Relative Efficacy of Amethocaine Gel and Lidocaine–Prilocaine Cream for Port-a-Cath Puncture in Children

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ABSTRACT. Background. Lidocaine–prilocaine cream (EMLA) is currently standard therapy to alleviate procedural pain in children. One of the disadvantages of lidocaine–prilocaine is the need to wait for 60 minutes for adequate skin anesthesia. Amethocaine gel (Ametop) is a new topical anesthetic that requires a shorter application time for skin anesthesia.

Objectives. **To compare the relative efficacy and safety of amethocaine gel and lidocaine–prilocaine cream in children with cancer undergoing Port-a-Cath puncture and to determine which patient factors influence judgments about pain.**

Methods. **Randomized, blinded, crossover study. Each child received either 1 g of amethocaine gel for 30 minutes, preceded by a placebo gel for 30 minutes, or 1 g of lidocaine–prilocaine cream for 60 minutes. Children rated the pain using the faces scale, for which scores ranged from 0 to 5. Parents and attending nurse operators rated pain on a 10-cm visual analog scale.**

Results. **Thirty-nine children participated. The mean age was 10.2 years (range: 5–16 years), and 69% were male. There were no differences in mean pain assessments between amethocaine and lidocaine–prilocaine as rated by the children (2.0 vs 0.5), parents (2.6 vs 6.4), or nurse operators (2.0 vs 0.9). No serious adverse effects were detected with either preparation. Pain scores assigned by parents and children were not influenced by age, gender, duration of diagnosis, or anesthetic regimen (amethocaine versus lidocaine–prilocaine) in the child. Nurses, however, rated pain higher for younger children, and in males during pretreatment with lidocaine–prilocaine.**

Conclusion. **Amethocaine achieves similar anesthesia to lidocaine–prilocaine during Port-a-Cath administration in children, with an application time that is half of lidocaine–prilocaine. Pain assessments were not influenced by age, gender, or duration of diagnosis of the child. Nurses may perceive that pain is greater for younger children and in males. *Pediatrics* 1999;104(3). URL: http://www.pediatrics.org/cgi/content/full/104/3/e31; *lidocaine–prilocaine, amethocaine, pain, children, Port-a-Cath puncture.***

ABBREVIATION. EMLA, lidocaine–prilocaine.

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Received for publication Jan 27, 1999; accepted Apr 1, 1999.

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Painful skin procedures are a major source of discomfort and distress to children, parents and health professionals. Lidocaine–prilocaine 5% cream (EMLA, eutectic mixture of local anesthetics, Astra Pharma), the first anesthetic licensed for use on intact skin, thus was considered a breakthrough in skin anesthesia. EMLA produces topical anesthesia in many painful cutaneous procedures[1–5] and is used worldwide for the management of procedural pain in children.[6]

One of the disadvantages of EMLA is the need to apply it for 60 minutes before the painful procedure.[6] This precludes its use in busy clinics and emergency situations. Amethocaine (tetracaine) 4% gel (Ametop, Smith & Nephew)[8] was marketed recently in Canada. It is also available in the United Kingdom, but is not yet available in the United States. Amethocaine has greater lipophilicity than does lidocaine or prilocaine and has demonstrated efficacy with application times of only 20 to 30 minutes.[9–12] Systemic absorption of lidocaine and prilocaine is extremely low, resulting in a wide margin of safety.[7] However, caution should be taken with use on diseased skin and in young infants because of the possibility of methemoglobinemia induced by metabolites of prilocaine. Other advantages of amethocaine may include a lower risk of methemoglobinemia, greater anesthetic potency, and a longer duration of action compared with EMLA.[8,13]

To date, most studies of amethocaine compare it with a placebo. Because EMLA cream is the current standard for children,[12] the objectives of our study were to compare the anesthetic effects and safety of amethocaine and EMLA in children undergoing Port-a-Cath puncture.

METHODS

The study was approved by the hospital's research ethics board. Written informed consent was given by all parents and assent by all children >7 years of age. The study was a randomized, blinded, crossover design. Randomization was performed using a computer-generated list. It included children with cancer undergoing Port-a-Cath puncture. Children younger than 5 years of age and children unable to rate their pain were excluded from participating.

Each child received either 1 g of amethocaine gel for 30 minutes, preceded by a placebo gel for 30 minutes, or 1 g of EMLA cream for 60 minutes. The Port-a-Cath application site was covered with a semipermeable occlusive dressing (OpSite Flexifix). The dressing was removed after 60 minutes, the skin was wiped dry and sterilized according to standard protocols, and the puncture was performed within 5 to 10 minutes. The children had two Port-a-Cath procedures performed at different times, and they

served as their own controls. Both preparations were applied by a research assistant who was aware of treatment allocation. To ensure blinding of children, their parents, and nursing staff to treatment group, the research assistant checked the site (ie, lifted the dressing) for the EMLA cream at 30 minutes as well (because it is known that EMLA is left on the skin for 60 minutes). We did not remove and reapply the EMLA so as not to interfere with the absorption characteristics of the preparation. Thus, by appearing to extend amethocaine application time to 60 minutes with an initial 30 minute placebo application and appearing to check the EMLA preparation after 30 minutes, the drugs could not be distinguished. The children, their parents, and the nurses did not see the study drug while it was being applied or removed from the skin.

Children rated the pain using the faces scale, for which scores ranged from 0 to 5.[14] Parents and attending nurse operators rated the pain on a continuous 10-cm visual analog scale. All children, parents, and nurses were trained to use the pain measures. Every effort was made to guarantee that the same nurse perform both procedures for each patient. The ease of the procedures was rated as "first attempt—easy", "first attempt—difficult," and "repeated procedure" by the nurse operator. Local reactions (blanching, erythema, or edema) were recorded by the nurse operator.

Sample Size Calculation and Statistical Analyses

Based on the SD of pain scores (~2 U of 10) during Port-a-Cath observed in our previous study of EMLA versus placebo[15] and a difference of at least one face (ie, 1/5), we calculated that at least 35 children serving as their own controls would be needed for a power of 80% and an α of 5%.

Pain scores and adverse effects were compared between groups using the paired Student's t test and χ^2 test, respectively. Linear regression was used to determine the effects of age, gender, duration of diagnosis, and treatment assignment on pain scores. $P < .05$ was considered statistically significant.

RESULTS

Data were available for 39 of 42 children recruited for the study. Two children were excluded because the Port-a-Cath was removed before the second drug was applied, and 1 child was excluded because of an infected central line (which precluded use of the anesthetic). Eighty-four percent of the children had acute lymphoblastic leukemia. The mean age (±SD) was 10.2 years (3.7); 69% were male; and the duration of diagnosis was 17.2 months (13.4). The average length of time in days between the application of both anesthetics was 18.3 days. Five nurses participated in the study.

Of the children, 51% (20/39) received EMLA cream for the first study drug application. There were no differences in pain assessments between amethocaine and EMLA as rated by the children, their parents, or the nurse operators (Table 1). Pain scores assigned by children and their parents were not influenced ($P > .05$) by age, gender, duration of diagnosis, or anesthetic regimen (amethocaine vs EMLA) in the child. Nurses, however, rated pain higher for younger children ($P = .003$) and higher in males ($P = .004$) during pretreatment with EMLA. The procedure was rated as "first attempt—easy" by the nurses for all children, in both arms of the study.

TABLE 1. Pain Assessments* for Amethocaine Gel and EMLA Cream During Port-a-Cath Puncture ($N = 39$)

	Amethocaine Gel		EMLA Cream		P
	Mean	SD	Mean	SD	
Children	2.0	1.4	1.5	1.5	.09
Parents	2.6	2.2	2.4	2.0	.54
Nurses	2.0	1.9	1.9	2.1	.78

* Children assessed pain using the faces scale; parents and nurses assessed pain using a 10-cm visual analogue scale.

Transient (and not clinically significant) erythema occurred in 19 children during amethocaine treatment, compared with 3 children during EMLA ($P < .001$). Blanching was observed during five treatments with amethocaine and 24 treatments with EMLA ($P < .001$).

In this study, it was important to keep the children blinded to the treatment to minimize the effect of bias. When asked which of the two study drugs had been applied for a shorter period, >70% of children said they could not distinguish between the two applications. The remainder were equally split between amethocaine and EMLA.

DISCUSSION

This study demonstrated that an application time of 30 minutes of amethocaine was clinically equivalent to 60 minutes of EMLA for Port-a-Cath procedures in children. We chose to compare the application times recommended by the respective manufacturers of amethocaine (Smith & Nephew) and EMLA (Astra Pharma). It is possible that a longer duration of application of amethocaine may have led to even greater anesthesia. However, our primary objective was to examine the purported advantage of amethocaine as a drug that requires only 30 minutes' application time to achieve adequate skin anesthesia. Our results indicate that amethocaine may be preferable to EMLA. Amethocaine is marketed commercially in Canada in a 1.5-g tube that delivers 1 dose. The cost is $3.24 (Canadian dollars). EMLA is marketed in a 5-g tube size that delivers ~2 doses. The cost is $5.00.

There is only one other pediatric trial comparing EMLA and amethocaine.[12] That study showed that a 60-minute application time for EMLA was more efficacious than 30 minutes of amethocaine for preventing venipuncture-induced pain. Limitations, however, included an open study design and the evaluation of pain by phlebotomists using a three-point scale.

We chose a δ value of one pain face on the faces scale as our clinically significant difference in children's pain. This difference is the minimum difference that can be detected with this scale.

The only adverse effects observed were erythema and blanching. Erythema was more common in the amethocaine group and blanching was more common in the EMLA group. These adverse effects have been reported previously.[12]

Another advantage of amethocaine over EMLA is that it does not commonly produce methemoglobinemia. In fact, injectable amethocaine has been given safely even to preterm infants.[16] Because the primary limiting factor for adopting EMLA in clinical practice in young infants has been the concern for methemoglobinemia, amethocaine may have a substantial role in that population.

It has been demonstrated previously that children

develop conditioned anxiety responses to painful procedures and associated objects.[17] In addition, most children do not habituate to repeated procedures over time.[17] Level of fear influences pain experience during a painful event.[18] We found that pain assessments in children and their parents were not influenced by factors other than the child's anxiety. These factors included the child's age, gender, and duration of diagnosis. Nurses, however, rated pain higher in males and in younger children during EMLA treatment. More research is needed to support these findings and to determine whether nursing perceptions of pain influence patient care practices.

CONCLUSION

In summary, amethocaine gel was found to be clinically equivalent to EMLA cream for alleviation of pain during Port-a-Cath puncture. We recommend that amethocaine be used instead of EMLA because of the shorter application time. Additional studies are required to document the comparative efficacy of amethocaine in other pediatric procedures.

ACKNOWLEDGMENTS

This work was supported in part by a grant from Smith & Nephew Medical Limited Montreal, Quebec.

We are indebted the nursing and medical staff of the Division of Hematology/Oncology, the participating children, and their parents.

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Pediatrics 1999;104;e31
DOI: 10.1542/peds.104.3.e31

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