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A Randomized Controlled Trial to Evaluate S-Caine Patch™ for Reducing Pain Associated with Vascular Access in Children

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Background: **A randomized, double-blinded trial was performed to evaluate the efficacy and safety of the S-Caine Patch™ (ZARS, Inc., Salt Lake City, UT), a eutectic mixture of lidocaine and tetracaine, for pain relief during venipuncture in children.**

Methods: **With institutional review board approval, parental consent, and patient assent, 64 children who were scheduled for medically indicated vascular access at two centers were randomly assigned (2:1) to receive either an S-Caine Patch™ or a placebo patch for 20 min before venipuncture procedures. The primary outcome measure was the child's rating of pain during venipuncture using the Oucher pain scale. Additional measures of efficacy included the blinded investigator's and an independent observer's four-point categorical scores. Variables were compared between treatments using Mantel–Haenszel summary chi-square tests or Pearson chi-square tests.**

Results: **The S-Caine Patch™ produced significantly greater pain relief compared with placebo (median Oucher scores of 0 *vs.* 60; $P < 0.001$). Fifty-nine percent of the children in the S-Caine Patch™ group reported no pain compared with 20% of the children in the placebo patch group. The investigator estimated that 76% of the children in the S-Caine Patch™ group experienced no pain during venipuncture *versus* 20% in the placebo patch group ($P = 0.001$). Independent observer ratings also favored the S-Caine Patch™ ($P < 0.001$). Mild skin erythema (< 38%) and edema (< 2%) occurred with similar frequencies between the groups.**

Conclusion: **This study demonstrated that a 20-min application of the S-Caine Patch™ is effective in lessening pain associated with venipuncture procedures. Adverse events after S-Caine Patch™ application were mild and transient.**

NONINVASIVE local anesthetic delivery systems are increasingly used in children to anesthetize the skin without the need for injections. This can reduce the pain and distress associated with procedures such as vascular access, immunization, and circumcision.[1,2] Children express considerable fear, behavior, and distress during medical procedures that involve needles.[3] Repeated painful procedures without the benefit of analgesia may cause sensitization of the somatosensory system, anticipatory fear, and heightened pain perception with subsequent exposure to needle-induced tissue injury.[1,4]

Although most topical formulations such as 5% lidocaine–prilocaine cream (EMLA; AstraZeneca, Wilmington, DE), 4% tetracaine gel (Amethocaine; Smith and Nephew Healthcare, Hull, United Kingdom), 4% lidocaine cream (L.M.X.4; Ferndale Laboratories, Inc., Ferndale, MI), and iontophoresis provide adequate cutaneous analgesia for a variety of clinical situations, there are limitations to most of these formulations, and there have been reports of adverse reactions. Lidocaine–prilocaine cream (5%) and iontophoresis of lidocaine cause initial skin blanching in almost all patients as a result of vasoconstriction, which may make vascular access more difficult.[5–7] Some newborn infants are vulnerable to methemoglobinemia after administration of prilocaine because of the immaturity of the methemoglobin reductase enzyme pathway. Although there have been few reports of 5% lidocaine–prilocaine cream causing methemoglobinemia in infants, other studies in neonates have not consistently supported these findings.[2,8,9] Limiting the dose and area of application can minimize this side effect. Iontophoresis requires equipment and training for appropriate application, and some children experience stinging pain during current application and skin burns from the electrodes.[5,10,11]

In clinical practice, a topical local anesthetic preparation that provides reliable analgesia with fast onset of action may have utility over those preparations that require longer application times. The commonly used topical local anesthetics in children have a slow onset time, except for iontophoresis, which works within 10 min. Time to onset of effective anesthesia depends on the physiochemical properties of the local anesthetics and the mode of delivery that determines penetration through the skin. Lidocaine–prilocaine cream (5%), 4% tetracaine gel, and 4% lidocaine cream require average application times of 60, 45, and 30 min, respectively to achieve effective analgesia.[6,12] More recently, a needle-free injection device (J-TIP; National Medical Products, Irving, CA) was introduced to deliver a local anesthetic under pressure into the subcutaneous tissue without a needle puncture. Compared with subcutaneous infiltration of local anesthetic, the needleless injector produced

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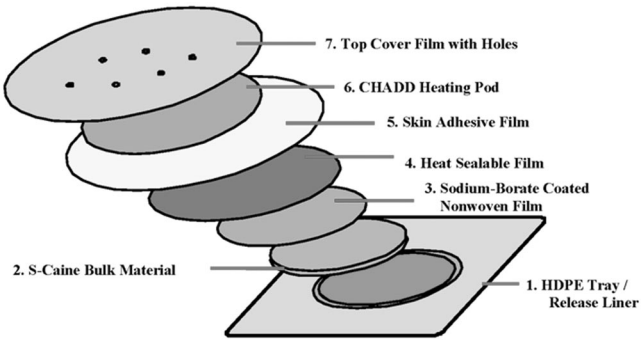

Fig. 1. The S-Caine Patch™ contains a controlled heat-aided drug delivery (CHADD) patch with a heat-generating medium, a bottom release liner, a drug reservoir for lidocaine and tetracaine, and a medical tape cover. HDPE = high density polyethylene.

less pain but poorer skin anesthesia during venous cannulation.[13]

To date, no single formulation or physical means of improving permeation of local anesthetics has gained universal acceptance, because of the above-stated limitations. We prospectively investigated the efficacy and tolerability of a novel delivery device, the S-Caine Patch™ (manufactured by ZARS, Inc., Salt Lake City, UT), a eutectic mixture of lidocaine and tetracaine that uses a controlled heating system to accelerate transcutaneous delivery and analgesic effect of local anesthetics.

Materials and Methods

After obtaining approval from the institutional review boards (Children's Hospital Boston, Boston, MA, and Children's National Medical Center, Washington, DC), 64 children and adolescents who required intravenous access or blood sampling were approached for participation in the study. Participation was offered to children aged 3–17 yr of any race and of either sex who did not meet the following exclusion criteria: known sensitivity to components (*i.e.*, sulfites, adhesives) of the test materials, damaged skin at the designated patch site, pregnancy or breast feeding, allergic skin hypersensitivity or allergy to amide or ester local anesthetics, use of analgesics during the past 24 h, and inability to understand or use the pain assessment tool. Informed consent included an understanding that the placebo patch would provide no anesthesia for the procedure to be undertaken.

S-Caine Patches™ are 6.25 × 7.5 cm and composed of a eutectic mixture of 70 mg lidocaine and 70 mg tetracaine in a ratio of 1:1 by weight, a bioadhesive layer, a heating element that generates a controlled amount of heat (39°–41°C), and a film cover (fig. 1). The excipients in the formulation are polyvinyl alcohol, Span 40, water, methylparaben, and propylparaben. The placebo patches used in this study were identical in appearance to the active patch, including the active heating element, but had olive oil in place of the active ingredients. The active and placebo patches were manufactured by Tapemaker, Inc. (St. Paul, MN).

Table 1. Summary of Skin Reactions (n = 64)

Characteristic	S-Caine Patch™ (n = 43)	Placebo Patch (n = 21)	*P* Value*
Erythema			
No erythema	21 (49)	12 (57)	0.21
Very slight erythema	13 (30)	8 (38)	
Well-defined erythema	9 (21)	1 (5)	
Moderate to severe erythema	0	0	
Severe erythema to slight eschar formation	0	0	
Edema			
No edema	43 (100)	19 (90)	0.19
Very slight edema	0	2 (10)	
Slight edema	0	0	
Moderate edema	0	0	
Severe edema	0	0	
Blanching			
No blanching	43 (100)	21 (100)	

Values are presented as n (%).

* Mantel-Haenszel summary chi-square, stratified by center.

Eligible patients were randomly assigned (2:1), according to computer-generated random numbers, to receive either one S-Caine Patch™ or one placebo patch before the vascular access procedure. All participants, including the investigators, the child, and the parents, were unaware of the identity of the treatment.

The study patches were applied for 20 min and then removed. The 20-min application time was based on an earlier clinical trial in adults that documented that a 20-min application time of the S-Caine Patch™ was effective in providing dermal anesthesia for venous access procedures (personal communication, Michael A. Ashburn, M.D., Medical Director, ZARS, Inc., August 2002).

After a 20-min patch application, the investigator removed the study patch and evaluated the treatment area for skin reactions. Erythema and edema were evaluated on five-category scales (table 1). Skin blanching was assessed in five categories: no blanching; slight, diffuse blanching with indistinct outline; more intense blanching with half of the treated site perimeter outlined; marked blanching with a distinct outline of the treated site; and extreme blanching with a distinct outline of the treated site. The investigator assessed the patient's skin type and behavior before the vascular access procedure using a three-point scale (tables 2 and 3).

The investigator determined the location of the venipuncture and the needle or catheter gauge, and the decision was based on the investigator preference, the age of the child, and the purpose of the procedure. The primary efficacy endpoint for the study was pain intensity as determined by the Oucher pain scale (consisting of a vertical six-photograph scale with a corresponding vertical numerical scale of 0–100 marked off in units of 10 points; 0 score indicates no pain and 100

Table 2. Patient Characteristics (n = 64)

Characteristic	S-Caine Patch™ (n = 43)	Placebo Patch (n = 21)	*P* Value
Sex, %			0.71*
Male	28 (65%)	12 (57%)	
Female	15 (35%)	9 (43%)	
Age, yr			
Mean ± SD	8.0 ± 4.6	7.7 ± 4.4	0.78†
Range	3–17	3–16	
Race			0.36‡
White	25 (58%)	15 (71%)	
Black	14 (32%)	4 (19%)	
Hispanic	4 (9%)	2 (10%)	
Height, cm			
Mean ± SD	126.3 ± 27	121.5 ± 27.3	0.49†
Range	70–182.5	72.5–165	
Weight, kg			
Mean ± SD	35.5 ± 23.5	29.6 ± 16.9	0.29†
Range	10.5–44	11.8–73.6	
Skin type			
I (always burns easily, rarely tans)	1 (2%)	2 (10%)	0.02*
II (burns moderately, tans gradually)	3 (7%)	4 (19%)	
III (never burns, deeply pigmented)	10 (23%)	7 (33%)	
IV (never burns)	13 (30%)	4 (19%)	
V (rarely burns)	6 (14%)	1 (5%)	
VI (burns minimally)	10 (23%)	3 (14%)	

* Mantel-Haenszel summary chi-square, stratified by center. † Two-way analysis of variance with factors: treatment group, center, and treatment by center. ‡ Mantel-Haenszel summary chi-square (white *vs.* other), stratified by center.

Table 3. Summary of Vascular Access Procedure (n = 64)

Variable	S-Caine Patch™ (n = 43)	Placebo Patch (n = 21)	*P* Value
Preprocedure behavior			0.59
Calm	21 (49%)	9 (43%)	
Slightly frightened	14 (32%)	7 (33%)	
Frightened	8 (19%)	5 (24%)	
Procedure, n (%)			0.69
Blood draw	16 (35%)	7 (33%)	
Intravenous access	26 (60%)	14 (67%)	
None specified	1 (5%)*	0	
Intravenous catheter gauge			0.36
18	1 (2%)	0	
20	5 (12%)	3 (15%)	
21	14 (33%)	4 (20%)	
22	20 (49%)	10 (50%)	
23	2 (5%)	3 (15%)	
Location of procedure			
Right antecubital vein	20 (46%)	8 (38%)	
Left antecubital vein	13 (32%)	7 (35%)	
Right hand	1 (2%)	1 (5%)	
Left hand	8 (19%)	5 (25%)	
Hand	1 (2%)	0	
Procedure duration	(n = 41)	(n = 20)	0.63
<1 min	29 (71%)	13 (65%)	
1–1.9 min	9 (22%)	5 (25%)	
2+ min	3 (7%)	2 (10%)	

* Patient was scheduled to undergo an unspecified procedure; however, the site staff determined that the procedure was not necessary and did not perform the procedure.

points indicates the worst possible pain), a self-assessment pain tool that has been tested for validity and reliability in children.[14] The children used the Oucher pain scale by selecting either a photograph or a number that most closely represented the level of pain intensity they experienced immediately after the venipuncture procedure. The investigator and independent observer separately evaluated the degree of analgesia provided by the study drug by completing a four-point categorical scale (figs. 3 and 4). Before discharge from the study center, the families were given a written description of potential delayed skin reactions and were instructed to call the study site if any skin reaction developed.

Sample Size

A difference in the binary pain response (yes–no pain) between the active drug and placebo groups of 50% was considered to be clinically significant. With a goal of detecting a 50% difference in the percentage of patients with pain between the two groups, sample sizes of 36 patients in the S-Caine Patch™ group and 19 patients in the placebo group would provide 90% statistical power ($\alpha = 0.05$, $\beta = 0.1$) based on the Fisher exact test (nQuery Advisor, version 4.0; Statistical Solutions, Saugus, MA). Statistical significance was adopted at the 5% level (two tailed). We elected to enroll 64 patients with a 2:1 randomization because of the potential for children to withdraw from the study after enrollment for a variety of reasons and also because of the potential loss at the follow-up telephone contact.

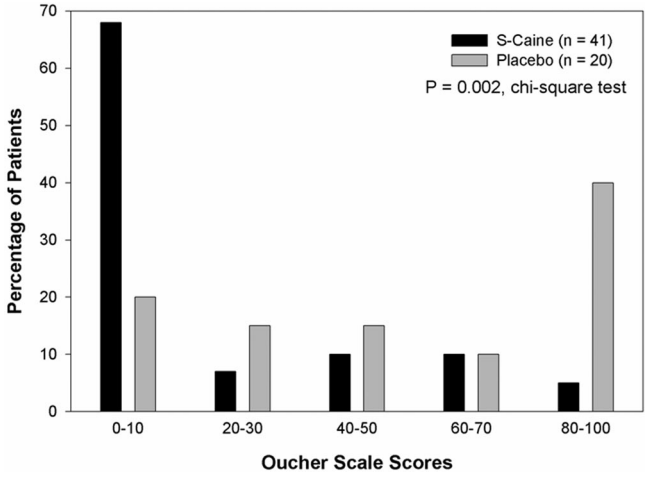

Fig. 2. There was highly significant difference between the S-Caine Patch™ and placebo groups based on the distribution of Oucher pain scores (chi-square test = 17.22; *P* = 0.002). The median Oucher scale score and interquartile range were lower in the S-Caine Patch™ group (0 and 0–35, respectively) compared with the placebo group (60 and 20–80, respectively) (*P* < 0.001, Mann–Whitney U test). In the S-Caine Patch™ group, 68% of patients had scores of 0–10, whereas only 20% of the placebo group had Oucher scale scores in this range.

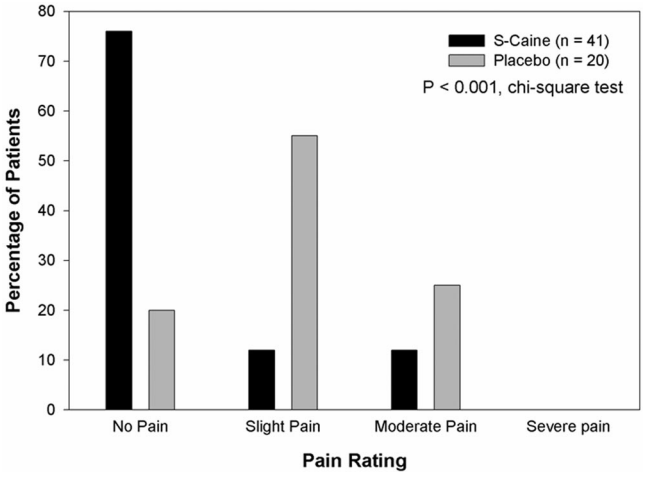

Fig. 3. The investigator's evaluation of patient pain showed significant pain relief with the S-Caine Patch™ compared with placebo ($P = 0.001$).

Statistical Analysis

To assess the comparability of treatment groups and study centers, age, height, weight, and preprocedure vital signs were compared using two-way analysis of variance, with the fixed factors of center and treatment. Race, sex, use of medications, and anesthetic history were compared between treatment groups using Mantel–Haenszel chi-square tests, adjusting for center. Erythema, edema, skin type, and blanching scores were compared between treatments using Mantel–Haenszel chi-square tests for ordered or dichotomous outcomes, stratified by center. Median and interquartile range Oucher scores were compared between the two groups using the nonparametric Mann–Whitney U test. Simple binary proportions were compared using the Fisher exact test. Statistical analysis was performed using the SPSS software package (version 12.0; SPSS Inc., Chicago, IL). Two-tailed values of $P < 0.05$ were regarded as statistically significant.

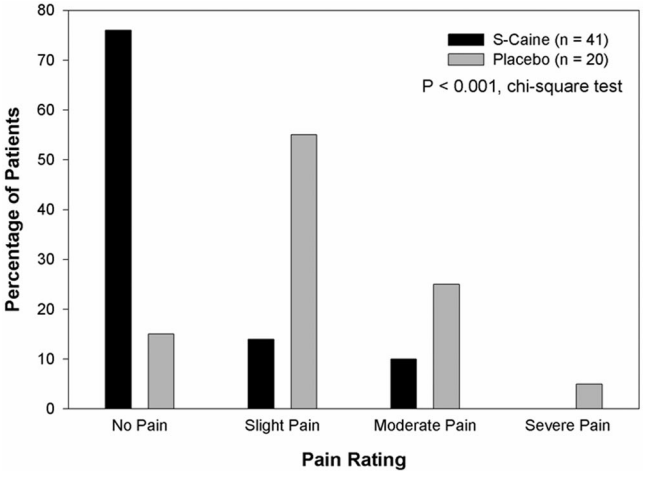

Fig. 4. The independent observer's evaluation of patient pain showed significant pain relief with the S-Caine Patch™ compared with placebo ($P = 0.001$).

Results

There were no clinically meaningful differences between the two centers in demographic, background, and procedure variables; therefore, data from both sites were combined for analysis. A total of 64 patients entered the study and were randomized to treatment: 43 to the S-Caine Patch™ group and 21 to the placebo patch group. A total of 61 patients completed the study; 41 in the S-Caine Patch™ group and 20 in placebo patch group were included in the efficacy analyses using Oucher pain scores. After the patch application, 2 children refused to undergo venipuncture because of severe anticipatory anxiety and agitation. Site staff determined that venipuncture was not necessary in a third child.

Demographic and baseline characteristics of patients are summarized in table 2 and were comparable between the S-Caine Patch™ and placebo patch groups except for skin type. Although race was comparable between the groups, significantly more African-American patients were enrolled at one center than at the other (53% *vs.* 6%; $P < 0.001$). A statistically significant difference existed for skin type with 67% of patients in the S-Caine Patch™ group having skin type IV, V, or VI compared with 38% of patients in the placebo patch group. Significantly more patients at one center had darker skin types than patients at the second center ($P = 0.002$) (table 2). Within the S-Caine Patch™ group, there were no differences in the Oucher scores (median and interquartile range) between light-skinned white and Hispanic children (0, 0–40) compared with African-American children (0, 0–33) ($P = 0.97$, Mann–Whitney U test). There were no differences in the pretreatment vital signs (tympanic temperature, heart rate, respiratory rate, blood pressure; $P > 0.05$) between the S-Caine Patch™ and placebo patch groups.

Forty-two percent of the patients in the S-Caine Patch™ group and 52% of the patients in the placebo patch group were using concomitant nonanalgesic medications at the time of enrollment in the study ($P = 0.58$). Twelve patients in the S-Caine Patch™ and 5 patients in the placebo patch groups had previous experience with a topical local anesthetic ($P = 0.9$). All but one patient, who had previous experience with topical local anesthesia, had previously received 5% lidocaine–prilocaine cream. Of the 17 who reported previous uses of topical local anesthetics, 12 were for injection or intravenous cannulation. Most of the patients who had received topical local anesthesia before the study indicated that the anesthetic had eliminated pain (75% and 60% in the S-Caine Patch™ and placebo patch groups, respectively). Eight of the patients in the S-Caine Patch™ group (67%) and 2 of the patients in the placebo patch group (40%) reported a favorable experience with the previous local anesthetic.

The children's preprocedure states of anxiety were not

significantly different between the two groups (table 3). There were no significant differences between the two groups with respect to the vascular access procedure site, duration, and use of needle gauges (table 3).

Patients in the S-Caine group reported significantly lower pain associated with the vascular access procedure compared with the placebo group (median Oucher scores of 0 *vs.* 60; $P < 0.001$, Mann–Whitney U test, and 25th–75th interquartile ranges of 0–35 *vs.* 20–80, respectively). Twenty-four patients (59%) reported no pain (Oucher score of 0) in the S-Caine group, whereas only 4 patients (20%) in the placebo group reported no pain ($P < 0.001$). Two patients (5%) in the S-Caine group reported severe pain (Oucher score of 100) and 4 patients (20%) in the placebo group reported severe pain. The distribution of Oucher scores differed significantly between the two groups (fig. 2). Furthermore, both investigator and independent observer evaluations corroborated the effectiveness of the active drug by reporting no pain during vascular access procedure in 31 patients (76%) in the S-Caine group (figs. 3 and 4).

Patients who received S-Caine Patch™ treatment had slightly more erythema and edema than patients who received placebo patch treatment, but the difference was not statistically significant. No blanching was observed in any patient (table 1). There were no other adverse events. No patient experienced a delayed allergic skin reaction.

Discussion

The S-Caine formulation contains a 1:1 (weight: weight) eutectic mixture of 70 mg lidocaine and 70 mg tetracaine. The term *eutectic mixture* refers to a mixture having a melting point lower than that of the individual components. Hence, the lidocaine and tetracaine are melted together into a liquid mixture that forms the oil phase of the drug product in the S-Caine Patch™. The formulation leads to local anesthesia by the release of lidocaine and tetracaine from the patch into the epidermal and dermal layers of the skin. When applied to the skin, heat passes from the S-Caine Patch™ to the treatment area, thereby increasing skin temperature. After application of the S-Caine Patch™, the skin reaches and maintains a temperature of approximately 39°–41°C. It is believed that the application of controlled heat enhances the delivery of the S-Caine drug formulation by both reducing the time required for anesthetic effect and increasing the total amount of drug delivered (fig. 1).

This study demonstrated that the S-Caine Patch™ reduced pain significantly compared with the placebo patch within a 20-min application time in children. A total of 59% of the children in the S-Caine Patch™ group were free of pain (Oucher score of 0) during the venipuncture compared with 20% of the children in the placebo patch group, signifying a decrease in pain experience with the active drug.

A relatively wide range of needle and catheter sizes was included in this trial. Selection of needle and catheter size was at the discretion of the investigator and was based on investigator preference, the indication for the venipuncture procedure, and the age of the child. In addition, selection of the location of the procedure was also at the discretion of the investigator using similar criteria. Because the size of the needle and the location of the procedure can impact the patient's pain experience, both of these variables have the potential to confound the results. Fortunately, there were no differences between the two study groups with regard to the distribution of needle and catheter size and location of procedure.

The success rate of vein entry and cannulation was 100% in both groups, possibly aided by the vasodilatatory effect produced by the heating element and by the direct pharmacologic action of tetracaine. This success rate is much higher than previously reported in clinical trials with 5% lidocaine–prilocaine cream and 4% lidocaine cream (60–84%); however, a variety of other factors may contribute to the success rates of venipuncture and vascular cannulation. Future direct comparison studies may address whether the choice of topical anesthetic affects technical success.[7]

The individual pain scores in both groups spanned from 0 to 100 on the Oucher Scale (range of the scale was 0–100). However, the majority of these scores in the S-Caine Patch™ group were close to the no-pain end of the scale (fig. 2). Such a dispersion of scores may reflect either wide variation in pain response or ineffectiveness of the S-Caine Patch™ in a small subgroup of patients. Although higher pain scores could result from poor pain control, in some children, pain perception could be amplified by fear, anxiety, poor coping style, and previous experience, despite effective control of pain associated with needle insertion.[3] Nevertheless, the reduction of pain associated with venipuncture would be of considerable clinical benefit in reducing the child's distress in subsequent venipuncture.

Transient and mild local skin reaction occurred in both the S-Caine Patch™ and placebo patch groups and consisted of slight erythema and very slight edema at the site of application in a few patients (table 1). Patients who received S-Caine Patch™ treatment had slightly more erythema and edema than patients who received a placebo patch, but the difference was not statistically significant. The occurrence of erythema in approximately half of the patients receiving the S-Caine Patch™ was expected because of the cutaneous vasodilatory actions of tetracaine and local heating, and it resolved spontaneously. Blanching did not occur in either group.

Iontophoresis of 4% lidocaine has been shown to provide rapid, effective topical anesthesia for superficial

dermatologic procedures, such as intravenous cannulation.[5,10,11] However, iontophoresis of lidocaine requires equipment and training for appropriate application. In addition, some children experience stinging pain during current application and skin burns from the electrodes.[5,10,11] None of the children in our study reported any discomfort associated with the application of the study patch, and the patch was well accepted by the children and their parents.

Recent studies in adults and children have demonstrated that topical formulations containing tetracaine are efficacious and may provide analgesia with a faster onset, a longer duration of action, and greater depth of anesthesia.[15,16] Tetracaine is commonly combined with lidocaine and epinephrine for repair of scalp and facial lacerations in children.[17] A second potential advantage in comparison to prilocaine-containing formulations such as 5% lidocaine–prilocaine cream is that methemoglobinemia has not been reported with either lidocaine or tetracaine, even when used for repair of mucous membrane lacerations.[18] After application to intact skin, tetracaine absorption and systemic exposure is negligible.[19,20] This is primarily a result of dermal metabolism by nonspecific esterases (to *N*-butyl-p-aminobenzoic acid), drug retention, and slow release from the stratum corneum, coupled with extremely rapid clearance by plasma pseudocholinesterases.[21] Tetracaine was undetectable in the blood of children aged 1–5 yr after topical application to intact skin.[19] Tetracaine blood concentrations were not measurable even after application to lacerations requiring suture repair.[21] The potential for systemic absorption of lidocaine through intact skin is also negligible because the mature skin of newborn infants is relatively impermeable to lidocaine.[22] After application of 5% lidocaine–prilocaine cream to children aged 3–12 months, the concentration of lidocaine reached 0.16 μg/ml, which is well below the concentrations considered to be toxic (> 5 μg/ml).[23] In another report of neonates who received multiple doses of 5% lidocaine–prilocaine cream applied to the heel four times a day, concentrations of lidocaine were less than 0.23 μg/ml, which is also well below the toxic level.[24]

We conclude that the S-Caine Patch™ decreases pain substantially during routine vascular access and cannulation and has a demonstrably shorter onset time than most local anesthetic formulations and delivery systems in current use. Further studies are warranted to compare the quality of analgesia conferred by the S-Caine Patch™ directly to different formulations routinely used for pediatric venipuncture.

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