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Use of the Synera™ Patch for Local Anesthesia Before Vascular Access Procedures: A Randomized, Double-Blind, Placebo-Controlled Study

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ABSTRACT

Objective. This randomized, double-blind, placebo-controlled, paired study compared the Synera™ patch, a drug delivery device comprised of an eutectic mixture of lidocaine (70 mg) and tetracaine (70 mg) whose onset is accelerated by a controlled heating device, with placebo. The objective of the study was to evaluate the efficacy of Synera in inducing local anesthesia before a vascular access procedure.

Design. Before the vascular access procedures, adult volunteers randomly received a concurrent application of Synera and placebo to the right and left antecubital surfaces. Forty subjects received 20-minute treatments. After each vascular access procedure, efficacy evaluations were completed by the subject, investigator, and an independent observer. Median subject-reported pain intensity, using the visual analog scale scores (VAS, 0–100 mm scale) were significantly lower for Synera than placebo (5 mm vs 28 mm, $P < 0.001$).

Results. Compared with placebo, more subjects reported adequate anesthesia following Synera (73% vs 31%, $P = 0.002$), and more subjects indicated they would use Synera again (70% vs 33%, $P = 0.006$). Investigators rated more subjects having no pain with Synera compared with placebo (63% vs 33%, $P = 0.021$), and more subjects having adequate anesthesia with Synera (60% vs 23%, $P = 0.004$). Independent observers rated 68% of subjects having no pain with Synera compared with 38% with placebo ($P = 0.015$). Side-effects were limited to localized pruritus and erythema. Erythema was more common with Synera than placebo (62% vs 42%, $P = 0.018$).

Conclusions. A 20-minute application of Synera consistently provided clinically useful anesthesia for vascular access procedures, and appears to be well suited for topical dermal anesthesia due to its reduced time required to produce adequate anesthesia and high subject and investigator acceptance.

Key Words. Topical Analgesia; Lidocaine; Tetracaine; Venipuncture; Heat-Facilitated Drug Delivery System

Introduction

There is increasing awareness of the importance of treating procedure-related pain, especially in children [1]. Patients undergoing vascular access procedures are often afraid of needles and the discomfort associated with injections [2]. This type of pain and/or fear can be stressful to patients, especially pediatric patients. Additionally, the emergence of new laser procedures and the increasing frequency of various diagnostic and therapeutic procedures continue to increase the need for effective topical anesthesia. As a result, topical anesthesia has received considerable clinical interest, and a number of painless alternatives to injected anesthesia have been studied, including patch delivery systems [3], iontophoresis [4], microneedle [5], and Powderjet technologies [6], as well as various creams and gels [7].

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Although several topical local anesthetic drugs can be used to anesthetize open wounds, few products effectively anesthetize intact skin. Various attempts to anesthetize intact skin using topical local anesthetics have met with limited success. Reports of successful skin anesthesia achieved with a mixture of lidocaine and tetracaine have appeared recently [8]. Specifically, a new transdermal drug delivery system that uses controlled heat to enhance the delivery of local anesthetics through the skin has been developed. The Synera patch (Endo Pharmaceuticals, Chadds Ford, PA, USA) is composed of a 1:1 eutectic mixture of tetracaine and lidocaine base and a controlled heat-aided drug delivery system to anesthetize intact skin. Use of Synera has been reported in volunteers [3] and in children undergoing vascular access procedures [9]. The purpose of this study was to compare Synera with placebo to evaluate the efficacy of Synera in inducing local anesthesia before a vascular access procedure.

Methods

This was a randomized, double-blind, placebo-controlled, paired study in adult volunteers who were undergoing a vascular access procedure. This study was conducted by investigators at the Columbia-Presbyterian Medical Center and the Children's National Medical Center. This study was approved by the Columbia-Presbyterian Medical Center Institutional Review Board and the Children's National Medical Center Institutional Review Board. All subjects gave informed consent before participating.

Synera is a drug delivery system that uses controlled heat to enhance the delivery of a 1:1 (w:w) eutectic mixture of 70 mg tetracaine base, United States Pharmacopeia and 70 mg lidocaine base, USP to the skin. Synera consists of a plastic tray, the drug formulation, an adhesive layer, the heating element, and a release liner. The heating element generates a controlled level of heating that ranges from approximately 36°C to 40°C for a consistent amount of time (approximately 2 hours). The placebo patches contained the controlled heating element, but contained olive oil in place of the active ingredients. The active and placebo were visually indistinguishable. The study patches were activated and applied by removing each patch from its airtight pouch, peeling the release liner, and applying the patch to the skin.

Subjects who presented to the study center for a vascular access procedure and who met study entry criteria were invited to participate in the study. A total of 40 subjects were planned; however, due to an error by one study center whereby subjects received a 30-minute study drug application rather than a 20-minute application, an additional 20 subjects were enrolled in the study. Subjects were required to be at least 18 years of age and could be of any race and either sex. Subjects were excluded from participation if they had a known allergy or sensitivity to lidocaine, tetracaine, or other local anesthetics or any component of the test materials; if they had taken concomitant prescription strength analgesic pain medication during the previous 24-hour period; if they had damaged, denuded, or broken skin at the designated patch site; or if they were pregnant or breast-feeding. A urine pregnancy test was completed at screening in all women of childbearing potential. There were no height or weight restrictions for entry into this study.

Subjects were to simultaneously receive both a Synera and placebo application for 20 minutes, with treatment sites randomized (1:1) between the right and left antecubital surfaces. Upon removal of the study patches, both treatment areas were evaluated for erythema, edema and any adverse skin reactions. Then the vascular access procedure was performed first on the right antecubital surface and then on the left. The type of vascular access procedure was recorded and the difficulty of the puncture was assessed using a 5-point scale (1 = insertion at first attempt through 5 = unable to do insertion). If the first attempt was unsuccessful and further attempts were required, the investigator was to stop the procedure and perform the pain evaluations before proceeding with further attempts. Study evaluations were completed by the subject, investigator, and an independent observer, who was a trained research nurse. Following all study evaluations, subjects were discharged from the study center. Subjects were contacted by the study center between 24 and 48 hours after the vascular access procedure for evaluation of delayed skin reactions.

The primary efficacy measure was patient report of pain intensity, obtained immediately after each vascular access procedure, using a 100 mm visual analog scale (VAS) [10] where 0 mm = no pain through 100 mm = the worst pain you can imagine. Patients were also asked to evaluate the efficacy of each treatment by answering yes or no to the following questions: "Did the local

anesthetic provide adequate pain relief for the vascular access procedure" and "Would you have local anesthesia administered using this form of anesthesia again if given the option?" The investigator and an independent observer separately rated the subject's pain using a 4-point categorical scale (no pain, slight pain, moderate pain, and severe pain). The investigator provided an overall impression of the treatments by answering yes or no to the following question: "Did the local anesthetic patch provide adequate anesthesia for the vascular access procedure?"

Safety evaluations included an assessment of skin reactions and adverse events. Immediately after each study patch was removed from the subject's skin, the investigator examined the site for erythema and edema. Erythema was rated using a 5-point categorical scale (no erythema; very slight erythema; well-defined erythema; moderate to severe erythema; or severe erythema [beet redness] to slight eschar formation [injuries in depth]). Edema was also evaluated using a 5-point categorical scale (no edema; very slight edema [barely perceptible]; slight edema; moderate edema [raised approximately 1 mm]; or severe edema [raised more than 1 mm and exceeding beyond area of exposure]). Adverse events were recorded.

Demographic, background, and preprocedure variables were summarized using descriptive statistics. To access the comparability of study centers, age, height, weight, and preprocedure vital signs were compared between centers using analysis of variance, with the factors of center and randomization group. Race, sex, and the use of medications were compared between centers using Mantel–Haenszel summary chi-square tests, adjusting for randomization group. Skin type was compared between centers using Mantel–Haenszel tests for ordered categories. Subject VAS scores were compared between treatments using Wilcoxon signed rank tests. Adequate anesthesia and whether the treatment would be used again were compared between treatments using McNemar chi-square tests. The investigator and observer pain intensity evaluations were compared between treatments using Wilcoxon signed rank tests. Assessment of adequate anesthesia was compared using McNemar chi-square tests. Adverse effects were tabulated by type, frequency, onset, duration, outcome, and relationship to treatment. Overall incidence of any effect and the incidence of individual effects were compared between treatments using sign tests.

Results

Forty subjects were assigned to receive 20-minute concurrent treatments with Synera and placebo. Twenty additional subjects at Center 2 incorrectly received a 30-minute application of each treatment. Data from the subjects who received the 30-minute applications were excluded from efficacy analyses, but not from safety analyses.

Minor protocol deviations occurred during the conduct of the study. One subject did not receive the placebo because the patch was defective, but did receive Synera and completed all evaluations for that patch. A few of the subjects who were assigned to a 20-minute application period had application times that were slightly longer or shorter than 20 minutes. Most of these occurrences were within 1 minute of 20 minutes. One subject had a placebo applied for 22 minutes, and one subject had Synera applied for 24 minutes. No data were excluded from safety or efficacy analyses due to these protocol deviations.

Two-thirds of the subjects who participated in the study were female. Nearly half of the subjects were Caucasian and 40% were African American. Of the subjects who received the 20-minute applications, the mean age was significantly higher for the subjects at Center 2 compared with Center 1 (31 vs 40 years, $P = 0.009$). All skin types except "always burns easily, rarely tans" were represented in the study (Table 1).

Each of the subject evaluations significantly favored Synera over the placebo. The median subject VAS score was lower for Synera compared with the placebo (5 mm vs 28 mm). Forty-nine percent of the subjects had lower VAS scores with Synera than placebo, and 17% had lower VAS scores with the placebo ($P < 0.001$). Results of subjects' overall evaluations of the treatments are presented in Figure 1. More subjects reported adequate anesthesia following Synera compared with the placebo (73% vs 31%). Fifty-nine percent of subjects indicated adequate pain relief with Synera and not the placebo, and 15% reported adequate pain relief with the placebo and not Synera ($P = 0.002$). More subjects indicated they would use Synera again compared with the placebo (70% vs 33%). Fifty-one percent of subjects reported that they would use Synera again but not the placebo, and 15% reported that they would use the placebo again but not Synera ($P = 0.006$).

The investigator and independent observer evaluations of subjects' pain are presented in Figure 2. Investigators rated 63% of subjects as

Table 1 Subject characteristics

Characteristic	Center 1 20 Minutes (N = 20)	Center 2 20 Minutes (N = 20)	*P* Value*	Center 2 30 Minutes (N = 20)
Sex, n (%)			1.000†	
Male	7 (35)	8 (40)		6 (30)
Female	13 (65)	12 (60)		14 (70)
Age (year)			0.009‡	
Mean ± SD	31.1 ± 8.9	39.8 ± 10.7		41.8 ± 9.5
Range	22–52	21–61		29–60
Race, n (%)			0.756†	
African American	3 (15)	11 (55)		10 (50)
Caucasian	10 (50)	8 (40)		10 (50)
Hispanic	5 (25)	0 (0)		0 (0)
Asian	0 (0)	1 (5)		0 (0)
Mixed	2 (10)	0 (0)		0 (0)
Skin type, n (%)			0.495†	
Always burns easily, rarely tans	0 (0)	0 (0)		0 (0)
Always burns easily, tans minimally	2 (10)	3 (15)		3 (15)
Burns moderately, tans gradually	8 (40)	4 (20)		4 (20)
Burns minimally, always tans well	2 (10)	3 (15)		7 (35)
Rarely burns, tans profoundly	5 (25)	5 (25)		2 (10)
Never burns, deeply pigmented	3 (15)	5 (25)		4 (20)

* Center differences for subjects who received 20-minute application of study drug.
† Mantel–Haenszel summary chi-square, stratified by center.
‡ Two-way ANOVA with factors: treatment, group, center, and treatment by center.

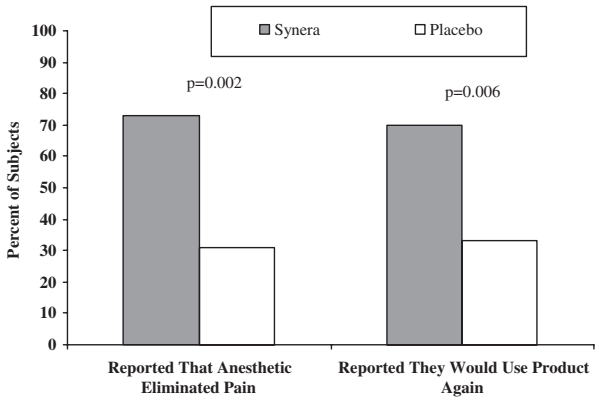

Figure 1 Subjects' overall evaluations. *P* values are from McNemar chi-square test.

having no pain with Synera treatment compared with 33% of subjects with the placebo treatment. Investigators considered 46% of subjects to have less pain with Synera than placebo, and 15% of subjects to have less pain with the placebo than Synera ($P = 0.021$). Independent observers rated 68% of subjects having no pain with Synera compared with 38% with the placebo. The independent observers considered 46% of subjects to have less pain with Synera than placebo, and 15% of subjects to have less pain with the placebo than Synera ($P = 0.015$). For the overall rating, the investigators considered more subjects to have adequate anesthesia with Synera compared with

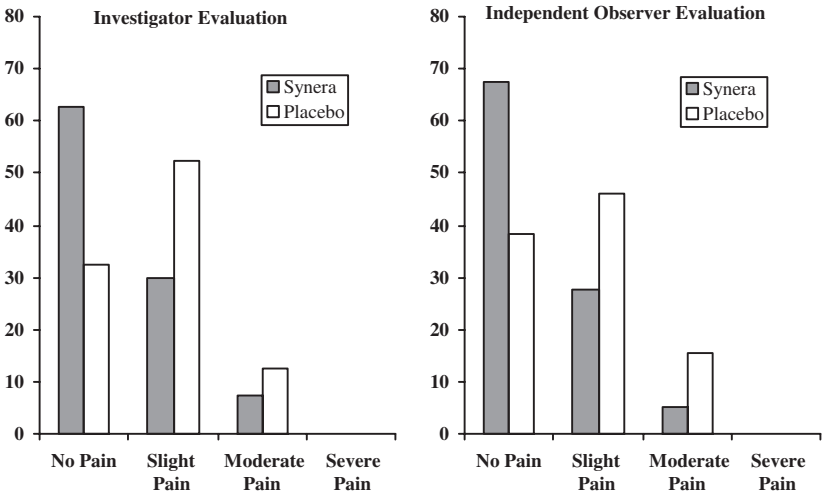

Figure 2 Investigator and independent observer evaluations of subjects' pain. Treatment differences were statistically significant for both the investigator's evaluation ($P = 0.021$) and independent observer's evaluation ($P = 0.015$) using Wilcoxon signed rank test.

placebo (60% vs 23%). They considered 54% of subjects to have adequate anesthesia with Synera and not the placebo, and considered 15% of subject to have adequate anesthesia with the placebo and not Synera ($P = 0.004$).

Both the 20- and 30-minute applications of Synera were well tolerated by subjects. Two subjects experienced adverse events at the treatment site for Synera. One subject reported itching at the patch application site and the other reported itching and erythema after patch removal. All adverse events were mild in severity and resolved without treatment within 3 hours. The evaluation of skin reactions demonstrated that more subjects had very slight or well-defined erythema (not reported as adverse events) with Synera compared with the placebo (62% vs 42%, $P = 0.018$). No edema or delayed skin reactions occurred.

Discussion

The results of this study show that a 20-minute application of Synera is effective in providing clinically useful anesthesia for vascular access procedures in adults. Statistically significant differences in subjects' pain scores favored Synera compared with the placebo. Moreover, the efficacy of the product was demonstrated by the improvement of different pain measurements assessed by the investigator and an independent observer.

Transdermal analgesia using local anesthetics can be accomplished using a variety of methods [11]. The eutectic mixture of lidocaine and tetracaine has been documented to provide clinically useful anesthesia in a wide variety of clinical situations requiring localized anesthesia when incorporated into the patch formulation [9], peel formulation [12–16], and as a cream formulation [8]. Each of these delivery vehicles for the eutectic mixture confers the advantages of convenience, painless application/removal, rapid onset of action, and minimal adverse effects. However, the patch delivery system confers unique advantages including the delivery of a specific amount of drug to a clearly defined area of skin. This can be difficult with gels or creams, especially when an occlusive dressing is required. Moreover, applying and removing the patch may be potentially easier as creams and gels often require an occlusive covering and can be messy to apply and remove.

Synera is clean and easy to use and does not cause pain or discomfort. Use of Synera increases the tolerability of injection and is likely to make patients more comfortable and less apprehensive about minor diagnostic and therapeutic procedures. This benefit should prove especially useful for pediatric patients and for adult patients undergoing procedures in extremely pain-sensitive areas.

Unlike other products containing the eutectic mixture of lidocaine and tetracaine, Synera is unique in that it also contains a heating component. External heating of the skin has been shown to induce changes in skin permeability, hemodynamics, blood flow distribution, and vasodilatation, and as a result controlled heat has been used to enhance transdermal drug delivery [17–19].

It is noteworthy that Synera consistently produced effective anesthesia with an application time as short as 20 minutes; this is one-third the time generally required by other topical local anesthetics. This is clinically important because clinicians are more likely to administer a topical local anesthetic that has a rapid onset. In today's fast-paced environment, physician time requirements may preclude the use of anesthesia altogether for some patients if the application time is considered to be excessive by the physician. Strategies to reduce time in the emergency department or in a busy clinical practice not only improve patient flow but also result in less inconvenience for patients and their family. The availability of a rapid onset topical local anesthetic is particularly advantageous for pediatric patients whose parents are anxious to have their child receive prompt care and to have any discomfort their child is experiencing alleviated.

Side-effects of the study patches application were limited to transient mild erythema and itching. Of note, Synera produced significantly more erythema than the placebo. The increased erythema observed with Synera may have resulted from the vasodilating action of tetracaine [20]. Vasodilitation would be a desirable effect for clinicians who are performing vascular access procedures.

There are several limitations to this study. First, this study was conducted in healthy adults, rather than in patients with a medical indication to undergo a vascular access procedure. It is possible that the adverse effects observed in patients may differ from that observed in healthy adults. In addition, as this study was conducted in adults, similar studies should also be conducted in children, as this product appears to have significant potential benefit to children. Finally, it will be necessary to determine whether Synera has a different impact on the success rate of vascular access

procedures, especially in children, compared with other products such as EMLA™.

Synera appears to be well suited for topical dermal anesthesia due to its reduced time required to produce adequate anesthesia and high subject and investigator acceptance. The addition of a patch delivery system will be a welcome addition to the growing armamentarium of topical local anesthetics.

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