CIÊNCIAS DA VIDA E DA SAÚDE
LIFE AND HEALTH SCIENCES
CIENCIAS DE LA VIDA Y LA SALUD

millenium 35

Millenium, 2(19), 35-44.

en

DOSAGEM DA MISTURA EUTÉTICA DE ANESTÉSICO LOCAL EM RECÉM-NASCIDOS: UMA REVISÃO SCOPING
EUTECTIC MIXTURE OF LOCAL ANESTHETICS' DOSAGE IN NEWBORNS: A SCOPING REVIEW
DOSIFICACIÓN DE MEZCLA EUTÉCTICA ANESTÉSICA LOCAL EN NEONATOS: UNA REVISIÓN SCOPING

Fátima Prior[1] https://orcid.org/0000-0003-2781-4314
Débora Querido[1] https://orcid.org/0000-0001-6756-2938
Íris Santos[1] https://orcid.org/0000-0002-1953-0349

[1] Hospital Dr. José de Almeida, Unidade de Cuidados Especiais Neonatais e Unidade de Cuidados Intermédios Pediátricos, Cascais, Portugal

Fátima Prior - fatima.frazao.prior@hospitaldecascais.pt | Débora Querido - debora.jorge.querido@hospitaldecascais.pt | Íris Santos - iris.dinis.santos@hospitaldecascais.pt

Corresponding Author
Fátima Prior
Avenida Brigadeiro Victor Novais Gonçalves
2755-006 – Alcabideche – Portugal
fatima.frazao.prior@hospitaldecascais.pt

RECEIVED: 29th May, 2022
ACCEPTED: 08th September, 2022

m19

Prior, F., Querido, D., & Santos, I. (2022).
Eutectic Mixture of Local Anesthetics' dosage in newborns: a scoping review. *Millenium, 2*(19), 35-44.
DOI: https://doi.org/10.29352/mill0219.27268

RESUMO

Introdução: A Mistura Eutética de Anestésico Local (EMLA) está facilmente disponível, não sendo amplamente utilizado na população neonatal por falta de evidência quanto a uma dose adequada para administração.
Objetivos: Identificar como o creme EMLA é utilizado para reduzir a dor, sem reação adversa, nos recém-nascidos sujeitos a procedimentos dolorosos.
Métodos: Revisão *scoping* para mapear a literatura respeitante à população, conceito e contexto (PCC) em estudo, considerando literatura obtida de bases de dados científicas e literatura cinzenta publicada entre 2002 e 2021, com texto completo disponível e sem restrições de linguagem.
Resultados: Doze documentos respeitantes a 2661 recém-nascidos – desde as 28 semanas de idade gestacional até recém-nascidos de termo – considerando a eficácia e descrevendo a quantidade e tempo de contacto com a pele do EMLA creme. Oito protocolos recomendam o uso de penso oclusivo. Um documento descreveu reações de palidez e eritema na pele
Conclusão: O EMLA é eficaz quando utilizado em recém-nascidos sujeitos a procedimentos dolorosos. A quantidade mais utilizada é de 0,5g em recém-nascidos pré-termo e 1g nos recém-nascidos de termo. O tempo mais frequente de contato com a pele é de 60 minutos. Sendo estas as dosagens mais frequentes, o intervalo identificado é de 0,5 a 2g na quantidade utilizada, e o tempo de contato com a pele de 3 a 180 minutos. A utilização de penso oclusivo é descrita na maioria dos protocolos.

Palavras-chave: recém-nascido; dor; anestésicos locais; EMLA Creme

ABSTRACT

Introduction: Although Eutectic Mixture of Local Anesthetics (EMLA) is an easily available solution, it is not yet widely used in neonatal care due to the lack of evidence of an effective administration dosage.
Objectives: Identify how EMLA cream is used to reduce pain, without adverse reaction, in newborn infants undergoing painful medical procedures.
Methods: A scoping review was conducted to map literature concerning a population, concept, context (PCC) question, considering literature from electronic databases and gray literature, published between 2002 and 2021, with full-text available and with no language restrictions.
Results: Twelve documents concerning a 2661 newborn population – from 28 weeks gestational age until full-term newborns – considering EMLA cream efficacy and describing EMLA cream's amount and skin contact time. Eight protocols recommend the use of an occlusive dressing. One paper identified pallor and erythema reactions.
Conclusion: EMLA is effective when used in newborns undergoing painful procedures. Although there is no consensus on EMLA cream's dosage, the most frequent amount used is 0,5g in pre-term newborns and 1g in full-term newborns. The most common time of skin contact is 60 minutes. Although this is the most frequent dosage, the amount ranges from 0,5 up to 2g, and the time of skin contact ranges from 3 to 180 minutes. Most of the protocols have included occlusive dressing use.

Keywords: newborn; pain; local anesthetics; EMLA Cream

RESUMEN

Introducción: Aunque el uso de la crema EMLA está fácilmente disponible, todavía no se usa ampliamente en la población neonatal debido a la falta de evidencia sobre la dosis adecuada para su administración.
Objetivos: Identificar la dosificación de la Mezcla Eutéctica Anestésica Local (EMLA) en recién nacidos para reducir el dolor, sin reacción adversa, en recién nacidos sometidos a procedimientos médicos.
Métodos: Se realizó una revisión *scoping* para mapear la literatura sobre la población, concepto y contexto (PCC) en estudio, considerando literatura obtenida de bases de datos científicas y literatura gris publicada entre 2002 y 2021, con texto completo disponible y sin restricciones de idioma.
Resultados: Doce documentos relacionados con 2661 recién nacidos, desde las 28 semanas de edad gestacional hasta recién nacidos a término, que consideraron la efectividad de la crema EMLA y describieron la cantidad y el tiempo de contacto con la piel de la crema EMLA. Ocho protocolos recomiendan el uso de un vendaje oclusivo. Un documento describía reacciones de palidez y eritema en la piel.
Conclusión: Doce documentos relacionados con 2661 recién nacidos, desde las 28 semanas de edad gestacional hasta recién nacidos a término, que consideraron la efectividad de la crema EMLA y describieron la cantidad y el tiempo de contacto con la piel de la crema EMLA. La mayoría de los protocolos recomiendan el uso de un vendaje oclusivo.

Palabras Clave: recién nacido; dolor; anestésicos locales; EMLA Crema

Prior, F., Querido, D., & Santos, I. (2022).
Eutectic Mixture of Local Anesthetics' dosage in newborns: a scoping review. *Millenium, 2*(19), 35-44.
DOI: https://doi.org/10.29352/mill0219.27268

INTRODUCTION

Newborns, in particular those who need to be admitted in neonatal intensive care units, undergo several procedures that cause pain, mostly procedures related with punction – venous, heel or lumbar punction.
Preventing acute pain in newborns by providing a combination of nonpharmacologic and pharmacologic therapy is the best way to prevent short and long-term consequences of adverse neurodevelopmental effects, especially in pre-term infants (Anand, 2019).
The Eutectic Mixture of Local Anesthetics (EMLA) is a mixture in equal parts of Prilocaine and Lidocaine and is known as an effective way to reduce pain during procedures. However, there are doubts about safe dosage in newborns, especially because of the risk of increasing Methemoglobinemia – identified in the 1990s (Frey & Kehrer, 1999; Dutta, 1999) – but that further studies demonstrated to be residual (ANMPS, 2016; EMA, s.d.).
The objective of this review is to identify how EMLA cream is used to reduce pain, without adverse reaction, in newborn infants undergoing painful medical procedures. Those procedures can be performed at a hospital, at primary care or even at home.
This aim is expressed in the research question "Which Eutectic Mixture of Local Anesthetics cream dosage is used in newborns undergoing painful procedures?"
A preliminary search for previous scoping reviews and systematic reviews – or their protocols registration – was made at Pubmed, Prospero and OSF, with no results. This scoping review protocol is registered at OSF with doi:10.17605/OSF.IO/YKD85.

Review Question and inclusion criteria
The research question **"Which Eutectic Mixture of Local Anesthetics cream dosage is used in newborns undergoing painful procedures?"** was defined with PCC methodology, where:

- Population: Healthy newborn infants up to 28 days old (considered preterm if born before 37 weeks gestational age, or full-term if born after 37 weeks gestational age).
- Concept: To understand which dosage of EMLA cream is needed to reduce pain related to medical procedures in newborns. This will be assessed by two described outcomes: (1) reducing pain during procedure – pain assessment with a validated scale/procedure – and (2) the dosage of EMLA cream used: amount, time of skin contact, and if an occlusive dressing was used.
- Context: Painful procedures during medical care can occur at different settings like hospital, primary care or even at home if the medical care is provided there.

1. METHODS

The present scoping review is guided by JBI Manual for Evidence Synthesis (Peters et al., 2020), and PRISMA ScR Extension Fillable Checklist (Tricco et al, 2018) is used to report guidance.

1.1. Search Strategy

In order to search for relevant literature, we used PubMed, CINAHL, MEDLINE and Cochrane Database of Systematic Reviews via EBSCO, as well as RCAAP (Repositórios Científicos de Acesso Aberto de Portugal), DGS'site (Direção Geral de Saúde) and SPN' site (Sociedade Portuguesa de Neonatologia) to review relevant gray literature in Portugal.
MeSh search terms were identified and the search phrase ((((Pain[MeSH Terms]) OR (acute pain[MeSH Terms])) OR (Pain, procedural[MeSH Terms])) AND (((Lidocaine, Prilocaine Drug Combination[MeSH Terms]) OR (Eutectic Mixture of Local Anesthetics[MeSH Terms])) OR (EMLA Cream[MeSH Terms]))) AND (Newborn[MeSH Terms]) was created. Filters "full-text", and "timeline 2002 - 2021" were applied, in order to find the most recent evidence with full access to the document. The filter "Apply equivalent subjects" at EBSCO was unselected. There was no idiom restriction. For gray literature search, the terms used in Portuguese were "EMLA", "dor" and "recém-nascido", with the same full-text and timeline filters at RCAAP, not applied on the other websites. The search was made in February 2022.
The inclusion criteria were: newborn population up to 28 days old (both pre-term and full-term); the EMLA cream's protocol should describe the amount of cream and time of skin contact; and EMLA cream must have shown effectiveness in pain reduction.
After retrieving the documents, evidence selection was made by deduplication, title analysis, abstract analysis, and full-text analysis.
There were identified 12 documents: 8 trials, 2 reviews and 2 guidelines, describing a population of 2.661 newborns from 28 weeks of gestational age until full-term.
Result's synthesis is presented in a table where key findings as amount of EMLA Cream and skin contact time are described, as well as other relevant considerations.
The PRISMA diagram (Page et al., 2021) (Figure1) shows how selection has progressed.

Prior, F., Querido, D., & Santos, I. (2022).
Eutectic Mixture of Local Anesthetics' dosage in newborns: a scoping review. *Millenium, 2*(19), 35-44.
DOI: https://doi.org/10.29352/mill0219.27268

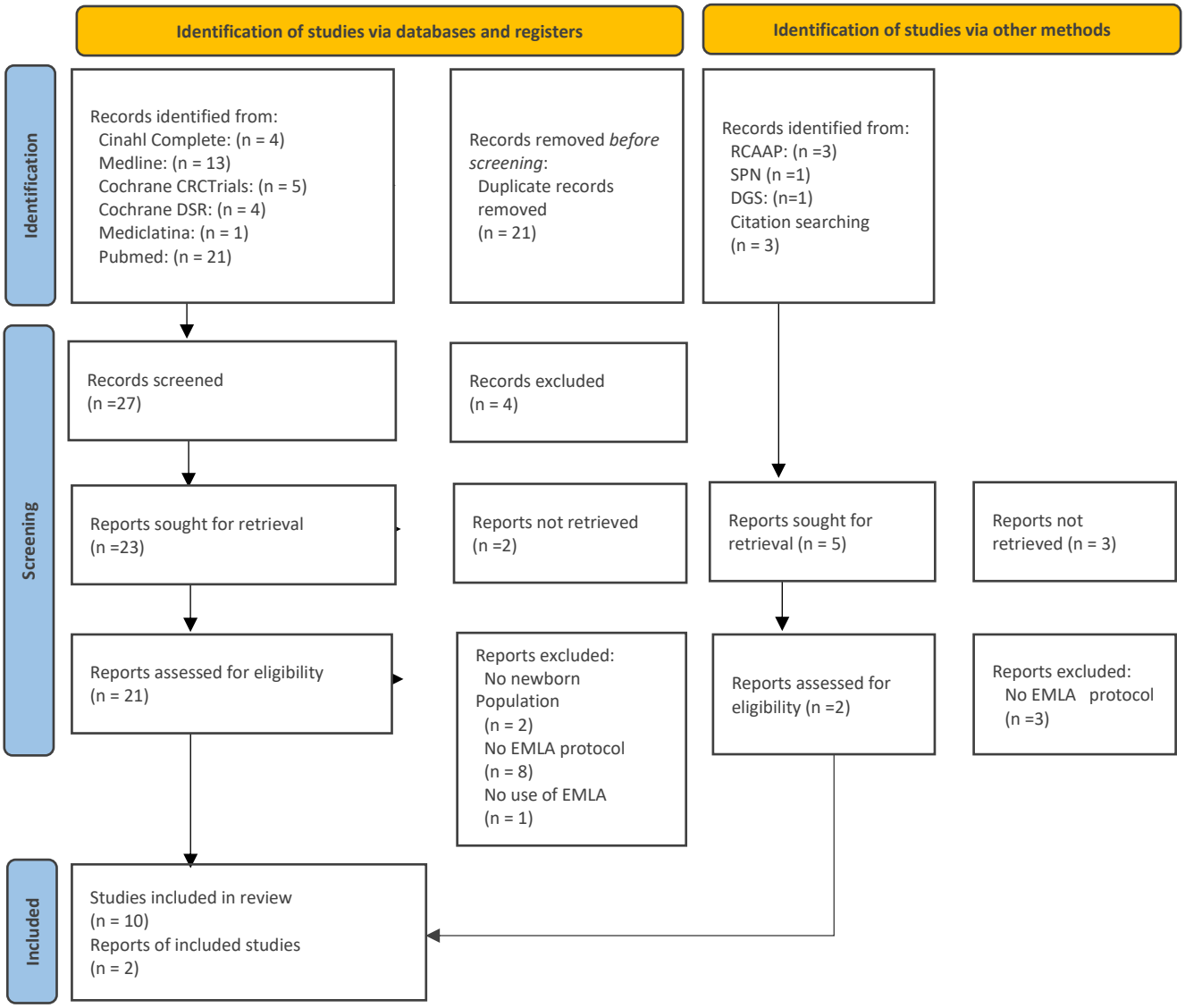

Figure 1 – PRISMA Flow Diagram

2. RESULTS AND DISCUSSION

The analysis of the 12 selected documents pointed to the following results.

2.1. EMLA cream's efficacy

The studies that compared EMLA cream with placebo demonstrated that EMLA is effective in pain reduction in newborns (Biran et al., 2011; Kaur et. al, 2003).

Studies comparing EMLA cream with oral sweet solutions are more controverse: one study shows that EMLA cream was more effective than sucrose (24% glucose oral solution) and that the combination of both EMLA cream and sucrose was even more effective (Al Qahtani et. al, 2014); another study concludes that 30% glucose was more effective than EMLA cream (Gradin et. al, 2002); and another study concludes that 25% glucose was as effective as EMLA cream (Guzmán-Arteaga et. al, 2013). The study that compares EMLA cream with pacifier and sucrose use, and with pacifier and sucrose association (Mucignat et al., 2004), concludes that the most effective was the combination between EMLA cream, pacifier sucking and sucrose administration.

Analyzing the results, we verified that EMLA cream is not effective at heel lancepain (Halimaa, 2003), but has shown efficacy at circumcision (Al Qahtani et. al, 2014; Brady-Fryer et. al, 2004; Modekwe et. al, 2019; Sharara-Chami et al., 2017), venipuncture (Biran et. al, 2011; Gradin et. al, 2002; Guzmán-Arteaga et. al, 2013; Halimaa, 2003), lumbar puncture (Kaur et. al, 2003), and subcutaneous injections (Mucignat et al., 2004).
At circumcision analgesia studies, EMLA cream alone is not as effective as Dorsal Penile Nerve Block (DPNB) (Modekwe et. al, 2019), but if used in association with sucrose and Ring Block (RB) it has demonstrated more efficacy than DPNB (Sharara-Chami et al., 2017).

2.2. EMLA cream's dosage

Two protocols didn't distinguish EMLA cream's dosage between pre-term and full-term newborns (Kaur et. al, 2003; DGS, 2012). Portuguese national guideline doesn't recommend the usage of EMLA before 32weeks of gestational age, recommending a 0.5g/dose of cream (DGS, 2012). The other study's population were late-premature (>34 weeks) and full-term newborns, with a recommendation of 1g/dose (Kaur et. al, 2003).

Pre-term Newborn

In the selected articles, preterm gestational age ranges from 28 (Guzmán-Arteaga et. al, 2013) to 37 (Halimaa, 2003) weeks.
The EMLA cream's protocol concerning pre-term newborns (Biran et. al, 2011; Brady-Fryer et. al, 2004; Rocha, 2004; Guzmán-Arteaga et. al, 2013; Halimaa, 2003; Mucignat et al., 2004; DGS, 2012) recommends the use of 0,5g of EMLA cream, although a systematic review identifies a 1,25g dosage for circumcision (Brady-Fryer et. al, 2004).
The systematic review included in this scoping identified a range between 3 and 180 minutes of EMLA cream skin contact. 60 minutes seems to be the most consensual skin contact time (Biran et. al, 2011; Guzmán-Arteaga et. al, 2013; Mucignat et al., 2004). However, one protocol considered that it might be effective from 30 minutes (Halimaa, 2003) and the two guidelines' protocols considered more time - 80 minutes (Rocha, 2004) and 90 minutes (DGS, 2012).

Full-term newborn

For full-term newborns, 1g of EMLA cream is the most frequent amount used (Al Qahtani et. al, 2014; Kaur et. al, 2003; Modekwe et. al, 2019; Mucignat et al., 2004). However, one protocol considered less quantitity (Gradin et. al, 2002), while a previous systematic review considered a range from 0,5 to 2g (Brady-Fryer et. al, 2004), and the Portuguese Neonatology Society considers a range from 1 to 2g (Rocha, 2004). One study specifies the distribution of 1g in 1 square inch (Kaur et. al, 2003), and the Portuguese national guidelines (DGS) recommend a maximum of 1g per day (DGS., 2012).
60 minutes is also the most consensual period of skin contact time for full-term newborns (Al Qahtani et. al, 2014; Gradin et. al, 2002; DGS, 2012), although one study used a 120-minute skin contact protocol (Modekwe et. al, 2019), and two other protocols considered a range from 60 to 80 minutes (Rocha, 2004) or to 90 minutes (Kaur et. al, 2003). A review identified a range from 10 to 180 minutes when the procedure is the newborn's circumcision (Brady-Fryer et. al, 2004).

2.3. Occlusive dressing use

Most of the retrieved protocols referred the use of an occlusive dressing during the EMLA cream's skin contact (Biran et. al, 2011; Rocha, 2004; Gradin et. al, 2002; Guzmán-Arteaga et. al, 2013; Kaur et. al, 2003; Modekwe et. al, 2019; Mucignat et al., 2004; DGS, 2012). Most of them do not identify how that dressing is done, although two of them identified the use of plastic wrap (Biran et. al, 2011; Mucignat et al., 2004), and another one identified the use of Tegaderm® dressing (Sharara-Chami et al., 2017). One study considered the dressing removal as a moment that can induce stress or pain, so an additional 10-minute time was given (Biran et. al, 2011).

2.4. EMLA's adverse reactions

Some reactions were identified on the considered studies, such as erythema and mild skin pallor (Brady-Fryer et. al, 2004). Methemoglobin levels were evaluated in one study during a period of 12 hours, with no significant rise (Halimaa, 2003).
Data results are summarized in Table1. It expresses EMLA cream's protocol, detailing: the amount of cream; time of skin contact; the use of an occlusive dressing and EMLA cream's effect reducing pain.

Prior, F., Querido, D., & Santos, I. (2022).
Eutectic Mixture of Local Anesthetics' dosage in newborns: a scoping review. *Millenium, 2*(19), 35-44.
DOI: https://doi.org/10.29352/mill0219.27268

Table 1 - Scoping EMLA

Title	Authors, Year and Country	Aim and Kind of document	Population, Intervention and Context	Key Findings
Effect of lidocaine-prilocaine eutectic mixture of local anaesthetic cream compared with oral sucrose or both in alleviating pain in neonatal circumcision procedure	Al Qahtani R, Abu-Salem LY, Pa K. 2014 Saudi Arabia	Assess the effectiveness of eutectic mixture of local anesthetic (EMLA) cream compared with oral sucrose and both in alleviating pain in neonatal circumcision. Clinical Trial prospective and randomized	- 90 full-term newborn males - Circumcision - Day care surgery department	- Amount of EMLA Cream: 1g - Skin contact: 60 minutes - Other considerations: use of occlusive dressing. N-PASS scores were significantly lower in group using combination of EMLA cream and oral sucrose (median = 5.2), comparing with using only EMLA cream (= 5.8), or only sucrose (= 8.5).
Analgesic Effects of EMLA Cream and Oral Sucrose During Venipuncture in Preterm Infants	Biran V, Gourrier E, Cimerman P, Walter-Nicolet E, Mitanchez D, Carbajal R. 2011 France	Assess EMLA analgesic effects thru sucrose plus application of a placebo cream or sucrose plus EMLA cream Clinical trial prospective, controlled, randomized, and double-blind.	- 76 Newborns younger than 37 weeks' gestational age (age range 28.4-36 weeks) - Venipuncture for blood sampling - NICUs	- Amount of EMLA Cream: 0.5g - Skin contact: 60 minutes - Other considerations: nonocclusive dressing (plastic wrap). Wait for additional 10 minutes to allow recovery from any constriction of the vein or any stress associated with removal of the dressing before procedure. This protocol was associated with Sucrose. DAN and PIPP scales and crying time measure demonstrated less pain score during and after procedure.
Pain relief for neonatal circumcision	Brady-Fryer B, Wiebe N, Lander JA. 2010 Canada	Assess the effectiveness and safety of interventions for reducing pain at neonatal circumcision. Systematic review of effectiveness	- 35 trials involving 1,997 newborns - Thirty-three trials enrolled healthy, full-term neonates, and two enrolled infants born preterm (>34.5 and >36 weeks). - Circumcision - Hospital settings	Pre-term: - Amount of EMLA Cream: 0.5g to 1.25g - Skin contact: 3 to 180 minutes before procedure Full-term: - Amount of EMLA Cream: 0.5g to 2g - Skin contact: 10 to 180 minutes before procedure - Other considerations: Erythema and mild skin pallor were observed with the use of EMLA. Methemoglobin levels were evaluated in two trials of EMLA, and results were within normal limits. Compared to placebo, EMLA was also effective, but was not as effective as DPNB. Both interventions appear to be safe for use in newborns. None of the studied interventions eliminated the pain response to circumcision.
Analgesia e Sedação	Rocha G, Proença E, Fernandes P, Matos A, Costa T, Carreiro H, Areias, A 2004 Portugal	Portuguese Neonatal Society Clinical consensus Guideline	- Pre-term and full-term newborns - Venipuncture, arterial punction, peripherally inserted central catheter, venous central catheter, lumbar punction, heel punction, vascular debridement (venous or arterial), supra-pubic punction, subcutaneous and intramuscular injection (with precaution – studied in children and not in newborns)	Pre-term: - Recommendation for >32weeks and >7 days of life. - Amount of EMLA Cream: 0.5g - Skin contact: 60 to 80 minutes Full-term: - Amount of EMLA Cream: 1g to 2g – maximum of 2g/day - Skin contact: 60 to 80 minutes - Other considerations: use of occlusive dressing
Pain Reduction at Venipuncture in Newborns: Oral Glucose Compared with Local Anesthetic Cream	Gradin M, Eriksson M, Holmqvist G, Holstein A, Schollin J. 2002 Sweden	To compare 30% oral glucose with EMLA cream. Controlled, randomized, and double-blind study.	- 201 Newborns with gestational age >36 weeks and a postnatal age >24 hours but <30 days at entry of the study. - Venipuncture - Neonatal intensive care units and maternity ward.	- Amount of EMLA Cream: 0.5 g - Skin contact: 60 minutes. Wait for 15 minutes to start procedure. - Other considerations: use of occlusive dressing on the dorsal aspect of the hand and covered it with an occlusive dressing. Concludes that 30% oral glucose seems to be better than EMLA.
Efecto Analgésico de la Solución Glucosada al 25% vs Crema EMLA. Evaluación por la Escala de PIPP	Guzmán-Arteaga, AN, Fajardo-Ochoa F, Ramírez-Rodríguez CA, Alvarez-Hernández G. 2013 Mexico	To compare 25% glucose with EMLA cream Controlled, randomized, and double-blind study.	- 24 Premature babies >28 and <36.6 weeks gestational age - Venipuncture for blood sampling - Hospital setting	- Amount of EMLA Cream: 0.5 g - Skin contact: 60 minutes. - Other considerations: use of occlusive dressing. Conclusion: 25% dextrose solution and the application of EMLA cream were equally effective.
Pain management in nursing procedures on	Halimaa SL 2003	To develop a process describing procedural pain	- Premature babies (<37 weeks, with no other specifications)	- Amount of EMLA Cream: 0.5 g - Skin contact: 30-60 minutes.

Title	Authors, Year and Country	Aim and Kind of document	Population, Intervention and Context	Key Findings
premature babies	Finland	management in premature babies Literature Review with content analysis	- Blood sampling, intravenous and arterial catheter placement, during reservoir injections, lumbar punctures, epidural placement, minor skin procedures, and in circumcisions. - Hospital settings	- Other considerations: concludes EMLA cream is safe for small newborn babies, detecting no significant rise in methemoglobin levels during a period of 12 hours. Is not effective in alleviating heel lance pain in newborn babies.
A Randomized Trial of Eutectic Mixture of Local Anesthetics During Lumbar Puncture in Newborns	Kaur G, Gupta P, Kumar A. 2003 India	To determine the efficacy of a topical anesthetic cream, eutectic mixture of local anesthetics (EMLA), in alleviating pain associated with lumbar puncture in newborns Randomized double-blind placebo-controlled trial	- 60 consecutive newborns (gestational age, >34 weeks) undergoing diagnostic lumbar puncture. - Topical application of 1 g of EMLA or placebo 60 to 90 minutes before lumbar puncture - Neonatal intensive care unit of a university teaching hospital	- Amount of EMLA Cream: 1g in a 1sq in area of skin. - Skin contact: 60-90 minutes. - Other considerations: use of an occlusive dressing. EMLA is an efficacious agent for reducing the pain associated with needle insertion and withdrawal during lumbar puncture in newborn.
Comparison of the Efficacy of Eutectic Mixture of Local Anesthetics (EMLA) and Dorsal Penile Nerve Block (DPNB) in Neonatal Circumcision	Modekwe VI, Ugwu JO, Ekwunife OH, Osuigwe AN, Obiechina SO, Okpalikel IV, Orakwe JC 2019 Nigeria	To determine how the analgesic efficacy of EMLA compares with that of DPNB in neonatal plastibell circumcision. Prospective randomized study	- 110 male full-term neonates - EMLA vs DPNB as preprocedural analgesia in circumcision. -Pediatric surgery unit	- Amount of EMLA Cream: 1g - Skin contact: 120 minutes. - Other considerations: use of occlusive dressing. EMLA produces analgesic effect. However, DPNB provides a better analgesia than EMLA for neonatal plastibell circumcision.
Analgesic effects of Emla cream and saccharose solution for subcutaneous injections in preterm newborns: a prospective study of 265 injections	Mucignat V, Ducrocq S, Lebas F, Mochel F, Baudon JJ, Gold F 2004 France	To compare the analgesic effects of non-nutritive pacifier sucking, oral administration of a 30% sucrose solution, local application of Emla and their association for subcutaneous injection of erythropoietin (EPO) in preterm infants Randomised, prospective study	- 33 Neonates <33 weeks gestational age >8 days of life were included if they were treated with EPO (three subcutaneous injections per week for 6 weeks). - Non-nutritive pacifier sucking Vs oral administration of 0.2–0.5 ml of a 30% sucrose solution with non-nutritive pacifier sucking Vs local application of EMLA with non-nutritive pacifier sucking Vs oral administration of 0.2–0.5 ml of a 30% sucrose solution with local application of EMLA and with non-nutritive pacifier sucking. - Neonatal Unit	- Amount of EMLA Cream: 0.5g - Skin contact: 60 minutes. - Other considerations: occlusive dressing with plastic wrap. Association use with pacifier and sucrose demonstrate being the most effective in pain reduction.
Orientações técnicas sobre o controlo da dor nos recém-nascidos (0 a 28 dias)	Direção-Geral da Saúde (DGS) 2012 Portugal	National guideline	- >32 weeks of gestational age and >7 days of life. - Venipuncture, arterial punction, peripherally inserted central catheter, venous central catheter, lumbar punction, vascular debridement, supra-pubic punction, subcutaneous and intramuscular injection.	- Amount of EMLA Cream: 0.5g/doses. Maximum 1g/day. - Skin contact: 60-90 minutes. - Other considerations: occlusive dressing. Not indicated if there is skin injury, congenital or idiopathic methemoglobinemia, or simultaneous treatment with paracetamol, phenobarbital, or phenytoin.
Combination Analgesia for Neonatal Circumcision: A Randomized Controlled Trial	Sharara-Chami R, Lakissian Z, Charafeddine L, Milad N, El-Hout Y. 2017 Lebanon	Determine the optimal pain management strategy for circumcision Double-blinded randomized controlled trial	- 70 Late preterm and term newborn (36-41 weeks) - Circumcision analgesia with EMLA + sucrose Vs. EMLA + sucrose + dorsal penile nerve block (DPNB) Vs. EMLA + sucrose + ring block (RB) Vs EMLA cream alone. - Nursery	- Amount of EMLA Cream: 1 g - Skin contact: 60 minutes. - Other considerations: wrapped with Tegaderm® dressing. The most effective analgesia is RB combined with oral sucrose and EMLA cream. Both DNPB and RB had lower scores than the first intervention group (EMLA + sucrose) and the control EMLA, particularly during the most painful stage.

Prior, F., Querido, D., & Santos, I. (2022).
Eutectic Mixture of Local Anesthetics' dosage in newborns: a scoping review. *Millenium, 2*(19), 35-44.
DOI: https://doi.org/10.29352/mill0219.27268

CONCLUSION

EMLA cream has shown efficacy to reduce pain in newborns undergoing painful procedures, especially on procedures where needles are used.
There is no consensus on which EMLA dosage is safe to use in newborns.
In pre-term newborns, 0,5g is the most frequent amount and 60 minutes is the most common time of skin contact, with ranges that can vary from 0,5 to 1,25g in the amount, and from 3 to 180 minutes in skin contact time.
Considering full-term newborns, 1g is the most frequent amount and 60 minutes is the most frequent skin contact time, with ranges that can vary from 0,5g up to 2g in the amount, and from 10 until 180 minutes in skin contact time.
Although most reviewed protocols have included the use of an occlusive dressing during the EMLA cream usage, there is no evidence of advantage in this procedure.

Implications of the findings for research

EMLA cream's efficacy in newborns has been described for decades, although there is still a lack of consensus in protocols and guidelines. This scoping systematizes information in order to helpfully encourage further studies on this matter, especially in pre-term newborns.

Limitations

Gray literature reviewed only considered Portuguese references.

REFERENCES

Al Qahtani, R., Abu-Salem, L. Y., & Pal, K. (2014). Effect of lidocaine-prilocaine eutectic mixture of local anaesthetic cream compared with oral sucrose or both in alleviating pain in neonatal circumcision procedure. *African Journal of Paediatric Surgery: AJPS,* 11(1), 56–61. https://doi.org/10.4103/0189-6725.129236

Anand, J. S. (2019). Discovering Pain in Newborn Infants. *Anesthesiology,* 131, 392–395 https://doi.org/10.1097/ALN.0000000000002810

Autoridade Nacional do Medicamento e Produtos de Saúde. (2016). Emla 25 mg/g + 25 mg/g creme lidocaína + prilocaína. Retrieved from: https://cdn.121doc.com/images/pt/product/8/Emla.pdf

Biran, V., Gourrier, E., Cimerman, P., Walter-Nicolet, E., Mitanchez, D., & Carbajal, R. (2011). Analgesic effects of EMLA cream and oral sucrose during venipuncture in preterm infants. *Pediatrics,* 128(1), e63-70. https://doi.org/10.1542/peds.2010-1287

Brady-Fryer, B., Wiebe, N., & Lander, J.A. (2004). Pain relief for neonatal circumcision. *Cochrane Database of Systematic Reviews*, 3, Art. No.: CD004217 https://doi.org/10.1002/14651858.CD004217.pub2

Direção-Geral da Saúde (2012). *Norma:024/2012- Orientações técnicas sobre o controlo da dor nos recém-nascidos (0 a 28 dias).* Retrieved from:https://www.dgs.pt/directrizes-da-dgs/orientacoes-e-circulares-informativas/orientacao-n-0242012-de-18122012-png.aspx

Dutta, S. (1999). Use of eutectic mixture of local anesthetics in children. *The Indian Journal of Pediatics*, 66(5), 707-715. https://doi.org/10.1007/BF02726260

European Medicines Agency. (s.d.). *Resumo da avaliação científica do EMLA creme e nomes associados.* Retrieved from: https://www.ema.europa.eu/documents/referral/emla-cream-article-30-referral-annex-ii_pt.pdf

Frey, B., & Kehrer, B. (1999). Toxic methaemoglobin concentrations in premature infants after application of a prilocaine-containing cream and peridural prilocaine. *European Journal of Pediatics*, 158(10), 785-788. https://doi.org/10.1007/s004310051204

Gradin, M., Eriksson, M., Holmqvist, G., Holstein, A., & Schollin, J. (2002). Pain reduction at venipuncture in newborns: oral glucose compared with local anesthetic cream. *Pediatrics*, 110(6), 1053-1057. https://doi.org/10.1542/peds.110.6.1053

Guzmán-Arteaga, A. N., Fajardo-Ochoa, F., Ramírez-Rodríguez, C. A., & Alvarez-Hernández, G. (2013). Efecto Analgésico de la Solución Glucosada al 25% vs Crema EMLA. Evaluación por la Escala de PIPP. *Boletin Clinico Hospital Infantil Del Estado de Sonora*, 30(2), 56–62.

Halimaa, S. L. (2003). Pain management in nursing procedures on premature babies. *Journal of Advanced Nursing,* 42*(6)*, 587-597. https://doi.org/10.1046/j.1365-2648.2003.02662.x

Kaur, G., Gupta, P., & Kumar, A. (2003). A randomized trial of eutectic mixture of local anesthetics during lumbar puncture in newborns. *Archives of Pediatrics & Adolescent Medicine,* 157*(11),* 1065–1070. https://doi.org/10.1001/archpedi.157.11.1065

Modekwe, V. I., Ugwu, J. O., Ekwunife, O. H., Osuigwe, A. N., Obiechina, S. O., Okpalike, I. V., & Orakwe, J. C. (2019). Comparison of the efficacy of eutectic mixture of local anesthetics (EMLA) and dorsal penile nerve block (DPNB) in neonatal circumcision. *Nigerian Journal of Clinical Practice, 22*(12), 1737–1741. https://doi.org/10.4103/njcp.njcp_266_19

Mucignat, V., Ducrocq, S., Lebas, F., Mochel, F., Baudon, J.J., & Gold, F. (2004). Analgesic effects of Emla cream and saccharose solution for subcutaneous injections in preterm newborns: a prospective study of 265 injections. *Archives de Pédiatrie*, 11(8):921-925. https://doi.org/10.1016/j.arcped.2004.03.028

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., & et al. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*, 372: n71. https://doi.org/10.1136/bmj.n71

Peters, M. D. J., Godfrey, C., McInerney, P., Munn, Z., Tricco, A.C., & Khalil, H. (2020). Chapter 11: Scoping Reviews. In: Aromataris, E., Munn, Z. (Editors). *JBI Manual for Evidence Synthesis*. https://doi.org/10.46658/JBIMES-20-12

Rocha, G., Proença, E., Fernandes, P., Matos, A., Costa, T., Carreiro, H., & et al. (2004). Analgesia e Sedação. Secção de Neonatologia, Consensos Nacionais em Neonatologia. Sociedade Portuguesa de Pediatria, pp. 45- 52. Retrieved from: https://www.spneonatologia.pt/wp-content/uploads/2016/11/201107201730-consensos_neonatologia__2004.pdf

Sharara-Chami, R., Lakissian, Z., Charafeddine, L., Milad, N., & El-Hout, Y. (2017). Combination Analgesia for Neonatal Circumcision: A Randomized Controlled Trial. *Pediatrics,* 140(6):e20171935. https://doi.org/10.1542/peds.2017-1935

Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., Moher, D., Peters, M. D. J., Horsley, T., Weeks, L., Hempel S., Akl, E. A., Chang, C., McGowan, J., Stewart, L., Hartling, L., Aldcroft, A., Wilson, M. G., Garritty, C., Lewin, S., & et al. (2018). PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. *Annals of Internal Medicine*, 169, 467–473. https://doi.org/10.7326/M18-0850

Prior, F., Querido, D., & Santos, I. (2022).
Eutectic Mixture of Local Anesthetics' dosage in newborns: a scoping review. *Millenium, 2*(19), 35-44.
DOI: https://doi.org/10.29352/mill0219.27268

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	5
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	5
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	5
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	5
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	6
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	6
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	6
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	6
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	6
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	6
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	7
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	7-17
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	-
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	7-17
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	7-17
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	7-17
Limitations	20	Discuss the limitations of the scoping review process.	18
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	17
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	18

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.
* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.
† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).
‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.
§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, & et al. (2018). PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Annual of Internal Medicine,169, 467–473. https://doi:10.7326/M18-0850