Received Date : 21-Jun-2016

Revised Date : 08-Nov-2016

Accepted Date : 24-Jan-2017

Article type : Regular Article

First time success with needle procedures was higher with a warm lidacaine and tetracaine patch than an eutectic mixture of lidocaine and prilocaine cream

Authors and affiliations:

Cozzi Giorgio M.D.[1], Borrometi Fabio M.D.[2], Benini Franca M.D.[3], Neri Elena Ph.D.[1], Rusalen Francesca M.D.[3], Celentano Loredana M.D.[2], Zanon Davide Pharm.D.[4], Schreiber Silvana R.N.[1], Ronfani Luca M.D.[5], Barbi Egidio M.D.[1]

1) Institute for Maternal and Child Health IRCCS Burlo Garofolo, Trieste, Italy
2) Pediatric Pain Service and Palliative Care, Department of Oncology, Pausilipon Hospital, AORN Santobono Pausilipon, Naples, Italy
3) Department of Women's and Children's Health, University of Padua, Padua, Italy
4) Pharmacy and Clinical Pharmacology Unit, Institute for Maternal and Child Health IRCCS Burlo Garofolo, Trieste, Italy
5) Clinical Epidemiology and Health Services Research Unit, Institute for Maternal and Child Health IRCCS Burlo Garofolo, Trieste, Italy

Running Title: Needle procedure success rate after topical anaesthesia

Corresponding Author: Cozzi Giorgio

Institute for Maternal and Child Health, IRCCS Burlo Garofolo

Via dell'Istria 65/1, 34137, Trieste, Italy

email address giorgiocozzi@gmail.com

Telephone number 00390403785380 Fax number 00390403785727

Abstract:

Aim: More than 50% of children report apian during venipuncture or intravenous cannulation and using local anaesthetics before needle procedures can lead to different success rates. This study examined how many needle procedures were successful at the first attempt when children received either a warm lidocaine and tetracaine patch or an eutectic mixture of lidocaine and prilocaine (EMLA) cream.

Methods: We conducted this multicentre randomised controlled trial at three tertiary-level children's hospitals in Italy in 2015. Children aged 3-10 years were enrolled in an emergency department, paediatric day hospital and paediatric ward and randomly allocated to receive a warm lidocaine and tetracaine patch or EMLA cream. The primary outcome was the success rate at the first attempt.

Results: The analysis included 172 children who received a warm lidocaine and tetracaine patch and 167 who received an EMLA cream. The needle procedure was successful at the first attempt in 158 children (92.4%) who received the warm patch and in 142 children (85.0%) who received the cream (p=0.03). The pain scores were similar in both groups.

Conclusion: This study showed that the first-time needle procedure success was 7.4% higher in children receiving a warm lidocaine and tetracaine patch than EMLA cream.

Keywords: eutectic mixture of lidocaine and tetracaine cream; local anaesthetic; needle procedure; procedural success rate; warm lidocaine and tetracaine patch

Key notes:

- Applying local anesthetics may influence success rates in children undergoing painful needle procedures.
- We compared how many needles were inserted at the first attempt when children received a warm lidocaine and tetracaine patch or an eutectic mixture of lidocaine and prilocaine (EMLA) cream.
- The three Italian hospitals who took part reported that the success rate was higher in children treated with the warm patch (92.4%) than the cream (85.0%).

Abbreviations

ARR, absolute risk reduction; CI, confidence intervals; EMLA, eutectic mixture of lidocaine and tetracaine; IQR, interquartile ranges; NNT, number need to treat; RR, relative risks

INTRODUCTION

Needle procedures are the most common painful and stressful interventions performed on children, with more than 50% reporting pain during venipunctures or intravenous cannulation (1). That is why pain management is recommended during these procedures (2). Topically applied local anaesthetics have been reported to be effective in reducing procedural pain and are widely used in these situations (3). Several formulations are available for this indication,

including tetracaine gel, 4% liposomal lidocaine cream, an eutectic mixture of lidocaine and prilocaine (EMLA) (4) and a warm lidocaine and tetracaine patch (5).

While an EMLA cream is one of the most commonly used local anaesthetics, with substantial evidence of efficacy and safety in children (6), several studies have shown the effectiveness of a warm lidocaine and tetracaine patch in providing pain relief during vascular access, both in adults and children (7,8). However, to our knowledge, only two studies have compared the effectiveness of the pain relief provided by an EMLA cream and a warm lidocaine and tetracaine patch. These studies showed that the warm lidocaine and tetracaine patch had a more rapid analgesic effect than EMLA cream, acting in 30 minutes instead of 60 minutes. However, apart from the time it took for them to start providing pain relief, both formulations were equally effective (9,10).

One relevant issue that needs to be addressed is the interference that these topical anaesthetics have with the actual needle procedures. Local anaesthetic formulations like EMLA cream containing prilocaine, , which is known to have a vasoconstrictor effect, resulting in epidermal blanching (11). However, after 60 minutes of application, EMLA cream does not cause a significant change in local skin blood flow (12) and it does not interfere with the success rate at the first attempt of venepuncture or intravenous cannulation (13). On the other hand, tetracaine is known to cause local vasodilatation, but the warm patch formulation, together with lidocaine, has a vasodilatatory effect that is less pronounced than other formulations that just contain tetracaine (14). To our knowledge, no study has compared the rates of needle procedure success at the first attempt using a warm lidocaine and tetracaine patch or EMLA cream in children as main outcome.

The aim of this study was to investigate the first-time procedural success rates in children who received a warm lidocaine and tetracaine patch or EMLA cream before undergoing venipuncture or intravenous cannulation..

METHODS

This study was a multicentre randomised controlled trial that involved three tertiary-level children's hospitals in Italy: the Institute for Maternal and Child Health IRCCS Burlo Garofolo, Trieste, the Pausilipon Hospital, AORN Santobono Pausilipon, Naples and the Academic Hospital of Padua, Padua. The study was conducted between April and December 2015. Children were recruited in three different hospital settings: emergency departments, paediatric day hospitals and paediatric wards. We enrolled children from three to 10 years of age who needed venepuncture or intravenous cannulation. The exclusion criteria were: children who required emergency care, the use of topical, enteral or parenteral analgesics up to eight hours before the time of enrolment, a known allergy or hypersensibility to local anaesthetics, damaged, denuded or broken skin at the designated needle procedure site, the presence of a cognitive impairment or the inability to verbally report pain sensations.

The eligible children were randomly allocated, to use Ralydan, a warm lidocaine and tetracaine patch (IBSA Farmaceutici srl, Lodi, Italy) or EMLA cream (AstraZeneca, Milano, Italy) on the site designated for the needle procedure.

Ralydan is a drug delivery system that uses controlled heat to enhance the delivery to the skin of a 1:1 eutectic mixture of 70mg lidocaine base and 70mg tetracaine base. It consists of a 8.5cm x 6.0cm patch composed of a plastic tray, the drug formulation, an adhesive layer, a heating element and a release liner. The patch is activated when exposed to air, which triggers a chemical reaction and it warms the skin up to a maximum temperature of 40°C soon after it has been applied.

The EMLA cream consists of an eutectic mixture of 25mg lidocaine and 25mg prilocaine and it is usually covered by a transparent occlusive dressing after it has been applied.

Operators who performed the procedure, examined the child's skin, identified the most suitable sites for the needle procedure and then decided where to apply the local anaesthetic. In order to provide analgesia for at least for two possible attempts, two warm lidocaine and tetracaine patches, or a tube of EMLA cream divided into two applications, were applied on two different sites on each child.

We know how long it would be before they took effect, so the warm lidocaine and tetracaine patches and the EMLA cream were applied at least 30 and 60 minutes, respectively, before the needle procedure (10). The topical analgesics were removed immediately before the needle procedure.

A randomisation list, stratified by centre, with a fixed block size of 10, was generated using a computer-based method by an independent epidemiologist at the Clinical Epidemiology and Public Health Research Unit of the IRCCS Burlo Garofolo, Trieste, Italy. Allocation concealment was guaranteed by the use of sealed, opaque envelopes, consecutively numbered, each containing the allocation group. After obtaining informed consent, the healthcare staff performing the needle procedures opened the envelope marked with lowest number available and assigned the patient to the corresponding group.

The primary outcome of this study was the success rate in performing venipuncture or intravenous cannulation at the first attempt. Secondary outcomes included: the procedural pain score, which was self-reported by children and recorded by the operator performing the procedure, whether operators thought that the local anaesthesia facilitated the procedure, whether the children would like the local anaesthesia to be used again before future needle procedures and the number and types of adverse events.

Children from three to seven years of age reported their pain using the Wong-Baker scale (15) and children aged eight years or more, and the operators, reported pain with the Numerical Rating Scale (16). For the statistical analyses, scores from both scales were transformed into a numerical value from zero for no pain to 10 for maximum pain, in accordance with previous

studies, which demonstrated that scores reported using these two scales overlapped (15,17). A pain score from five to seven was considered to demonstrate moderate pain, while eight to 10 was considered as severe pain. The procedural pain score was assessed immediately after the first needle procedure was attempted. Adverse events were recorded by the operator before the needle procedure - after they had removed the patch or cream - and 10 minutes after the procedure.

Data were recorded using a standardised form, which was filled out by the operator who performed the procedure. The following variables were also collected for each procedure: the children's age, sex and weight, the presence of fever or dehydration, the type, site and reason for the procedure, the job title and experience of the operator performing the procedure, the concomitant use of non-pharmacological distraction techniques and the hospital department where the procedure was performed.

The study protocol had received approval from the Independent Bioethic Committee of the Institute for Maternal and Child Health IRCCS Burlo Garofolo and all the children's parents provided written, informed consent for their participation. The study was registered with ClinicalTrial.gov (NCT02519660) before the enrolment of the first participant.

Statistical analyses

This study was designed as a superiority trial. The data available in literature enabled us to estimate that the first-time success rate in children using the EMLA cream would be 85% (13,18). We hypothesized a success rate of 95% for the children using a warm lidocaine and tetracaine patch and by using the Fleiss method with continuity correction, we estimated that 320 subjects -160 for each group – would be needed to carry out the study, with alfa = 0.05 and beta = 0.20.

Analyses were carried out according to the intention-to-treat principle. Continuous variables were reported as medians and interquartile ranges (IQR) and categorical data as numbers and percentages, relative risks (RR) and 95% confidence intervals (95% CI). For the primary outcome of the study the number needed to treat (NNT) was calculated as the inverse of the absolute risk reduction (1/ARR). Moreover, for categorical variables, the differences between the groups were evaluated with the chi-square test with the non-parametric Mann-Whitney U test, since a non-normal distribution of data was shown both visually and with the Kolmogorov-Smirnov test. The data were analysed with SPSS software, version 21.0 (IBM Corp, Armonk, New York, USA). A double sided p value of <0.05 was considered statistically significant.

RESULTS

During the study period, we assessed 401 children for eligibility. Of these 13 declined to participate and 32 were excluded because they did not fulfil the study criteria, as 27 of them needed emergency care, three had used analgesic less than eight hours before enrolment and two had cognitive impairment. We enrolled 356 children: 178 were randomised to receive the warm lidocaine and tetracaine patch and 178 to receive the EMLA cream. After the application of the local anaesthetic, 17 children (4.8%) enrolled in the emergency department - six with a warm lidocaine and tetracaine patch and 11 with EMLA cream - did not undergo the procedure, because their clinical status was modified. Consequently, the analysis comprised 172 children treated with a warm lidocaine and tetracaine patch and 167 children treated with EMLA cream (Figure 1). In two children, one using a warm patch and one using the cream, the procedure was performed in a site not protected by the local anaesthetic. However, following the intention-to-treat principle, these subjects were included in their respective randomisation groups. No subject was lost during the follow up.

The baseline characteristics of the two groups were similar (Table 1). The mean age was six years old in both groups, ranging from 4.3-9.0 years in the warm patch group and from 4.0-8.0 years in the EMLA cream group (p=0.51). There was a slight prevalence of males in the EMLA group, but this was not statistically relevant (62.9% versus 52.9%, p=0.06).

The success rate at the first attempt was higher in children using the warm lidocaine and tetracaine patch (n=158, 92.4%) than the EMLA cream (n=142,85.0%) (RR 1.09, 95% CI 1.01-1.17; p=0.03) (Table 2). The number need to treat (NNT), that is the number of children needed to be treated with a warm lidocaine and tetracaine patch in order to avoid one procedural failure, when compared to the EMLA cream, was 14 (1/0.074). With regards to the primary outcome of the study, we also performed a sensitivity analysis that considered all the randomised patients, including the subjects who had not received the needle procedure (17=4.8%) or had received it in a site not protected by local anaesthetic (2=0.5%). All these patients were classified as successful or all unsuccessful events. This sensitivity analysis showed no changes in the results of the study. The secondary outcomes results are reported in Table 2. The number of adverse events was higher in children using a warm lidocaine and tetracaine patch. However, adverse events in the two groups were not significantly different, as 11 children (6.4%) in the warm patch group versus five children (3.0%) in the EMLA cream group (p=0.14) experienced them. Only minor local adverse events were reported in both groups (Table 3).

DISCUSSION

This study was based on a large sample of children and showed that applying a warm lidocaine and tetracaine patch resulted in a higher first-time resulted in a higher first-time success rate, for venipuncture and intravenous cannulation in children, than following the application of EMLA cream.

Venipuncture and intravenous cannulation are procedures that are frequently performed in children, and they are a well-known source of iatrogenic pain and distress. It has been proved that applying a local anaesthetic before a needle procedure decreases children's pain and distress and increases the success rate of the procedure (13,18-20). Therefore, success at the first attempt is crucial in limiting

pain and distress in children and their parents and in sparing time and disposable materials. For these reasons, it is important to choose the formulation of local anaesthetic that results in the highest rate of success at the first attempt.

When it came to the influence of different local anaesthetics on the needle procedure success rate, specific comparisons were only available for tetracaine gel and EMLA cream and these showed that tetracaine gel did not significantly increase the successful first-time cannulation rate compared to EMLA cream (21,22).

Only two trials have previously compared a warm lidocaine and tetracaine patch and EMLA cream (9,10). The principal aim of both trials was to compare the analgesic effect of the two formulations and their effect on the procedural success rates were only reported as secondary outcomes. The trial performed on adult patients (10), did not show any difference between the two formulations on the procedural success rate and neither did the only existing paediatric trial (9). However, the paediatric study was flawed by the fact that the success rate was measured for both anaesthetics after 30 minutes of application, which is different from what is recommended in daily practice, as it is well known that the analgesic effect of the EMLA cream starts after 60 minutes of application (9). Moreover, it has been demonstrated that the EMLA cream may initially cause vasoconstriction, reducing the success rate of procedures performed within 60 minutes of it being applied (18,23). Our study was the first to investigate the effect of a warm lidocaine and tetracaine patch compared to EMLA cream on the success rate of needle procedures in children as the main outcome. We found a first-time success rate with a warm lidocaine and tetracaine patch of 92.4%, which was comparable to previous studies (8,10). On the other hand, the success rate of success for the EMLA cream was 85%, which was also comparable with previous paediatric studies, that ranged from 51% to 86% (13,21,24).

Our results confirmed that a warm lidocaine and tetracaine patch and EMLA cream provided equally useful pain relief and that the number of children reporting significant procedural pain in this study was comparable to previous ones (8,25).

According to our data, the number needed to treat that would have beed necessary to avoid a venipuncture or cannulation failure was 14. Even though this was a high number, its impact should be considered in relation to the thousands of needle procedures performed daily using a local anaesthetic.

This study did not include a cost-benefit analysis. However, we used a tube of EMLA cream (4.5 Euros) or two warm lidocaine/tetracaine patches (6.6 Euros) for each child. As theEMLA cream was slightly cheaper, further studies on this topic are needed.

This study had some limitations. First of all, it was not blinded, as blinding was not possible, given the different visible characteristics of the two drug formulations. Second, we did not include children younger than three years, but a warm lidocaine and tetracaine patch is not approved for this age group. Third, we did not use a vein visibility score (26) that would have allowed us to highlight the most complicated procedures. Further studies focused on children at high risk of needle procedure failure should be performed in the future, as they might show a more favourable NNT. Fourth, we did not collect the exact time of the analgesic application before procedures and how much time passed between the drug removal and the needle procedure execution. Thus, we cannot say how accurately the time protocol was respected in our study. Finally, data were analysed following the intention to treat principle and the children who underwent a needle procedure in a site not protected by local anaesthetic were not excluded from the analysis of our results. On the contrary, we excluded 17 children randomised to the intervention groups from the analysis, as they had not been subjected to the procedure because of their clinical status was modified. However, these children on made up 4.8% randomised cohort and their inclusion in the analysis would not have changed the results.

CONCLUSION

This multicentre randomised clinical trial showed that a warm lidocaine and tetracaine patch led to a higher successful first-time venipuncture and intravenous cannulation rate in children when compared to EMLA cream. While this advantage may be of little statistical relevance in the general paediatric

population, it may be more relevant in children with difficult venous access. Further studies that focus on children at high risk of procedural failure are therefore needed.

CONFLICT OF INTEREST

Egidio Barbi and Fabio Borrometi received grants from IBSA Farmaceutici srl, who manufacture the patch featured in this study, for an expert meeting and one lecture. Franca Benini received a grant from IBSA Farmaceutici srl for an expert meeting. The other authors have no conflicts of interest to declare.

FUNDING

This research did not receive any specific external funding.

References

1. Fradet C, Mc Grath PJ, Kay J, Adams S, Luke B. A prospective survey of reactions to blood tests by children and adolescents. *Pain* 1990; 40:53-60.
2. Krauss BS, Calligaris L, Green SM, Barbi E. Current concepts in management of pain in children in the emergency department. *Lancet* 2016; 387:83-92.
3. Duff AJ, Gaskell SL, Jacobs K, Houghton JM. Management of distressing procedures in children and young people: time to adhere to the guidelines. *Arch Dis Child* 2012; 97:1-4.
4. Lander JA, Weltman BJ, So SS. EMLA and amethocaine for reduction of children's pain associated with needle insertion. *Cochrane Database Syst Rev* 2006; 19:CD004236.
5. Sethna NF, Verghese ST, Hannallah RS, Solodiuk JC, Zurakowski D, Berde CB. A randomized controlled trial to evaluate S-Caine patch for reducing pain associated with vascular access in children. *Anesthesiology* 2005; 102:403-8.

6. Rogers TL, Ostrow CL. The use of EMLA cream to decrease venipuncture pain in children. *J Pediatr Nurs* 2004; 19:33-9.
7. Curry SE, Finkel JC. Use of the Synera patch for local anesthesia before vascular access procedures: a randomized, double-blind, placebo-controlled study. *Pain Med* 2007; 8:497-502.
8. Singer AJ, Taira BR, Chinesa EN, Gupta N, Chipley J. Warm lidocaine/tetracaine patch versus placebo before pediatric intravenous cannulation: a randomized controlled trial. *Ann Emerg Med* 2008; 52:41-7.
9. Soltesz S, Dittrich K, Teschendorf P, Fuss I, Molter G. Topical anesthesia before vascular access in children. Comparison of a warmth-producing lidocaine-tetracaine patch with a lidocaine-prilocaine patch. *Anaesthesist* 2010; 59:519-23.
10. Sawyer J, Febbraro S, Masud S, Ashburn MA, Campbell JC. Heated lidocaine/tetracaine patch (Synera, Rapydan) compared with lidocaine/prilocaine cream (EMLA) for topical anaesthesia before vascular access. *Br J Anaesth* 2009; 102:210-5.
11. Wilder-Smith E, Chow A. Water immersion and EMLA cause similar digit skin wrinkling and vasoconstriction. *Microvasc Res* 2003; 66:68-72.
12. Wiles MD, Dickson E, Moppett IK. Transient hyperaemic response to assess vascular reactivity of skin: effect of topical anaesthesia. *Br J Anaesth* 2008;101: 320-3.
13. Schreiber S, Ronfani L, Chiaffoni GP, Matarazzo L, Minute M, Panontin E et al. Does EMLA cream application interfere with the success of venipuncture or venous cannulation? A prospective multicenter observational study. *Eur J Pediatr* 2013; 172:265-8.
14. Wiles MD, Dobson SA, Moppett IK. The effect of a new topical local anaesthetic delivery system on forearm skin blood flow reactivity. *Anaesthesia* 2010; 65:178-83.
15. Garra G, Singer AJ, Taira BR, Chohan J, Cardoz H, Chisena E et al. Validation of the Wong-Baker FACES Pain Rating Scale in pediatric emergency department patients. *Acad Emerg Med* 2010; 17:50-4.

16. Von Baeyer CL, Spagrud LJ, McCormick JC, Choo E, Neville K, Connelly MA. Three new datasets supporting use of the Numerical Rating Scale (NRS-11) for children's self-reports of pain intensity. *Pain* 2009; 143:223-7.
17. Hicks CL, von Baeyer CL, Spafford PA, van Korlaar I, Goodenough B. The Faces Pain Scale-Revised: toward a common metric in pediatric pain measurement. *Pain* 2001; 93:173-83.
18. Baxter AL, Ewing PH, Young GB, Ware A, Evans N, Manworren RC. EMLA application exceeding two hours improves pediatric emergency department venipuncture success. *Adv Emerg Nurs J* 2013; 35:67-75.
19. Spandorfer PR, Alessandrini EA, Joffe MD, Localio R, Shaw KN. Oral versus intravenous rehydration of moderately dehydrated children: a randomized, controlled trial. *Pediatrics* 2005; 115:295-301.
20. Yen K, Riegert A, Gorelick MH. Derivation of the DIVA score: a clinical prediction rule for the identification of children with difficult intravenous access. *Pediatr Emerg Care* 2008; 24:143-7.
21. Newbury C, Herd DW. Amethocaine versus EMLA for successful intravenous cannulation in a children's emergency department: a randomized controlled study. *Emerg Med J* 2009; 26:487-91.
22. Pywell A, Xyrichis A. Does topical Amethocaine cream increase first-time successful cannulation in children compared with a eutectic mixture of local anaesthetics (EMLA) cream? A systematic review and meta-analysis of randomized controlled trials. *Emerg Med J* 2015; 32:733-7.
23. Bjerring P, Arendt-Nielsen L. Depth and duration of skin analgesia to needle insertion after topical application of EMLA cream. Br J Anaesth 1990; 64:173-7.
24. Lander J, Hodgins M, Nazarali S, McTavish J, Ouellette J, Friesen E. Determinants of success and failure of EMLA. *Pain* 1996; 64:89-97.

25. Minute M, Badina L, Cont G, Montico M, Ronfani L, Barbi E et al. Videogame playing as distraction technique in course of venipuncture. *Pediatr Med Chir* 2012; 34:77-83.

26. Riker MW, Kennedy C, Winfrey BS, Yen K, Dowd MD. Validation and refinement of the difficult intravenous access score: a clinical prediction rule for identifying children with diffucult intravenous access. *Acad Emerg Med* 2011; 18:1129-34.

Tables

Table 1. Patients' characteristics

Patients' characteristics	Warm lidocaine and tetracaine patch group (n=172)	EMLA group (n=167)	p value
Age in years, median (IQR)	6.0 (4.3-9.0)	6.0 (4.0-8.0)	0.51
Male sex (%)	91 (52.9)	105 (62.9)	0.06
Weight in kilograms, median (IQR)	24.0 (18.0-30.0)	23.0 (18.0-30.0)	0.66
Presence of fever, number (%)	20 (11.6)	20 (12.0)	0.92
Presence of dehydration, number (%)	5 (2.9)	10 (6.0)	0.17
Aim of the procedure, number (%): - diagnosis - therapy	 143 (83.1) 29 (16.9)	 134 (80.2) 33 (19.8)	 0.49
Type of the procedure, number (%): - venipuncture - intravenous cannulation	 87 (50.6) 85 (49.4)	 83 (49.7) 84 (50.3)	 0.87
Site of the procedure, number (%):			

- cubital fossa - hand - cubital fossa and hand	118 (68.6) 50 (29.1) 4 (2.3)	113 (67.7) 50 (29.9) 4 (2.4)	0.98
Distraction during the procedure, number (%)	117 (68.0)	108 (64.7)	0.51
Operator performing the procedure, number (%): - nurse - doctor	165 (95.9) 7 (4.1)	158 (94.6) 9 (5.4)	0.57
Procedures performed by the operator in the previous month, number (%): <5 5-10 >10	10 (5.8) 37 (21.6) 124 (72.5)	5 (3.0) 32 (19.2) 130 (77.8)	0.35
Department in which the procedure was performed, number (%): - emergency department - paediatric day hospital - paediatric ward	59 (34.3) 94 (54.7) 19 (11.0)	56 (33.5) 83 (49.7) 28 (16.8)	0.30

Table 2. Main study outcomes

Main study outcomes	Warm lidocaine and tetracaine patch group (n=172)	EMLA group (n=167)	Risk ratio (95% CI)	p value
Procedural success at the first attempt, number (%)*	158 (92.4)	142 (85.0)	1.09 (1.01-1.17)	0.03
Self-reported pain score, median (IQR)	0.0 (0.0-2.0)	0.0 (0.0-2.0)	-	0.07
Self-reported pain score >4, number (%)	18 (10.5)	15 (9.0)	1.17 (0.61-2.24)	0.65
Pain score reported by the operator, median (IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	-	0.80
Children that would use the local anaesthetic again before future needle procedures, number (%)§	155 (91.7)	154 (92.8)	0.99 (0.93-1.05)	0.72
Operators who thought that local anaesthesia facilitated the procedure, number (%)	159 (92.4)	154 (92.2)	1.00 (0.94-1.07)	0.94

∗ Available for 171 subjects in the warm lidocaine and tetracaine patch group

§ Available for 169 subjects in the warm lidocaine and tetracaine patch group and for 166 in EMLA group

Table 3. Adverse events, number and types

Adverse events	Warm lidocaine/tetracaine patch group (n=172)	EMLA group (n=167)	p value
Number (%)	11 (6.4)	5 (3.0)	0.14
Types: - local hyperaemia - local burning - local pain during the application or removing the anaesthetic - local blanching	 3 3 4 1	 1 0 0 4	

Figure legend:

Figure 1. Study algorithm (intention to treat analysis)