

Topical 4% Amethocaine Gel Reduces the Pain of Subcutaneous Measles-Mumps-Rubella Vaccination

Lisa O'Brien, MSc*†§; Anna Taddio, BScPhm, PhD‡||; Moshe Ipp, MD¶; Morton Goldbach, MD¶; and Gideon Koren, MD*†§¶

ABSTRACT. *Objectives.* Ametop gel (4% amethocaine) is a relatively new topical anesthetic that produces anesthesia within 30 to 45 minutes and therefore may be appropriate for use in busy outpatient settings. The objective of this study was to assess the efficacy and safety of 4% amethocaine in reducing the pain of subcutaneous measles-mumps-rubella vaccination in 1-year-old infants.

Methods. A double-blind, randomized, placebo-controlled trial was conducted in pediatric outpatient clinics.

Results. A total of 120 infants participated in the study; 60 were followed up for assessment of antibody titers after 1 month. Either 1 g of amethocaine or placebo was applied for 30 minutes before vaccination. The Modified Behavioral Pain Scale was used to assess pain; the mean (standard deviation) pain scores for the amethocaine group ($n = 61$) was 1.5 (1.6) versus 2.3 (2.2) for the placebo group ($n = 59$). The rate of vaccination success (88% and 87%) was not different between treatment groups.

Conclusions. 4% Amethocaine significantly reduces the pain of measles-mumps-rubella vaccination in infants when compared with placebo and does not seem to interfere with subsequent development of protective antibody levels. Because of its relatively short application time (30 minutes), 4% amethocaine may be suitable for busy clinics and emergency departments. *Pediatrics* 2004; 114:e720–e724. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-0722; local anesthetic, amethocaine, tetracaine, pain, infants, vaccination.

inations also comes with the burden of pain and distress.

Topical local anesthetics are 1 viable option for decreasing the pain of routine immunizations. Lidocaine-prilocaine (EMLA; AstraZeneca, Mississauga, Ontario, Canada) has been shown to be effective for decreasing the pain of immunization^{4–7}; however, it is still not routinely used for this indication in infants and children. Lidocaine-prilocaine's long onset of action (minimum 60 minutes) and its relatively short duration of action (1–3 hours) may limit its use in busy clinical settings. More recently, amethocaine 4% gel (Ametop; Smith and Nephew, Montreal, Quebec, Canada), an ester-type local anesthetic also known as tetracaine, has emerged as an alternative to 5% lidocaine-prilocaine. Amethocaine has an onset of action of between 30 and 45 minutes and a duration of action of 4 to 6 hours. Amethocaine has been shown to decrease the pain of venipuncture, intravenous cannulation, and subcutaneous venous access in pediatric populations^{8–12}; its efficacy for reducing pediatric vaccination pain has not been previously documented. The current study sought to determine the efficacy and safety of a 30-minute topical application of 4% amethocaine for reducing the pain associated with subcutaneous measles-mumps-rubella (MMR) vaccination in infants.

METHODS

The study protocol for this randomized, double-blind, placebo-controlled trial was approved by the Research Ethics Board of the Hospital for Sick Children (Toronto, Ontario, Canada). Participants were recruited by a research assistant from 2 shared pediatric outpatient clinics in Toronto between December 2001 and April 2003. Healthy 1-year-old infants who were receiving their routine 1-year MMR vaccination were included in the study. Infants who presented with fever or illness that prevented administration of the vaccine or those who had a history of allergy or sensitivity to ester anesthetics were excluded from participation. Participants who arrived at the clinic with previous premedication with a systemic analgesic were not excluded from completing the study as systemic analgesics have not been shown to be effective in reducing the pain from an acute localized insult. The premedication rates between the 2 groups were later compared. Parents were informed of the study objectives and design through an information summary sheet. Written parental consent for infant participation in the trial was obtained on the day of the infant's 1-year clinic appointment.

The study pharmacist randomized each patient to receive either 4% amethocaine gel (Ametop) or placebo before the administration of the MMR vaccine; a 4-block randomization design was used. The placebo (Aquatain; Whitehall-Robins, Mississauga, Ontario, Canada) was visually and cosmetically identical to 4% amethocaine. One gram of drug or placebo was dispensed in unit-dose 5-mL oral syringes, heat sealed to prevent evaporation,

ABBREVIATIONS. MMR, measles-mumps-rubella; MBPS, Modified Behavioural Pain Scale.

Routine vaccinations are 1 of the most common sources of iatrogenic pain in infants and children¹; however, this pain is not routinely managed. In the United States and Canada, the recommended childhood immunization schedule calls for up to 20 injections within the first 18 months of life^{2,3}; nevertheless, the protection conferred by these vac-

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Accepted for publication Jul 23, 2004.

doi:10.1542/peds.2004-0722

No conflict of interest declared.

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and stored in a refrigerator at the study site for up to 1 week, after which it was discarded if unused and redispensed. Amethocaine is commercially available in 1.5-g tubes that produce ~1 g of topical amethocaine (~\$5.50 per tube CAD); currently, no amethocaine patch formulations are available.

On the day of vaccination and on arrival at the clinic, an observer who was unaware of the treatment assigned applied exactly 1.0 g of 4% amethocaine gel or placebo to the upper, outer part of the infant's arm and covered it with a dressing (Opsite; Smith and Nephew). The time of application of the study gel was recorded. The observer removed both the dressing and the study gel after 30 to 45 minutes and recorded the time of removal. The gel was wiped from the skin with a paper tissue. Within 1 to 5 minutes after the removal of the study gel, local skin reactions were assessed by the pediatrician according to a 4-point rating scale (none, mild, moderate, and severe). The vaccination procedure was performed by 1 of 2 study pediatricians within several minutes of gel removal; pediatricians were unaware of treatment assigned to infants.

The vaccination procedure was videotaped with a color camera (Sony Digital Handycam TRV18; Toronto, Ontario, Canada). A mirror was mounted on the wall behind the examining table so that the observer could film the infant's reaction both face on and from the mirror image. The observer stood ~3 ft from the infant and did not interfere with the procedure. The entire vaccination procedure was taped until the infant settled down.

Parents held their infant during the procedure, as this was the normal practice in the clinic. Before the vaccination, parents were told that they did not have to do anything differently because of the video camera; however, they were asked not to comfort the infant for 30 seconds after the vaccine was given. After that time, they could do whatever they would normally do. It was assumed that any potential distress caused by the request to withhold comforting for 30 seconds would be equally distributed among the treatment groups as a result of randomization and therefore would not affect the outcome of interest. A standardized immunization procedure was followed; immediately before the injection, the vaccination site was cleaned with an alcohol swab by the pediatrician, who then administered a 0.5-mL subcutaneous dose of the reconstituted MMR vaccine (Priorix; GlaxoSmithKline, Oakville, Ontario, Canada) with a 1.6-cm 25-gauge needle.

At least 1 month after the vaccination, both a phlebotomist and the observer visited the homes of participants and obtained a 5-mL blood sample from infants to measure their postvaccination MMR antibody titers. Blood was collected in plain red-topped Vacutainer tubes; once the blood specimen was obtained, the observer delivered it to the virology laboratory at the Hospital for Sick Children, where it was separated and frozen until analysis.

Outcome Measures

Modified Behavioral Pain Scale

A trained observer, who was unaware of the treatment assigned to each participant, scored the pain of vaccination from the videotapes using the Modified Behavioral Pain Scale (MBPS).¹ The MBPS is a behavioral measure that examines facial expression, cry, and body movement by assigning each behavior a score; scores for each observed behavior are summed, resulting in a total score per phase (before and after painful event); the minimum score is 0, and the maximum score is 10. The MBPS was used to score baseline pain and postvaccination pain for each vaccination procedure. In all instances, the prevaccination pain scores were assessed 5 seconds before the commencement of the vaccination; scores from 0 to 3 were assigned for each individual category of facial expression, cry, and body movement. Postvaccination pain scores were assessed within 15 seconds after the vaccination; facial expression and body movement scores ranged from 0 to 3, whereas cry scores ranged from 0 to 4. Scores were totaled for each phase; the difference between the pre- and postvaccination scores was taken as the final MBPS score. Interrater reliability for this scale was calculated for a randomly selected 20% of the sample; a κ statistic >0.8 was achieved.

Antibody Response

Commercially available assay kits were used to determine antibody titers. immunoglobulin G antibody titers for measles, mumps, and rubella were measured by enzyme-linked immu-

nosorbent assays (Zeus Scientific, Raritan, NJ; Bio-Rad, Redmond, WA). Measles and mumps antibody levels were reported as arbitrary units (AU); titers <27 AU were considered negative (not protective against disease), titers >40 AU were considered positive (protective against disease), and titers that fell between these values were considered indeterminate. Rubella antibody titers were reported as international units per milliliter; titers <10 IU/mL were considered negative, titers >20 IU/mL were considered positive, and titers that fell between these values were considered indeterminate.

Statistical Analysis

Infant pain response as determined by MBPS scores were analyzed using the *t* test. Patient demographics including gender, age, race, weight, and pain history were compared between the 2 arms of the study by χ^2 and *t* tests when appropriate. The significance level (probability) was set at .05 for all tests. The secondary outcome for the study was determination of antibody titer levels as determined by enzyme-linked immunosorbent assay; the proportion of patients who did not develop titers considered protective against disease was compared between groups using the χ^2 test. The significance level (probability) was set at .05.

A sample size of 48 patients per group was calculated using data from a previous study of vaccination pain with 5% lidocaine-prilocaine (EMLA)⁵; this would show a 50% difference in pain scores with a standard deviation that was 2-fold this difference (ie, effect size of 0.5). To account for possible dropouts and technical failures in videotaping and blood collection, we recruited a sample of 120 participants.

RESULTS

A total of 120 patients participated in the vaccination portion of the study; 60 participants were also followed up for assessment of antibody titers. Demographic data are presented in Table 1. No significant differences were found between the treatment groups. Seven percent of the placebo group had premedication (acetaminophen) on the day of vaccination compared with 16% of the amethocaine group ($P > .05$). When previous painful experiences were analyzed with regard to gender, it was found that significantly more boys in the amethocaine group had previous painful experiences than girls ($P < .001$). No difference was found between the groups in terms of the proportion of boys circumcised and uncircumcised ($P = .112$).

The mean duration of application of the study gels was not significantly different between the 2 treatment groups: 31 ± 5 minutes for the amethocaine group compared with 33 ± 5 minutes for the placebo group ($P > .05$). The time between removal of the study gel and the beginning of the vaccination procedure was not different between the amethocaine and placebo groups: 3.1 ± 2.9 minutes and 3.4 ± 3.0 minutes, respectively ($P = .590$).

At baseline, the mean MBPS score in the amethocaine-treated group was not different from that of the placebo group ($P = .399$; Table 2). The difference between baseline and postinjection scores was significantly lower in the amethocaine group when compared with the placebo group (1.51 vs 2.29, respectively; $P = .029$; Table 2).

Blood was collected for antibody analysis from 60 of the 120 participants, 30 per treatment group. The average time between blood collection and vaccination was ~60 days. The majority of participants who did not have blood collected for antibody analysis were lost to follow-up or had a technical failure in which the blood sample could not be obtained; there

TABLE 1. Demographic Data for Infants who Were Randomized to 4% Amethocaine or Placebo Group Before MMR Immunization

	Placebo Group (N = 59)	Amethocaine Group (N = 61)	P Value
Gender			.201
Female	33	27	
Male	26	34	
Age, d, mean (SD)	383 (30)	375 (13)	.052
Ethnicity			.563
White	41 (70%)	48 (79%)	
Black	3 (5%)	1 (2%)	
Asian	5 (8%)	5 (8%)	
Other	10 (17%)	7 (11%)	
Weight, kg, mean (SD)	10.02 (1.28)	9.95 (1.19)	.748
Mother's age, y, mean (SD)	34.3 (4.9)	32.9 (5.4)	.122
Prima parity	40%	62%	.017
Duration of last nap, min, mean (SD)	63 (43)	63 (41)	.977
Time between vaccination and last feed, min	140 (58)	154 (115)	.413
Previous painful experience	10 (7/10 = circumcision)	20 (16/20 = circumcision)	.045

Bonferroni correction used: $\alpha = .0045$. *t* test and χ^2 analyses were used.

TABLE 2. Outcomes for Pain, Antibody Response, and Local Skin Reactions After Exposure to Amethocaine and Placebo

Outcome	Placebo Group	Amethocaine Group	P Value
Pain (mean MBPS scores; SD)	(n = 59)	(n = 61)	
Baseline (total score)	3.0 (2.0)	3.3 (2.1)	.399
Postinjection (total score)	5.3 (2.5)	4.8 (2.6)	.309
Difference	2.3 (2.2)	1.5 (1.6)	.029*
Postvaccination antibody response	(n = 90)†	(n = 90)†	
Combined measles, mumps, and rubella immunity			
Immune, %	79 (88)	78 (87)	.823
Geometric mean, SD			
Measles, AU	55.0 (35.8)	53.2 (43.9)	.863
Mumps, AU	163.3 (55.0)	119.3 (74.9)	.012*
Rubella, IU/mL	140.4 (65.0)	107.8 (84.0)	.098
Local skin reactions	(n = 59)	(n = 61)	
Redness	26	52	<.001*
Pallor	16	29	.018*
Edema	4	27	<.001*

T test and χ^2 analysis were performed.

* Statistically significant at the $P = .05$ level.

† Overall immunity determined by combining individual antibody types for each participant.

were no differences between the groups in terms of reasons for blood collection failure ($P = .085$). Infant history of previous pain played a role in participation in follow-up blood collection; significantly more people without previous pain in the amethocaine group did not have their infants blood collected ($P = .048$). For participants for whom a blood sample was obtained, the rate of vaccination success (antibody titers positive for measles, mumps, and rubella) was similar between the groups: 88% for the placebo group and 87% for the amethocaine group ($P = .823$; Table 2).

Local skin reactions are described in Table 2. The amethocaine group experienced significantly more skin reactions than the placebo ($P < .001$). The most common reactions were erythema, followed by edema and pallor. A greater number of participants in the amethocaine group developed >1 skin reaction (eg, erythema plus edema) after exposure to the drug: 19 infants in the amethocaine group compared with 4 infants in the placebo group developed multiple skin reactions ($P < .001$). None of the skin reactions was deemed clinically significant.

DISCUSSION

This study demonstrated that 4% amethocaine reduces the pain of MMR vaccination. In addition, the

topical application of amethocaine did not seem to interfere with the development of protective levels of antibody titers. The results of this study are consistent with previous studies that have shown 5% lidocaine-prilocaine (EMLA) to be effective at reducing the pain of immunization.⁴⁻⁷ When a 60-minute application of lidocaine-prilocaine was tested in infants aged 3 to 28 months for diphtheria-pertussis-tetanus vaccination, pain scores were significantly lower in the lidocaine-prilocaine group when compared with placebo. Taddio et al⁵ also found that a 60-minute application of lidocaine-prilocaine was effective at reducing the pain of diphtheria-pertussis-tetanus vaccination in 4- to 6-month-old infants. Similar results were produced when lidocaine-prilocaine was used for diphtheria-tetanus-acellular pertussis-inactivated poliovirus-*Haemophilus influenzae* type b and hepatitis B immunization in infants up to 6 months of age.⁷ All of these studies used a 60-minute application time for lidocaine-prilocaine.

Placebo-controlled trials are not always considered ethical, particularly when standard, effective interventions are in place for given indications and therefore are available with which to compare the drug of interest. Lidocaine-prilocaine has been shown to be effective for reducing immunization pain; however,

currently, no standard treatment for this type of pain exists in clinical practice. As such, in designing this trial to determine amethocaine's efficacy for vaccination pain, the use of a placebo was found to be acceptable, as participants would not be receiving other local anesthetics, such as 5% lidocaine-prilocaine. Methodologically, placebo-controlled trials are more efficient than active controlled trials as smaller sample sizes are usually required to prove efficacy.

Halperin et al⁶ conducted a study similar to the one presently conducted with amethocaine, except that they used 5% lidocaine-prilocaine and evaluated a different formulation of the MMR vaccine. The Priorix MMR vaccine (GlaxoSmithKline) used in the present study has been shown to be less painful than the Merck MMRII vaccine (Merck, Kirkland, Quebec, Canada) used in the Halperin study.¹³ When the difference in total MBPS pain scores from this study were compared with that of Halperin's study,⁶ the pain scores are lower for the present study (1.51 ± 1.63 for amethocaine and 3.1 ± 0.20 for lidocaine-prilocaine); however, the difference between active and placebo drugs is similar (ie, magnitude of effect).

Ester anesthetics, including amethocaine, have been shown to possess antimicrobial activity *in vitro*,^{14,15} but the significance of this in a clinical setting has not been examined. This antimicrobial activity leads to concerns regarding the inactivation of live attenuated vaccines: is efficacy altered when these vaccines are administered after exposure to amethocaine? We did not find a difference in success rate between the amethocaine and the placebo groups in terms of the proportion of patients who developed immunoglobulin G antibody titers that were considered protective against measles, mumps, and rubella. In addition, when the geometric mean for the measles and mumps antibody titers in this study were examined for the amethocaine and placebo groups, both groups were found to develop antibody levels considered protective against their respective diseases. It should be noted, however, that there was a significant difference between the amethocaine and placebo groups in terms of the geometric mean for the mumps titers. Antibody levels were lower in the amethocaine group ($P = .012$); however, the levels were still protective. This study had a power of 80% to detect a 31% difference in measles antibody titers, a 26% difference in mumps antibody titers, and a 24% difference in rubella antibody titers between the 2 treatment groups at a significance level of $P = .05$ (sample power 2.0).

It is reassuring that the results of the current study are consistent with studies that have also found that the topical application of local anesthetics (eg, lidocaine-prilocaine) has not adversely affected antibody response to vaccination.^{6,7} It is unlikely that topical administration of a local anesthetic such as amethocaine would affect the immunogenicity of a vaccine as the site of action of the drug is at the epidermal junction, whereas the vaccine is administered subcutaneously below this region.

Local skin reactions were commonly observed in study participants who received amethocaine. Reactions including erythema, pallor, and edema were

reported more often in the amethocaine group than in the placebo group. The presence of these reactions is consistent with other reports from topical amethocaine use.^{8,10,16} Erythema is the most commonly reported local skin reaction; this reaction is transient. Amethocaine has vasodilatory properties that account for the characteristic erythema produced when it is used for cutaneous anesthesia. Pallor and edema are cutaneous reactions that are reported less commonly. Of importance, none of these reactions was judged by the blinded physicians to be clinically significant. It should be noted that although the site of vaccination was observed and redness in response to amethocaine could be potentially visualized, the primary endpoints were measured from a videotape that focused on facial response and not the site of injection.

In routine clinical practice, several vaccines are commonly administered to infants at 1 visit; therefore, >1 potential application site for amethocaine exists. It therefore is important to ascertain the safety of amethocaine at concurrent application sites. To date, 3 pediatric trials have used amethocaine at multiple sites^{9,17,18}; however, no study has specifically evaluated the safety of concurrent applications. One study was unable to detect amethocaine in blood samples obtained from participants immediately after a 30-minute topical application of amethocaine to the dorsum of each hand.¹⁷ As expected, local erythema at the site of application was the most commonly reported adverse effect in all 3 studies. High systemic concentrations of amethocaine are not expected as bioavailability from a topical application is low (~15%).¹⁹ It therefore is unlikely that simultaneous applications of topical amethocaine to normal, healthy, intact skin would pose major safety concerns, particularly as amethocaine is rapidly metabolized in the skin and blood by nonspecific esterases.

Amethocaine was able to decrease the pain of vaccination within 30 minutes of application; this is half of the time of lidocaine-prilocaine. Amethocaine and lidocaine-prilocaine have been shown to produce comparable skin anesthesia for minor medical procedures when used for their recommended application times; however, amethocaine has a shorter onset of action.^{8,12} Several studies have shown amethocaine's superiority to lidocaine-prilocaine after 30- to 45-minute application times. In a double-blind volunteer study comparing a 30-minute application of amethocaine and that of lidocaine-prilocaine, all participants were anesthetized to pinpricking after a 30-minute amethocaine application compared with 20% of those who were exposed to lidocaine-prilocaine for the same amount of time ($P < .001$).²⁰ In a double-blind, randomized, controlled trial, it was found that when used for venipuncture, amethocaine produced anesthesia in more participants than lidocaine-prilocaine after a 30-minute application time (60% vs 15%; $P < .01$).¹⁸ After a 40-minute application time, amethocaine was found to produce clinically acceptable anesthesia in a greater number of patients who underwent intravenous cannulation than lidocaine-prilocaine (85% vs 66%; $P < .05$).¹⁰ A

randomized, double-blind, placebo-controlled trial comparing the same 2 drugs after a 45-minute application time again found amethocaine to be superior to lidocaine-prilocaine for reducing the pain of intravenous cannulation ($P < .001$).²¹

A shortened duration of application increases the feasibility of routinely using local anesthetics such as amethocaine in busy clinical practices and emergency departments. Amethocaine gel is currently available in Australia, Canada, New Zealand, and the United Kingdom; however, it has not been approved for use in the United States (Smith and Nephew, personal communication, 2003).

CONCLUSIONS

Iatrogenic pain is an important phenomenon that must not be ignored in pediatric medicine, particularly when safe and effective interventions are available to manage it. Local anesthetics are a viable option for the relief of cutaneous pain. It has been shown that parents are willing to pay to decrease the pain and distress of childhood vaccinations.²² Pretreatment with 4% amethocaine gel has been shown to reduce significantly the pain associated with subcutaneous MMR vaccination in 1-year-old infants when compared with placebo; topical administration of amethocaine does not seem to interfere with the subsequent development of protective levels of antibody titers. Amethocaine's efficacy, combined with its rapid onset of action, may allow for its routine use in busy clinical practices as it can be applied during a routine wait in a pediatrician's office; however, additional investigation of its safety during vaccination is recommended before widespread clinical use.

ACKNOWLEDGMENTS

This study was sponsored by Smith and Nephew Ltd (Montreal, Quebec, Canada).

We thank the nurses from the pediatric practice of Drs Ipp and Goldbach for help throughout the study, Kim Hober for expertise in phlebotomy, and Lily Rabinovich for virologic work.

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Pediatrics 2004;114:e720

DOI: 10.1542/peds.2004-0722

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