the sensor can't detect the hemoglobin saturating particle), which may lead to decreased tissue oxygen availability, once hemoglobin is saturated by the toxic metabolite o-toluidine.^(26,27) It may be either congenital or acquired, being more frequent the acquired form.^(28,29) The most common congenital cause of methemoglobinemia is B5-reductase (CB5R) cytochrome deficiency, by autosomic recessive inheritance.⁽³⁰⁾ Methemoglobin levels below 3% are considered normal. Between 3 and 15%, clinical manifestations are seldom observed, and when present, only grayish skin color is perceived. When serum levels surpass 15%, systemic features are seen as dyspnea, metabolic acidosis, heart arrhythmias, seizures and central nervous system depression.⁽²⁴⁾ The clinical picture is generally mild, and the treatment consists in withdrawing the inducer agent, high flux oxygen administration and serum levels monitoring. Methemoglobin returns to baseline levels within 36 hours.⁽³¹⁾

When significant clinical changes are seen (dizziness, headache, anxiety, dyspnea, manifestations of low heart output, drowsiness and seizures), methylene blue should be used as specific antidote.⁽³²⁾ A systematic literature review on EMLA[®] for acute newborn pain treatment has shown that the risk of methemoglobinemia is low following a single cream dose.⁽¹⁷⁾ In full term newborns, the dose used was 0.5 to 2 g, and in preterm newborns the dose ranged between 0.5 and 1.25 g.⁽¹⁷⁾ According to the authors,

the safety data on repeated dose EMLA[®] in preterm neonates are insufficient, however, single dose was shown to be safe in 26 weeks-old pregnancy or older neonates.⁽¹⁷⁾ Prilocaine concentration following EMLA[®] use is considerably lower than the toxic level, considered as 5 mg/dl.⁽³³⁾

Procedures where topical EMLA[®] analgesia can be used

Among the main procedures in newborn babies with an indication for topical anesthesia are: venous and arterial puncture, heel puncture, lumbar puncture and percutaneous catheter installation. For procedures pain treatment, topical analgesia can still be used as adjuvant therapy. EMLA[®] was also studied for pain control in neonates during circumcision, and was shown to be effective in physiological and behavioral changes reduction. However, in this case, other more effective analgesic measures should be considered, as dorsal penis nerve blockade.^(34,35)

The chart 1 and 2 shows EMLA[®] clinical trials in newborns during the most common mild to moderate pain procedures.

COMMENTS

Venous puncture

– Lindh V, Wiklund U, Hakansson S. (2000)⁽²⁰⁾: changes on heart rate, spectral heart rate variation, and crying incidence during venous puncture were analyzed. The results showed increased heart rate in the control group, with no between groups differences on crying frequency. The crying time was not evaluated. It was concluded that EMLA[®] reduces the venous puncture stress response.

– Acharya AB, Bustani PC, Phillips JD, et al. (1998)⁽²¹⁾: the results showed no statistical significance for any control and treated groups variables .

– Abad F, Diaz-Gómez NM, Domenech E, et al. (2001)⁽³⁶⁾: 24% glucose was more effective than EMLA[®] for pain control.

– Gradin M, Eriksson M, Holmqvist G, et al. (2002)⁽³⁷⁾: PIPP (Premature Infant Pain Profile) score was better in the glucose group versus EMLA[®], as well as the crying duration. Heart rate was not different between the groups.

– Larsson BA, Tannfeldt G, Langercrantz H, et al. (1998)⁽¹⁹⁾: the EMLA[®] treated group had statistically significant less pain during venous puncture, and no complication was seen.

Chart 1- EMLA® clinical trials in newborns during venous or arterial puncture

Study	Procedure	Design	Pregnancy age/ Age	Patients #	Dose/ time	Variables
Lindh V, Wiklund U, Hakansson S. (2000) ⁽²⁰⁾	Venous puncture	Randomized, controlled, double-masked	Heathy newborns; 3 days	60	Not drescribed/ 1 hour before	Heart rate and crying time
Acharya AB, Bustani PC, Phillips JD, et al. (1998) ⁽²¹⁾	Venous puncture	Randomized, controlled, double-masked	26 to 33 weeks	19	0.5 mL with 1h occlusion	Heart rate, oxygen saturation, blood pressure, facial activity, crying, local reactions, MetHb concentration
Abad F, Diaz-Gómez NM, Domenech E, et al. (2001) ⁽³⁶⁾	Venous puncture	Randomized, controlled, double-masked	Full term newborn	51	1g for 45'to 60'	Crying time, heart rate, respiratory rate and oxygen saturation
Gradin M, Eriksson M, Holmqvist G, et al. (2002) ⁽³⁷⁾	Venous puncture	Randomized, controlled, double-masked	> 36 weeks newborns, > 24 h and < 30 days of life	201	0.5g, occlusion for 1 h	PIPP, crying duration and local reactions
Larsson BA, Tannfeldt G, Langercrantz H, et al. (1998) ⁽¹⁹⁾	Venous puncture	Randomized, controlled, double-masked	Full term newborns	120	0.5ml , occlusion for 1 h	NFCS and crying
Gourrier E, Karoub P, El Hanache A, et al. (1995) ⁽³⁹⁾	Venous and arterial puncture	Cohort, non-randomized study	Full term and pre-term newborns	116	1.25g (in > 2Kg babies) 1to 2 hours occlusion	Heart rate, oxygen saturation and behavioral pain score

NFCS – neonatal facial coding scale; PIPP – preterm infant pain profile.

The literature points to EMLA® effectiveness on venous puncture pain control, which looks less effective than glucose. However, the different methodologies, particularly regarding the evaluated parameters and the evaluation scales, render these results inconclusive.

Percutaneous catheter placement

– Garcia OC, Reichberg S, Braion LP, et al. (1997)⁽³⁸⁾: the heart rate was attenuated on the EMLA® treated group ($P < 0.05$). Respiratory rate was attenuated only during the puncture. Blood pressure and oxygen saturation were not significantly changed between the groups. The values for heart and respiratory rates, blood pressure and oxygen saturation were not described in the study.

One single study evaluated EMLA® during percutaneous catheter placement, using only physiological parameters as analysis variables, which have interference from several aspects not considered, such as accommodation phenomena, newborns age and hospitalization time.

Arterial puncture

– Gourrier E, Karoub P, El Hanache A, et al. (1995)⁽³⁹⁾: mean pain behavioral score was lower in the EMLA® treated group. Similarly, the mean heart rate was lower in the EMLA® treated group. Arterial puncture looks to be more painful, when compared with venous puncture. EMLA® looks to be more effective on pain treatment during venous puncture than during artery puncture.

Regarding arterial puncture, there are no sufficient literature data to either indicate or contraindicate EMLA® for the procedure. Arteries are known innervated structures, and that arterial puncture causes moderate pain. The use of EMLA® looks promising during this procedure.

Lumbar puncture

– Enad D, Salvador A, Brodsky NL, et al. (1995)⁽⁴⁰⁾: EMLA® was not effective for lumbar puncture pain. The scale used and the values found were not described in the study.

Chart 2 – Clinical trials using EMLA® in newborns during lumbar puncture, heel puncture and percutaneous catheter placement

Study	Procedure	Design	Pregnancy age	Patients #	Dose / time	Variables
Enad D, Salvador A, Brodsky NL, et al. (1995) ⁽⁴⁰⁾	Lumbar puncture	Randomized, controlled, double-masked	≥ 34 weeks newborns	49	1g for 1 h	Heart rate, blood pressure, O ₂ saturation and behavioral response (0-3 score)
Kaur G, Gupta P e Kumar A. (2003) ⁽⁴¹⁾	Lumbar puncture	Randomized, controlled, double-masked	≥ 34 weeks newborns	60	1g occlusion for 60' to 90'	NFCS, heart rate, O ₂ saturation
Ramaioli F, Amici De D, Guzinska K, et al. (1993) ⁽⁴³⁾	Heel puncture	Randomized, controlled, double-masked	29-36 weeks newborns	20	0.5g for 30'	Heart rate, blood pressure, respiratory rate and Prechtl behavioral scale.
Mcintosh N, van Vem L, Brameyer H. (1994) ⁽⁴⁴⁾	Heel puncture	Placebo controlled	26 to 34 weeks newborns	35	Not reported	Heart rate, respiratory rate, blood pressure, O ₂ saturation, and CO ₂ concentration
Larsson BA, Jylli L, Langercratz H, Olsson GL. (1995) ⁽⁴²⁾	Heel puncture	Randomized, controlled, double-masked	36.8 to 42.6 weeks newborns	112	0.5g occlusion 10', 20', 30', 40', 50', 60', 90' and 120'	Crying and flexion pattern (legs and arms movements)
Stevens B, Johnston C, Taddio A, et al. (1999) ⁽⁴⁵⁾	Heel puncture	Randomized, controlled, double-masked	30 to 36 weeks newborns	120	0.5g occlusion for 30' (phase I) and occlusion 1 h (phase II)	PIPP and MetHb levels
Garcia OC, Reichberg S, Braion LP, et al. (1997) ⁽³⁸⁾	Percutaneous catheter placement	Randomized, controlled, double-masked	Very low weight newborns	13	1 to 1.25g 1 h before	Heart rate, respiratory rate, systolic blood pressure, O ₂ saturation, clinical methemoglobinemia parameters

NFCS - newborn facial coding scale; PIPP- preterm infant pain profile.

– Kaur G, Gupta P e Kumar A. (2003)⁽⁴¹⁾: EMLA® effectively reduced pain during insertion of the needle into the lumbar region.

The results on analgesia during lumbar puncture warrant further investigation, based on the different results probably because the different methodologies used.

Heel puncture

– Larsson BA, Jylli L, Langercratz H, Olsson GL. (1995)⁽⁴²⁾: the crying duration was not significantly different between the EMLA® and control treated groups.

– Ramaioli F, Amici De D, Guzinska K, et al. (1993)⁽⁴³⁾: no significant between groups differences were identified for any of the variables.

– Mcintosh N, van Vem L, Brameyer H. (1994)⁽⁴⁴⁾: this study suggests that EMLA® does not reduce pain during heel puncture.

– Stevens B, Johnston C, Taddio A, et al. (1999)⁽⁴⁵⁾: no difference was found between the treatment and control groups for heel puncture.

All studies pointed to lack of EMLA® efficacy on heel puncture, even using different methodologies. Probably different skin textures and local blood flow

determine this results compared to EMLA® in other body tissues.

No article evidenced methemoglobinemia in preterm newborns with one single EMLA® dose. Literature data, although encouraging, are still not sufficient to assure the safety of repeated EMLA® dosing.⁽¹⁷⁾

FINAL COMMENTS

Topical analgesia has been studied as a relevant therapeutic tool for pain control, particularly in procedures causing mild to moderate pain. Opiates adverse effects frequently limit their use in these procedures.^(17,46) Thus, pain during such procedures trends to be ineffectively treated. Non-drug control interventions for the painful neonatal experiences have also been studied, with emphasis on sweet oral solutions and breast milk, with proven effectiveness during several procedures except for heel puncture.^(5,6,47)

In Brazil, the scientific community most tested topical anesthetic in newborns is EMLA®. The studies conducted so far lead to different conclusion, mainly depending on the procedure performed.⁽³⁶⁻⁴⁵⁾ These differences are also due to very different methodologies, with small samples, failures on pregnancy age specification, inaccurate data on dosage and cream covered area, different scales and different evaluation variables, different times of exposure to the cream (ranging from 30 to 120 minutes), different skin characteristics and local blood flow.^(17,48) Thus, further studies are warranted to allow more a wider topical analgesia recommendation as a therapeutic strategy during the most performed neonatal painful procedures.

It is seen in clinical practice that topical analgesia, although safe regarding risk of methemoglobinemia, is still a seldom used resource. This can be attributable to the difficulty of designing pain evaluation protocols to be used in connection with treatment

protocols. As pain is not appropriately diagnosed, can't be correctly treated. For this, the possibility of implementing direct pain evaluation methods, e.g., infrared spectroscopy,^(49,50) can be useful to show that preterm neonates can conduct and cortically interpret noxious stimuli. Comparison of indirect and direct pain evaluation methods results may enlighten the best evaluation strategy, minimizing methodology biases and making the proposed treatments able to render more accurate conclusions.

RESUMO

Recém nascidos prematuros são submetidos a muitos procedimentos invasivos dolorosos durante o período de internação, necessários à manutenção da estabilidade clínica. Uma boa opção a ser considerada no tratamento de intervenções que causam dor de intensidade leve a moderada é a anestesia tópica, que tem como vantagem a ausência de efeitos sistêmicos. No Brasil o medicamento tópico disponível e mais utilizado para essa situação é a mistura eutética de lidocaína e prilocaína (EMLA®). Sua eficácia para o tratamento da dor durante procedimentos cutâneos é bem estabelecida em crianças e adultos. A utilização em neonatos tem sido investigada pela comunidade científica também em decorrência do risco aumentado para desenvolvimento de metemoglobinemia. Os procedimentos mais realizados em recém-nascidos nos quais a anestesia tópica poderia ser indicada como terapia principal são: punção venosa e arterial, punção de calcanhar, punção lombar e a instalação de cateter percutâneo. Os estudos realizados até então tem levado a diferentes conclusões, dependendo principalmente do procedimento a ser realizado e em função de metodologias muito diversificadas. A alternativa de uma avaliação direta da experiência dolorosa poderia minimizar o viés metodológico permitindo uma avaliação mais precisa da eficácia da anestesia tópica assim como comparar os métodos indiretos utilizados até então.

Descritores: Anestesia local; Dor; Recém nascido; Prematuro

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