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Topical analgesia during needle-related procedures in children: a clinical practice guideline

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ABSTRACT

During intensive and long-lasting treatments, short-term or emergency care, children often undergo minor needle-related procedures (ie, venepuncture, venous cannulation and puncture of central venous access ports). The use of topical analgesia topical analgesia before these procedures can reduce needle-related pain. There is, however, uncertainty about the type of local anaesthetic (ie, eutectic mixture of topical analgesia (EMLA) or tetracaine-containing creams (eg, Rapydan) that should be used.

Therefore, a clinical practice guideline (CPG) was developed to establish a comprehensive, evidence-based overview and provide recommendations for clinical practice.

A comprehensive multidisciplinary panel was assembled, comprising 16 professionals and patient representatives in the Netherlands. A systematic literature review was performed, and after dual appraisal of all articles, results were extracted and meta-analyses were performed. The Grading of Recommendations Assessment, Development and Evaluation methodology was used to assess, extract and summarise the evidence. An in-person meeting was held to discuss the evidence, complete an evidence-to-decision framework and formulate recommendations.

In total, ten randomised controlled trials comprising 1808 children formed the evidence base for the recommendations. We recommend the use of EMLA in children who need to undergo a minor needle-related procedure, with minimal application duration of 60 min (strong recommendation, very low-quality evidence). We suggest the use of tetracaine-containing creams only when rapid cannulation/puncture (ie, within 30–60 min) is required (weak recommendation, very low-quality evidence).

In this CPG, we provide recommendations regarding the choice of local anaesthetic for needle-induced pain during minor procedures in children. With these recommendations, we aim to reduce procedural pain and thereby contribute to improving care for children.

INTRODUCTION

Children with cancer frequently need to undergo minor needle-related procedures such as venepunctures, venous cannulation and accessing a central venous access port. This also accounts for children with other types of diseases or for other types of care such as emergency treatment. These (repeated) procedures can be of great impact on quality of life and can cause high levels of distress, anxiety and non-compliance to therapies, even on long term.[1–3] Management of needle-induced pain is important and relevant to all fields of pediatric medicine. The use of topical analgesia before a needle-related procedure has been proven to reduce pain in children.[2–4] Different types of topical analgesia are available and can be used safely. An eutectic mixture of topical analgesia (EMLA) is the most commonly used pharmacological local anaesthetic and consists of a mixture of lidocaine and prilocaine and can be applied as either cream (also available as a generic preparation as well, 2.5%/2.5%) or patch (25 mg/25 mg).[5] In addition, Rapydan, a patch with a mixture of lidocaine, tetracaine (70 mg/70 mg) and a heating element or other tetracaine-containing creams such as Ametop (4% containing tetracaine HCl) are also used.[1] Both types of topical analgesia are effective by blocking nerve cell sodium influx and thus inhibiting depolarisation and thereby conduction of the pain signal.[5] EMLA and tetracaine-containing creams have different characteristics and differ in, for example, costs and application duration. Tetracaine-containing creams are proven effective within 30–45 min after application, whereas EMLA is proven effective after a minimum of 60 min of application.[1–3] Importantly, topical analgesia should be offered to every child before undergoing a minor needle-related procedure.[4] However, there is a lack of evidence regarding which type of local anaesthetic should be given to a child in a particular (clinical) situation as both types of drugs seem to be effective. Therefore, our aim was to develop a clinical practice guideline (CPG) regarding the use of topical analgesia in reducing needle-induced pain during minor procedures in children to establish a comprehensive overview of evidence and to provide recommendations for clinical practice.

METHODS

Guideline panel

A national, comprehensive multidisciplinary panel was assembled, comprising 16 professionals from the Netherlands. The panel included paediatric oncologists, general paediatricians, paediatric oncology researchers, a clinical psychologist, a child life specialist, a paediatric oncology nurse, a paediatric anaesthesiologist, a hospital pharmacist, epidemiologists, guideline methodologists and a patient and parent representative (see online supplemental material S1). Members were invited on the basis of their experience and knowledge on the topic. The core group (DCS, DMK, RLM, LCMK, WJET,

EAHL) provided all the preparatory documents including methodology, study details and results.

Between 2019 and 2020, multiple in-person panel meetings were held to rank outcomes, discuss evidence and formulate recommendations.

Guideline scope

With this guideline, we aimed to develop a CPG regarding the use of topical analgesia in reducing needle-induced pain during minor procedures in children from 1 to 18 years. Non-pharmacological interventions were not included within the scope of this guideline.

Existing guidelines and clinical questions

Existing national and international guidelines on the use of topical analgesia in children published until November 2019 were searched (Guideline International Network (GIN),[6] National Institute for Health and Care Excellence (NICE),[7] International Pediatric Oncology Guidelines in supportive care Network (IPOG),[8] American Society of Clinical Oncology (ASCO),[9] Dutch Federation for paediatrics (NVK)[10]) and evaluated for the applicability and completeness of these guidelines (using the AGREE II checklist). In the absence of an applicable evidence-based guideline, a clinical question was defined by the core group. The main Patient–Intervention–Control–Outcome (PICO) question for this guideline was if, in children aged 1–18 years undergoing a minor needle-related procedure (P), tetracaine-containing creams or patches (I) are more effective than EMLA cream or patches (C) on pain-intensity and other outcomes (O). As no patients participated in this research, no ethics committee approval was required for the formation of this guideline and no informed consent was required.

Search strategy and selection criteria

An extensive systematic literature search (see online supplemental material S2) was performed. We searched the electronic databases PubMed, Embase and Cochrane CENTRAL (initial search 24 September 2019, top-up search December 2020).

Inclusion and exclusion criteria were defined by the core group. Only randomised controlled trials (RCTs) comprising participants aged 1–18 years old were included. Participants should have undergone a minor needle-related procedure, defined as venepuncture, venous cannulation or puncture of central venous access ports (in both outpatient and inpatient settings). Studies were included that compared EMLA cream or patch with a tetracaine-containing cream or patch. All different tetracaine-containing drugs (Ametop, Rapydan, other author-defined) and their possible mixtures were included in order to create a comprehensive overview. All application times were included, that is, this was not limited to the manufacturers' recommended application time. When applicable, results were pooled by the researcher (DS).

Evidence selection and quality assessment

Study identification was performed independently by two reviewers (DS, DMK). Initially, titles and abstracts were screened, followed by full text assessment. Discrepancies were resolved by consensus. Detailed information from each eligible study was extracted into evidence tables. The methodological quality of each single study was assessed and scored for risk of bias. The Risk of Bias tool V.2 from the Cochrane Handbook was used.[11]

All evidence was outlined in the summary of findings tables. The quality of the total body of evidence was assessed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[12 13] The data extraction, risk of bias assessment and GRADE assessment were independently performed by two reviewers (DS and DK). Discrepancies were resolved by consensus or a third reviewer (EAHL).

Primary and secondary outcomes were defined and prioritised according to the GRADE system. The following outcomes were determined by the guideline panel: pain intensity (1) self-reported, (2) by-proxy reported (doctors or caregivers) and (3) by-proxy reported (parents), first-time success rate of the procedure, adverse events and costs. The allocated hierarchy for the defined outcomes is shown in online supplemental material S3.

Translating evidence into recommendations using the evidence-to-decision framework

The GRADE evidence-to-decision framework was used to translate evidence into recommendations.[13] Within this framework, for every clinical question, the benefits and harms, resource use, equity, acceptability and feasibility were discussed and recommendations were formulated by the guideline panel. If no studies were identified, we carefully considered expert consensus (expert opinion). Final recommendations had to be unanimously supported by all panel members.

The GRADE terminology for evidence-based guidelines was used, such as 'we suggest' or 'we recommend'.[12] Within the overview of all recommendations, a colour coding system was used to improve understandability and to emphasise the strength of the recommendations.

RESULTS

In total, 527 unique citations were identified in the literature search (March 2020) and in the search update in January 2023. 10 primary studies (all RCTs) were included with a total number of 1808 participants (see figure 1). All primary study characteristics are shown in table 1 and more extensively in online supplemental materials S4.

An overview of the included studies, the evidence tables and the GRADE assessments are found in online supplemental materials S5. In table 1, the conclusions of evidence of the included

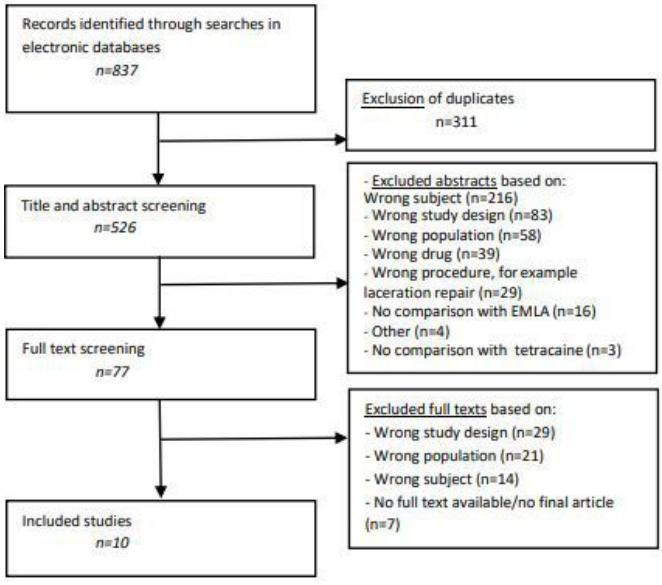

Figure 1 Study selection process. EMLA, eutectic mixture of topical analgesia.

Table 1 Primary study characteristics related to local anaesthetic use prior to a minor painful procedure in children

Article	Intervention group	Control group (EMLA)
Arendts and Stevens[18], RCT (177 patients)	**Tetracaine** group (97 patients), no information dosage applied. Applied for 1 hour. Mean age 4.8 years (range 0–13)	**EMLA** group (80 patients), no information dosage applied. Applied for 1 hour. Mean age 4.9 years (range 0–12)
Arrowsmith and Campbell[16], RCT (120 patients)	**Tetracaine** group (60 patients), no information dosage applied. Mean duration of application 2.04 hours (SD 1.0) Mean age 8.0 years (SD 4.0)	**EMLA** group (60 patients), no information dosage applied. Mean duration of application 1.93 hours (SD 1.0) Mean age 6.8 years (SD 4.0)
Bishai *et al*[15], RCCT (39 patients)	**Tetracaine** group (39 patients), no information dosage applied. Application duration 30 min (30 min placebo plus 30 min tetracaine) - Total group mean age 10.2 years (SD 3.7)	**EMLA** group (39 patients), no information dosage applied. Applied for 60 min. Total group mean age 10.2 years (SD 3.7)
Choy *et al*[17], RCT (34 patients)	**Tetracaine** group (17 patients), 1 gram applied. Application duration 30–45 min. - Median age 5 years (range 1–14)	**EMLA** group (17 patients), 2 grams applied on each site. Application duration at least 60 min. Median age 5 years (range 1–13),
Cozzi *et al*[19], RCT (339 patients)	**Lidocaine/tetracaine** (1:1 mixture of 70 mg lidocaine and 70 mg tetracaine) (167 patients), no information dosage applied. Application duration 60 min. Lidocaine/tetracaine 6.0 years (4.3–9.0 IQR)	**EMLA** group (172 patients), no information dosage applied. Applied for 30 min. Median age 6.0 years (4.0–9.0 IQR),
Lawson *et al*[20], RCT (94 patients)	**Tetracaine** group (47 patients), 1 gram applied. Mean application time 40.5 min (SD 1.9, range 35–45) Total group mean age 7.3 years (range 3–12)	**EMLA** group (47 patients), 2 grams applied. Mean application time 41.4 min (SD 2.4, range 35–45) Total group mean age 7.3 years (range 3–12)
Newbury,[23] 2008, RCT (697 patients)	**Tetracaine** group (337 patients), on average 1.2 grams applied. 45 min of application. Mean age 6.9 years (SD 4.3)	**EMLA** group (342 patients), on average 2.9 grams applied. 90 min of application Mean age 7 years (SD 4.2)
Rømsing *et al*[14], RCT (60 patients)	**Tetracaine** group (40 patients), 1 gram applied. Mean time of application 46.5 min (SD 5.6) No mean value, age range 3–15 years	**EMLA** group (20 patients), 2 grams applied. Mean time of application 60.4 min (SD 1.7). No mean value, age range 3–15 years
Soltesz *et al*[1], RCT (200 patients)	**Lidocaine/tetracaine** (70 mg lidocaine and 70 mg tetracaine), (100 patients) no information dosage applied. Median duration of application 35 min (25–75 percentile 30–42.5) Median age 7 (25–75 percentile 5–10)	**EMLA** group (100 patients), no information dosage applied. Median duration of application 35 min (25–75 percentile 30–45) Median age 4 (25–75 percentile 4–8.5)
Van Kan *et al*[2], RCT (66 patients)	**Tetracaine** group (34 patients), 1 gram applied. 30 min of application. Median age 6 (range 1–15)	**EMLA** group (32 patients), 2.5 grams were applied. 60 min of application. Median age 8 (range 1–15)

EMLA, eutectic mixture of topical analgesia; RCT, randomised controlled trial.

studies are presented. In table 2, a list of all recommendations is shown.

All recommendations and their evidence-to-decision processes are discussed per subject. Only conclusions and important considerations of the guideline panel are shown. Recommendations are shown in table 3, full details are shown in online supplemental material S6.

Recommendations

We recommend the use of EMLA (as standard of care) in children who need to undergo a minor procedure (strong recommendation, very low quality of evidence).

We suggest the use of tetracaine-containing creams or patches in children when rapid cannulation or puncture (within 30–60 min) is required (weak recommendation, very low quality of evidence).

Table 2 Conclusions of evidence related to local anaesthetic use prior to a minor painful procedure in children

Are tetracaine-containing creams or patches more effective as a local anaesthetic than EMLA in children aged 1–18 years, undergoing a minor painful procedure such as venepuncture, central venous access port puncture or venous cannulation?	
Tetracaine cream vs EMLA > 60 min	
Pain intensity, self-reported	**Quality of evidence**
Significantly lower pain scores in tetracaine group in one study.[14] No significant difference in one study.[15]	⊕◯◯◯ (2 studies) Very low
Pain intensity, by-proxy reported	**Quality of evidence**
Significantly lower pain scores in the tetracaine group in one study.[16] No significant differences in two studies.[15 19]	⊕◯◯◯ (2 studies) Very low
Pain intensity, by-proxy reported, parents	**Quality of evidence**
No significant differences between the groups.[15]	⊕⊕◯◯ (1 study) Low
First-time cannulation success rate	**Quality of evidence**
No significant differences in three studies.[2 3 18] Pooled standardised mean difference not significant.*	⊕◯◯◯ (3 studies) Very low
Lidocaine/tetracaine vs EMLA > 60 min	
Pain intensity, self-reported	**Quality of evidence**
No significant differences between the groups.[19]	⊕⊕◯◯ (1 study) Low
Pain-intensity, by-proxy reported	**Quality of evidence**
No significant differences between the groups.[19]	⊕◯◯◯ (1 study) Very low
First-time cannulation success rate	**Quality of evidence**
Significantly higher success rate in lidocaine/tetracaine group.[19]	⊕◯◯◯ (1 study) Very low
Tetracaine cream vs EMLA < 60 min	
Pain intensity, self-reported	**Quality of evidence**
Significantly lower pain scores in the tetracaine group.[20]	⊕⊕⊕◯ (1 study) MODERATE
Lidocaine/tetracaine cream vs EMLA < 60 min	
Pain-intensity, by-proxy reported	**Quality of evidence**
Significantly lower pain scores in lidocaine/tetracaine group.[1]	⊕⊕◯◯ (1 study) Low
First-time cannulation success rate	**Quality of evidence**
No significant differences.[1]	⊕◯◯◯ (1 study) Very low

*Calculated by researcher.
EMLA, eutectic mixture of topical analgesia.

Table 3 Overview of recommendations regarding local anaesthetic use prior to a minor painful procedure in children

Recommendation	Strength of recommendation	Quality of evidence
We recommend the use of EMLA cream or patch in children who need to undergo a needle-related procedure.	Strong	**Very low** quality of evidence
We suggest the use of tetracaine-containing creams or patches in children when rapid cannulation or puncture (within **30–60** min) is required.	Weak	**Very low** quality of evidence

The colour coding emphasises the strength of the recommendation and shows if something is advised, green (strong) or yellow (moderate) or discouraged orange (moderate) or red (strong).
EMLA, eutectic mixture of topical analgesia.

Evidence

Tetracaine cream vs EMLA applied >60 min.

In total, seven studies reported on tetracaine cream versus EMLA applied for more than 60 min. Two studies reported on self-reported pain scores, with significantly lower *self-reported* pain scores in the tetracaine group in one study[14] versus no significant difference in another study[15] (very low-quality evidence). Three studies reported on by-proxy-reported pain scores (either reported by doctors or nurses or by parents). Significantly lower doctor-reported pain scores were seen in the tetracaine group in one study[16] versus no significant difference in two studies[15 17]. In addition, no significant difference for pain scores *reported by parents* was reported in one study (low-quality evidence).[15] Three studies reported on first-time cannulation success rate, for which no significant differences were seen (very low-quality evidence),[18] (Newbury 2008[2 3]). After pooling the results of these studies, a total risk ratio (RR) of 1.03 (0.96, 1.11) was calculated. Adverse events were discussed in two studies. Erythema was reported significantly more often in the tetracaine group,[18] whereas blanching was reported significantly more often in the EMLA group.[15]

Lidocaine/tetracaine vs EMLA applied >60 min.

One study reported on lidocaine/tetracaine (Rapydan vs EMLA applied for more than 60 min[19]). There were no significant differences for self-reported or by-proxy-reported pain scores between the groups (very low to low-quality evidence). A significantly higher first-time cannulation success rate was found in the lidocaine/tetracaine group (n=158/171, 92.4%) compared with the EMLA group (n=142/167, 85%), with an RR of 1.09 (95% CI 1.01 to 1.17, p=0.03) (very low-quality evidence). Adverse events such as blanching or burn were reported but did not differ significantly between groups.

Tetracaine vs EMLA applied <60 min

One study reported on tetracaine vs EMLA applied less than 60 min[20 20], demonstrating significantly lower self-reported pain scores in the tetracaine group (moderate quality evidence). Significantly more erythema was seen in the tetracaine group.

Lidocaine/tetracaine vs EMLA applied <60 min

One study reported on lidocaine/tetracaine vs EMLA applied less than 60 min[1]. In this study, significantly lower by-proxy-reported pain scores were seen in the tetracaine group (low quality evidence). No significant difference was reported for first-time success rate of cannulation (86% in EMLA group vs 83% in lidocaine/tetracaine group) (very low quality evidence). Adverse events were not reported in this study.

Translating evidence into recommendations

Tetracaine-containing creams vs EMLA applied >60 min

Benefits and harms were thoroughly discussed by the guideline panel. Some studies[14 16] show a significant difference in pain scores in favour of the tetracaine-containing groups. In three other studies,[15 17 19] for six outcomes (pain reported by proxy, self-reported), no significant differences in pain scores were reported. In one study,[19] a significant difference in first-time cannulation success rate was reported in favour of lidocaine/tetracaine 92.4% (n=158/171) and EMLA 85% (n=142/167); RR 1.09 (95% CI 1.01 to 1.17), p=0.03 and a number needed to treat of 14. However, in three out of four studies,[2 3 18] no significant differences in first-time success rate of cannulation were reported. Overall, there might be some effect in favour of tetracaine-containing creams, but we cannot consider it large. The main undesirable effects were considered adverse events of the anaesthetic used: both tetracaine-containing creams and EMLA have their adverse events, but they are small, temporary and self-limiting. In addition, the costs of tetracaine-containing creams are much higher than costs of EMLA,[21 22] and this was also taken into an account in our recommendation. Completing the evidence-to-decision framework, the guideline panel unanimously decided that there is no obvious superiority for tetracaine-containing creams or patches over EMLA (when applied >60 min) for most outcomes.

Tetracaine-containing creams vs EMLA applied <60 min

Two single studies[1 20] showed significantly lower pain scores in the tetracaine-containing groups. In one study,[1] the first-time cannulation success rate was reported with no significant differences between the groups. The guideline panel unanimously felt that the evidence demonstrated in favour of tetracaine-containing creams and patches in the studies that compared tetracaine-containing creams or patches to EMLA applied less than 60 min. However, we decided towards a *weak* recommendation because of the small number of included studies.

DISCUSSION

In children, needle-induced pain and distress are unnecessary and often avoidable. The use of a local anaesthetic (dermal application) should be standard of care for every child undergoing a needle-related procedure, unless the intervention is required for emergency care. In this CPG, we formulated recommendations about the type of local anaesthetic best applicable to a child in a clinical situation. Hereby, we aim to reduce procedural pain and thereby contribute to pain, fear and stress reduction in needle-related procedures.

For this study, we performed an extensive search in available literature and assessed all articles in the same manner using the GRADE methodology very strictly. Then, we assessed and evaluated all evidence with a multidisciplinary panel comprising all professionals involved in this type of care for children. In addition, we made an effort to show all our additional considerations in our evidence-to-decision framework in order to be as transparent as possible. For that manner, every caregiver can easily assess if our recommendation is applicable for his or her specific practice. Eventually, these recommendations were implemented in standard of care in the Princess Máxima Center for Pediatric Oncology in the Netherlands.

According to the identified evidence, tetracaine-containing creams are not superior to EMLA, when applied for at least the minimal duration to be effective. There is no conclusive evidence that tetracaine-containing creams have a higher first-time cannulation success rate, as hypothesised often.[3 19] However, it might be beneficial that the tetracaine-containing creams are effective within 30–45 min. For both types of topical analgesia, adverse events are transient and reversible and pain levels were comparable in the seven identified studies. Costs can differ between countries, but generally Rapydan is more expensive than EMLA. This should be taken into consideration for each country or institute separately.

The guideline panel identified some gaps in knowledge and future directions for research. To provide more guidance, there is need for more evidence about different types of topical analgesia. For example, children with cancer often undergo intensive and long-lasting courses of treatment with frequent needle-related procedures. Therefore, future studies should address the effectiveness of local anaesthetic creams or patches in children undergoing repeated needle-related procedures. Future studies should focus on, among others, longitudinal data collection to study the effects of local anaesthetic use and pain intensity over a longer period of time with repeated procedures. Also, the use and implementation of non-pharmaceutical interventions to reduce pain are very relevant, but that is outside the scope of this guideline. This is very important and should always be considered besides pharmacological interventions.

In conclusion, when there is a time constraint and rapid cannulation or puncture is required within 30–45 min, tetracaine-creams are suggested as first choice. For all other elective, non-emergent needle-related procedures in children, EMLA cream or patch is recommended, obviously used according to prescription (>60 min application). Future research should provide more evidence in order to strengthen these recommendations. Eventually, this will optimise care for children with cancer and thereby improve their short-term and long-term quality of life. Implementation of this evidence-based guideline can contribute to improving the quality of life of children with cancer. In addition, these recommendations will also provide a clear statement towards clinicians, children and parents and provide them guidance. However, it remains important to always consider the benefits and harms for a child individually.

Collaborators On behalf of the procedural local anaesthetics guideline panel: Laura Beek, Desiree D.L. Bezemer, Tessa van Gastel, Melanie M. Hagleitner, Rogier Lange, Ida Ophorst, Tirza Schuerhoff, Judith Spijkerman, Marianne D. van de Wetering.

Contributors DS collected data, created evidence to decision frameworks and prepared documents for guideline panel meetings. DS wrote the manuscript and acts as a guarantor. DMK collected data and contributed to critically review the evidence. EAHL contributed to critically review the evidence and helped form the evidence to decision frameworks. WJET, RLM, LCMK and MOM critically reviewed the evidence and manuscript. The guideline panel consisting of LB, DDLB, TvanG, MMH, RL, IO, TS, JS, MDvandeW, critically reviewed evidence and helped us formulate recommendations. They also reviewed the full manuscript.

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