Brief Report

Brief report: A randomized controlled trial of Synera™ versus lidocaine for epidural needle insertion in labouring parturients

[Compte-rendu court : Une étude randomisée contrôlée du Synera™ vs lidocaïne dans l'insertion de l'aiguille péridurale chez les parturientes en travail]

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Purpose: Skin infiltration with lidocaine, although brief, can be very stressful, painful, and may perpetuate anxiety. Synera™, a local anesthetic patch, which contains an oxygen-activated heating component to enhance the delivery of a eutectic mixture of lidocaine (70 mg) and tetracaine (70 mg), has provided analgesia for minor, dermatological procedures. We hypothesized that the analgesic effect of Synera™, for pain in labouring parturients, would be superior to the traditional infiltration of lidocaine prior to epidural needle insertion.

Methods: With Institutional Review Board approval, we recruited women, who consented to epidural labour analgesia and who met the following criteria: older than 18 yr; body mass index less than 45 $kg \cdot m^{-2}$; and with no history of hypersensitivity to any study medications. We randomized the labouring parturients into Synera (SS) or placebo (PL) groups. Group SS received the Synera™ patch and infiltration with saline prior to epidural needle insertion. Group PL received a placebo patch and infiltration with 2% lidocaine.

Results: The groups were similar with respect to age, estimated gestational age, gravidity, parity, and body mass index. The subjects' pain, with epidural placement, was significantly greater in the SS group ($P < 0.001$). More SS subjects required additional, deep, local anesthetic infiltration compared to PL ($P = 0.02$).

Conclusion: The Synera™ patch provided inferior analgesia, for performing epidural labour analgesia in labouring parturients, compared to traditional infiltration with 2% lidocaine.

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Objectif *: L'infiltration cutanée réalisée avec de la lidocaïne, bien qu'elle soit brève, peut être très stressante, douloureuse, et peut même accentuer l'anxiété. Synera™ est un timbre transdermique d'anesthésiant local qui contient une composante chauffante, activée au contact de l'oxygène, afin d'améliorer la libération d'un mélange eutectique de lidocaïne (70 mg) et de tétracaïne (70 mg). Ce timbre a été utilisé pour réaliser une analgésie lors d'interventions dermatologiques mineures. Nous avons émis l'hypothèse que l'effet analgésique de Synetra™ serait plus prononcé que l'infiltration conventionnelle de lidocaïne avant l'insertion de l'aiguille péridurale pour traiter la douleur chez les parturientes en travail.*

Méthode *: Avec l'accord du Comité d'éthique de notre institution, nous avons recruté des femmes ayant consenti à une analgésie péridurale pour le travail obstétrical qui répondaient aux critères suivants : plus de 18 ans, indice de masse corporelle inférieur à 45 $kg \cdot m^{-2}$ et sans antécédent d'hypersensibilité aux médicaments à l'étude. Nous avons réparti aléatoirement les parturientes en travail en deux groupes : Synera (SS) ou placebo (PL). Le timbre Synera™ accompagné d'une infiltration de solution salée a été administré au groupe SS avant l'insertion de l'aiguille péridurale. Le groupe PL a reçu un timbre placebo et une infiltration de lidocaïne 2 %.*

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Résultats *: Les deux groupes étaient comparables au niveau de l'âge, de l'âge gestationnel évalué, de la gravidité, du nombre de grossesses et de l'indice de masse corporelle. La douleur lors de l'insertion de l'aiguille péridurale était significativement plus élevée dans le groupe SS (P < 0,001). Un nombre plus élevé de patientes du groupe SS ont nécessité une infiltration d'anesthésiant local supplémentaire et plus profonde par rapport au groupe PL (P = 0,02).*

Conclusion *: Le timbre Synera™ a procuré une analgésie moins efficace lors de l'analgésie péridurale pour le travail obstétrical chez les parturientes en travail, en comparaison de l'infiltration conventionnelle avec de la lidocaïne 2 %.*

INFILTRATION with lidocaine is common practice prior to lumbar epidural placement in labouring parturients. Skin infiltration, although brief, can be very stressful and painful for patients.[1] The initial discomfort of the infiltration procedure may perpetuate patient anxiety, potentially making the parturient less cooperative and increasing her perception of pain during subsequent interventions. To reduce this discomfort, various topical alternatives have been investigated with varying degrees of success.[2–4] To aid in the absorption of local anesthetics, drug delivery tools such as ionophoresis have been used in conjunction with these topical alternatives.[5] Synera™ (Endo Pharmaceuticals, Chadds Ford, PA, USA) consists of a thin, uniform layer of a local anesthetic formulation with an integrated, oxygen-activated, heating component intended to enhance the delivery of the drug. The drug formulation is an emulsion in which the oil phase is a eutectic mixture of lidocaine (70 mg) and tetracaine (70 mg).

For minor dermatological procedures, Synera™ provided better analgesia than standard lidocaine infiltration.[6,7] A eutectic mixture of local anesthetics (EMLA) cream, an alternative topical analgesic, is inconvenient to apply and has limited depth of absorption. However, EMLA has been used as topical anesthesia for epidural and spinal needle insertion with mixed results.[3,4,8,9] Synera™ is simple and convenient to use and has a potentially greater depth of penetration.[10] We hypothesized that the analgesic effect of Synera™, for pain in labouring parturients, would be superior to traditional infiltration of epidural needle insertion with lidocaine.

Methods

This trial was registered with ClinicalTrials.gov (NCT00564785). With Institutional Review Board approval, we recruited women, considering labour epidural analgesia, who were older than 18 yr, with a body mass index less than 45 $kg \cdot m^{-2}$. Subjects were excluded if they had; a history of hypersensitivity to any study medications or para-aminobenzoic acid, active dermatitis, or an open wound at the patch application site.

After we obtained written informed consent, we allocated the subjects, according to a computer-generated randomization, into one of two groups; Synera™ (SS) or placebo (PL); and we used sealed, opaque envelopes to achieve allocation concealment. We applied the Synera™ patch to subjects allocated to group SS, followed by saline infiltration (3 mL), and applied an identically-sized, placebo patch to patients in the PL group, followed by infiltration with 3 mL of 2% lidocaine. The Synera™ and placebo patches both contain the heating component distinctive to the Synera™ analgesic patch. The patches were applied for a minimum of 20 min, the recommended application time for the Synera™ patch. An anesthesiologist, not involved in placement of the epidural catheters, applied the patches at the intended epidural site and then prepared the infiltration solution. Anesthesia providers, blinded to each patient's group allocation, placed the epidural. With subjects in the sitting position, epidurals were sited between L2–L5, with an 18-G Tuohy needle. The skin was infiltrated using a 25-G 0.75 inch needle. With the infiltration needle inserted its full length, lidocaine was injected following a small wheal deposition.

Each subject's discomfort with epidural needle insertion was assessed with a verbal rating scale (VRS) extending from 0–10, where 0 is no pain and 10 is the worst pain imaginable. The scale was explained to the patients at the time of obtaining informed consent. Similarly, with the same VRS scale and prior to asking each patient for her VRS response, the blinded, anesthesia provider was asked to assess the pain of epidural needle insertion that they perceived each patient had experienced. The blinded anesthesia provider also assessed the ease of epidural insertion, according to the following four-point scale; 0 = poor, subject uncooperative, with the need for repositioning after infiltration; 1 = fair, subject attempting to maintain position, slight arching of back noted with spontaneous return to position; 2 = good, no gross movement of subject noted, however tightening of back paraspinous muscles noted; 3 = excellent, subject fully cooperative. If, during the insertion of the epidural, the subject requested further analgesia, additional, deep infiltration with 3 mL of lidocaine was administered.

Data from a pilot study suggested that the mean VRS of epidural needle insertion with lidocaine, local

anesthetic infiltration was 4.2.[1] To detect a three-point reduction in mean VRS, assuming a common standard deviation of 3, 16 subjects were required per group (5% significance level, 80% power), for a total of 32 subjects. Demographics, patch application time, and VRS scores were analyzed with the Student's *t* test. The need for deep infiltration was analyzed with a Chi-square analysis, while the epidural insertion scores, gravidity, and parity were assessed using a Mann Whitney U test. Results with $P < 0.05$ were considered statistically significant.

Results

Thirty-five subjects met the inclusion criteria. Two subjects refused to participate. Thirty-three subjects were successfully recruited and subsequently randomized. One subject was withdrawn because the patch failed to adhere to her skin for the minimal required time of 20 min. There was no difference between groups in terms of age, estimated gestational age, gravidity, parity, or body mass index (Table I). The duration of patch application was similar in the two groups (Table II). The subjects' recorded VRS, with epidural placement, was significantly higher in the SS group ($P < 0.001$), as was the anesthesia providers' VRS of perceived pain ($P < 0.01$). A greater number of SS subjects required additional deep infiltration ($P = 0.02$). The four-point scale, used to subjectively estimate the quality of subject cooperation during epidural placement, was not significantly different between groups (Table II). The subjects' recorded VRS and the anesthesiologists' VRS rating scores were similar in the two groups.

TABLE I – Patient demographics

Group	*Synera™ (n = 16)*	*Placebo (n = 16)*	*P-value*
Age (yr)	27.1 ± 6.6	29.4 ± 5.8	0.29
BMI ($kg \cdot m^{-2}$)	31.6 ± 7.9	32.4 ± 5.0	0.73
EGA (weeks)	38.5 ± 2.3	36.6 ± 4.8	0.16
Gravidity	2 [1 – 3]	2 [1 – 4]	0.57
Parity	0 [0 – 1]	2 [0 – 3]	0.23

Data are provided as mean ± SD, or median [interquartile range]. EGA = estimated gestational age; BMI = body mass index.

TABLE II - Results

	Synera™ (n = 16)	*Placebo (n = 16)*	*P-value*
Duration of patch application (min)	31 ± 7	36 ± 17	0.32
Subject VRS	6 ± 2	4 ± 2	0.001
Anesthesia providers' perceived VRS	5 ± 2	3 ± 2	0.01
Epidural insertion score	3 [2 – 3]	3 [1 – 3]	0.98
Need for deep infiltration	8 (50%)	2 (12.5%)	0.02

Data are mean ± SD, median [interquartile range], or *n* (%). VRS = verbal rating scale.

Discussion

The primary objective of this study was to compare the analgesic effect of Synera™, compared to subcutaneous infiltration with lidocaine, in managing the pain of epidural needle insertion. Synera™ consists of a thin, uniform layer of a eutectic mixture of lidocaine (70 mg) and tetracaine (70 mg), with an integrated, oxygen-activated heating component, intended to enhance its delivery. Synera™ provided inferior analgesia, in comparison to traditional subcutaneous infiltration.

Elson *et al.*[3] successfully used EMLA to reduce the pain of epidural insertion in a cohort of elective Cesarean deliveries. Eutectic mixture of local anesthetics was also successfully used for spinal needle insertions in women undergoing tubal ligations.[8] However, a study of women receiving labour epidurals found no difference in analgesia between EMLA and lidocaine infiltration.[4] Synera™, unlike EMLA, is simple and convenient to use, and has a potentially greater depth of penetration.[10]

This investigation has several limitations. Studying patients in active labour may have affected the primary outcome. However, labouring parturients typically receive no sedation for epidural needle insertion and commonly report discomfort during the procedure. The results may have differed, had the study cohort consisted of patients undergoing elective Cesarean delivery, who do not experience labour pain. Furthermore, the stage of labour and pre-epidural procedure pain was not controlled. Additionally, patients were not asked about the discomfort associated with the initial needle insertion, but rather their overall VRS. The possibility exists that Synera™ provided good analgesia for the initial, superficial insertion of the needle, but not for deeper levels of discomfort. However, our aim was to determine whether or not the patch provided adequate analgesia throughout the entire procedure. Perhaps Synera™ and other topical analgesics are just the first step in obtaining good analgesia for epidural placement, prior to subcutaneous, local anesthetic infiltration, and may play a role for anxious and needle-phobic patients. However, this possibility needs to be confirmed in future studies.

The small size (2.7 × 2.2 cm ellipse) of the patch made it a challenge to apply over the intended site. An individual, who was experienced in performing labour epidurals, had to place the patch, limiting the

ability to delegate this duty. Our non-validated (but clinically designed) measure of epidural insertion ease was not significantly different between the two groups. This likely reflects the increased need for deep infiltration in the Synera™ group and possibly influenced the patients' overall cooperation. In conclusion, the Synera™ patch, alone, did not provide adequate analgesia for epidural needle placement and cannot be recommended for this application.

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