Egyptian Journal of Anaesthesia (2014) **30**, 387–392

HOSTED BY

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Egyptian Society of Anesthesiologists

Egyptian Journal of Anaesthesia

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Research Article

Transplacental transfer and neonatal influences of sonophoretically administered sufentanil versus epidural sufentanil in labor peridural analgesia: A randomized prospective double-blind contemplate

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Received 5 January 2014; revised 2 April 2014; accepted 22 April 2014
Available online 9 June 2014

KEYWORDS

Anesthetic techniques;
Transdermal;
Obstetric;
Analgesics opioid;
Sufentanil

Abstract *Background:* Labor sufentanil impact on the newborn is debatable. This randomized double-blind investigation examined the transplacental conveyance and neonatal influences of sonophoretic versus epidural sufentanil for labor analgesia and its outcome on breast-feeding.
Methods: 60 Healthy parturient women receiving labor epidural analgesia were enrolled in the study. They were administered epidural bupivacaine (12-ml bolus then 10 ml/h of 0.125%) solely (Group I, $n = 20$) or with sonophoretically transdermally administered sufentanil (Group II, $n = 20$) or with epidurally administered sufentanil (Group III, $n = 20$). Sufentanil received by Groups II and III was 15 μm followed by 10 ml/h of 0.25 μm/ml solution.
Results: Sufentanil was detected in five umbilical arterial (UA) samples in Group III versus in two UA samples in Group II. Neonatal Neurologic and Adaptive Capacity Score (NACS) at 24 h was lowest in Group III ($P = 0.04$). On postpartum day 1, Group III women reported breast-feeding

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Peer review under responsibility of Egyptian Society of Anesthesiologists.

 http://dx.doi.org/10.1016/j.egja.2014.04.003

difficultly (25%) more oftentimes than Group II women (10%), or Group I women (5%) ($P = 0.05$). There was 45% breast-feeding difficulty in each group according to lactation consultant's assessment ($P = 1.0$). At 6 weeks postpartum, more Group III women were not breast-feeding (35%) than Group II women (10%) or Group I (10%) ($P = 0.004$).

Conclusion: Sufentanil transplacental transport and fetal exposure appeared greater in epidural than in sonophoretic sufentanil. The former group women were facing more difficulty at starting breast-feeding on postpartum day 1 and were more apt to have stopped breast-feeding 6 weeks postpartum than the latter group women.

1. Introduction

Different clinical practices were associated with breast-feeding problems. Nevertheless, minimal is acknowledged around the validity of obstetrical pain management procedures and analgesia effects on breast-feeding conduct [1].

The issue of ''not having sufficient milk'' was much more addressed by those women who had epidural analgesia. Additional studies conducted prospectively are required to institute whether a causal relation exists between epidural analgesia and breast-feeding problems [1].

Disputation exists regarding the outcome of opioid-supplemented parturition epidural analgesia on neonatal well-being after delivery. Initial investigations in this field were centered on the consequence of epidural analgesia on the neonate's neuro-behavior, and they yielded inconsistent results [2,3].

The clinical significance of altered neurobehavioral scores is controversial [4], but observational grounds suggest an influence on the newborn's power to breast-feed [5]. Breast milk is regarded the optimal nutrition for neonates [6].

Sonophoresis refers to the use of ultrasound for the transdermal delivery of drugs. It was shown to increase the skin permeability to a wide range of therapeutic agents including hydrophilic molecules, macromolecules [7] and various low and high molecular weight medications including heparin and insulin [8]. Especially low-frequency sonophoresis (LFS) which utilizes low-frequency ultrasound [7]. This novel technology offers promising potential for noninvasive and non-painful drug administration. Sonophoretic cavitation was proposed to be the mechanism through which low-frequency ultrasound delivers drugs transdermally, effectively [9] and safely through the stratum corneum which is the natural barrier which limits substances penetration through the skin with future trends even in the field of gene delivery and cutaneous vaccination [10].

Neonatal issues (e.g., newborn does not lock properly onto the breast or suckle considerably, palate anomalies) and motherly issues (e.g. nipples problems, deficient training) can impact breast-feeding. Regional anesthesia has become progressively favorable for child birth analgesia. Nevertheless, its impact on breast-feeding has been questioned [5].

The worry concerning epidural analgesia and breast-feeding is that epidural pharmaceutics, especially opioids, traverses the placental barrier impairing neuro-behavior scores, which ultimately may possess an outcome on breast-feeding. This fear has not been verified as only few studies specifically investigated whether epidural analgesia affects breast-feeding [3].

This controlled, randomized, double-blind research work was intended to examine the transplacental transport of sonophoretically administered transdermal sufentanil as compared to epidural sufentanil in childbirth peridural analgesia and to ascertain if they do influence breast-feeding.

2. Materials and methods

The work protocol was authorized by Cairo University Hospital ethical committee. 60 Healthy multiparous parturient women who presented for an attempted vaginal delivery at term, who previously breast-fed a kid for at minimal 6 weeks and intended to breast-feed this child were randomly double-blinded included in this study. After accepting or requesting epidural analgesia, the patient was randomly appointed to one of three cardinal groups according to a computer-generated randomization block using sealed opaque envelopes opened immediately before placement of the epidural.

The studied patients were administered epidural bupivacaine solely (Group I, $n = 20$) or with sonophoretic transdermal sufentanil (Group II, $n = 20$) or with epidural sufentanil (Group III, $n = 20$).

The study transdermal solution was applied, using an oil sprayer, to a rectangular area of 15 cm × 7 cm on the front aspect of the left thigh of the studied patients in a circular regular clockwise motion at average speed of 1 cm/s using the portable ultrasonic probe of lipo X machine (LP 200, South Korea) (Fig. 1) emitting low frequency (30KHz) ultrasonic cavitational waves adjusted at its highest intensity while applying firm pressure over the skin after being sterilized with sterillium (Bode Chemie, Hamburg). Skin area chosen must be of healthy intact unshaved skin with no signs of hyperkeratosis. This circular motion was maintained with average circular circumference of 10 cm till all of the study solution was absorbed.

Written acknowledged consent was obtained before the start of aching unpleasant contractions. If the parturient was administered any intravenous analgesics during birth e.g. meperidine or other narcotics, she was not entitled in this research work.

If the parturient underwent cesarean section, she was also excluded from the contemplate.

The neonatologist, trained to perform the Neurologic and Adaptive Capacity Scoring System (NACS), assessed the infant by the blinded pediatrician. The NACS is an assessment of alertness, response to light and sound and passive and active tone reflexes. Its evaluated score is between 0 and 40.

The use and dose of any postoperative drugs administered in the postpartum period were reported from the patient's medical records. Also, whether or not supplemental bottle feeding was received by the infant was ascertained by reviewing the infant's medical record.

Figure 1 Liop X machine.

The blinded breastfeeding consultant observed the mother lactation and reported a 12-point B-R-E-A-S-T Feeding Observation Form [11]. This forms a part of a breast-feeding education course sponsored by the World Health Organization and the United Nations Children's Fund. The breast-feeding consultant, in addition to identifying any breast-feeding problems, gave a judgment concerning whether the child was having difficultness with lactation (none, mild, moderate, or severe).

The (yes or no questionnaire) (Table 1) and the B-R-E-A-S-T Feeding Observation Form (Table 2) were previously used in similar relevant studies. All mothers were called by one member of the research team at 6 weeks postpartum to find out whether they were still lactating.

If the mother was not lactating at 6 weeks postpartum, she was asked as to whether this was associated with difficultness the infant experienced with breast-feeding.

3. Statistical analysis

Pilot observational study results revealed the basic design protocol for the current study determining definition of the study groups and the sample size. What medications, if any, were given during childbirth was determined by reviewing the medical records. Much difficultness in assessing effect of anesthetics was met in the pilot study with firstborns. Thus, the current study was limited to those who breastfed previously.

Different routes of sufentanil administration were applied among patients in the pilot study. Thus, in the present study patients were designed to receive either no labor sufentanil, sonophoretic transdermal sufentanil or epidural sufentanil.

Power analysis revealed that a sample size of 60 would be enough to render 80% power to detect a difference between the no sufentanil group, sonophoretic transdermal sufentanil group and epidural sufentanil group. These values render an overall significance level of 0.05, based on two pairwise two-tailed tests. Kruskal–Wallis tests were used to compare continuous variables among groups while chi-square tests were used to compare binary outcomes.

4. Results

60 Women were entitled in this clinical research, successfully completed the study protocol and their results analyzed. Childbirth and Demographic data were comparable among groups, as were the period of labor analgesia and type of delivery. More than 90% had a normal spontaneous vaginal delivery and the rest were forceps-assisted vaginal deliveries (Table 3).

No significant difference was attainable in Apgar score among the three cardinal groups at 1 or 5 min (median score of 9 in all three groups at 1 and 5 min). Moreover, no significant difference among the studied groups was met regarding the number of infants who received supplemental bottle feeding (Table 4).

Significant differences were found among the three studied groups concerning the total amount of bupivacaine received but not among groups II and III concerning the total amount of sufentanil received. On the other hand, sufentanil concentrations in the umbilical cord differed among groups but bupivacaine cord concentrations did not. This is shown in Table 4.

Table 1 Breast-feeding conditions of the infants as judged by the mother.

	No sufentanil group (n = 20)	Sonophoretic transdermal sufentanil group (n = 20)	Epidural sufentanil group (n = 20)	P value
Infant drops asleep	11	12	18	0.21
Infant spits	10	18	17	0.09
Infant unhappy after feeding	10	5	16	0.29
Infant feeds from one breast	7	4	10	0.71
Infant feeds frequently	7	5	5	0.69
Infant refuses to nurse	13	15	16	0.06
Infant's sucking is not effective	3	7	12	0.09
Infant fails to latch on the nipple	15	17	17	0.35
Infant nursing time is long	15	7	14	0.79

Table 2 Breast-feeding conditions as judged by the lactation consultant.

	No sufentanil group (n = 20)	Sonophoretic transdermal sufentanil group (n = 20)	Epidural sufentanil group (n = 20)	P value
Infant is not responding to breast	5	12	12	0.17
Infant cannot hold the breast	8	14	10	0.47
Infant is not rooting	3	9	12	0.17
Infant's mouth is closed	6	16	8	0.48
Infant's lower lip turned in	8	13	11	0.41
Infant's tongue is not visible	6	12	9	0.69
Cheeks are pulled in	3	4	4	1.12
Infant sucks rapidly	8	17	8	0.89
Infant smacks	4	11	6	0.71
Infant fails to latch on	2	7	9	0.13
Infant drops asleep	16′	18	17	0.91
Infant sucking is poor	10	12	13	0.88

Table 3 Patients demographic data and childbirth characteristics.[a]

	No sufentanil group (n = 20)	Sonophoretic transdermal sufentanil group (n = 20)	Epidural sufentanil group (n = 20)
Age in years	32 (24–40)	34 (20–39)	31 (23–43)
Height in cm	160 (151–170)	158 (148–169)	157 (147–171)
Weight in kg	84 (68–106)	81 (66–98)	83 (65–112)
Duration of peridural analgesia, min	288 (33–776)	304 (40–787)	279 (35–775)
Oxytocin used, number of patients	18	16	17
Highest oxytocin dose, mU	7 (3–19)	6 (2–21)	7 (3–19)
NSVD, number of patients	17	19	19
Parity	3 (3–5)	3 (1–7)	2 (2–3)

[a] Demographic data of the patients according to their groups are presented as median and range or number of patients. NSVD = normal spontaneous vaginal delivery (the rest were assisted deliveries by forceps).

Table 4 Apgar scores, drug concentrations, NACS and breast feeding.[a]

	No sufentanil group (n = 20)	Sonophoretic transdermal sufentanil group (n = 20)	Epidural sufentanil group (n = 20)	P value
Apgar score at 1 min	9 (7–10)	9 (8–9)	9 (8–10)	0.53
Apgar score at 5 min	9 (8–9)	9 (8–9)	9 (8–10)	0.62
External bottle feeding	68%	73%	76%	0.62
Total sufentanil in labor, μg	Nil	18 (3–45)	22 (6–40)	0.0001′
Sufentanil in cord, pg/ml	Nil	5 (0–12)	12 (0–25)	0.0001′
Total bupivacaine in labor, mg	78.5 (40–178)	50.4 (26.5–283.7)	48 (19–76)	0.0001′
Bupivacaine in cord, ng/ml	12.1 (0.2–63.5)	9.2 (0.1–53.6)	8.9 (0.1–52.7)	0.54
NACS score at 24 h	34 (23–40)	32 (18–40)	31 (19–40)	0.04
BF difficulty at 24 h postpartum by mother	1 (5%)	2 (10%)	5 (25%)	0.05
BF difficulty at 24 h postpartum by BF consultant	9 (45%)	9 (45%)	9 (45%)	1.2
Failed BF at 6 weeks	2 (10%)	2 (10%)	7 (35%)	0.004′

[a] Data are recorded according to the patient's group assignment and are presented as median and range or percent. BF = breast-feeding; NACS = neurologic and adaptive capacity scoring system. BF = breast feeding. ′P value < 0.005 statistical significance.

The median (range) total dose of sufentanil in sonophoretic transdermal sufentanil group was 18 (3–45) μm and in epidural sufentanil group was 22 (6–40) μm. Though sufentanil was administered in the epidural and sonophoretic transdermal groups in comparable doses, sufentanil epidural and sonophoretic transdermal groups MV plasma concentrations of sufentanil were in the ratio of 6:1. UV/MV sufentanil ratios were 0.45 in sonophoretic transdermal sufentanil group and 0.83 in epidural sufentanil group. Sufentanil was detected in five UA samples i.e. in 5 neonates in epidural sufentanil group, whereas it was detected in exclusively two samples in sonophoretic transdermal sufentanil group.

Breast feeding problems reported at 24 h after delivery in the maternal overall assessment were in 8 patients (13%). 3 of these were mild problems, 4 were moderate and one was severe.

On postpartum day 1, women who were randomly appointed to acquire epidural sufentanil reported breast-feeding difficultly (25%) more oftentimes than women who were randomly appointed to acquire sonophoretic transdermal sufentanil (10%), or no sufentanil (5%) and this achieved statistical significance (P = 0.05).

Most of the issues reported were related to the infant being sleepy (45%), the infant being unable to latch on the nipple

(20%) and the infant being fuzzy refusing to feed (16%). This is revealed in Table 1.

On the other hand, there was also no significant disagreement among groups in breast-feeding difficulty according to the lactation consultant's assessment (45% difficulty in each group; $P = 1.0$).

In the breastfeeding consultant's evaluation at 24 h after childbirth 27 of 60 infants (45%) were identified as having breast-feeding difficultness. The magnitude was comparable in all groups. Of the 27 cases, 15 were categorized as mild (56%), 10 were categorized as moderate (37%), and 2 were categorized as severe (7%). One severe breast-feeding difficulty occurred in the epidural sufentanil group (Group III), and two problems occurred in the sonophoretic transdermal sufentanil group (Group II). The problems most frequently encountered were the infant being sleepy (29%) and the lip being turning in (16%), without statistical variation between the groups (Table 2).

Much more mothers who were administered epidural sufentanil reported difficultness (25%) than those whom were administered sonophoretic transdermal sufentanil (10%) or no sufentanil (5%) ($P = 0.05$).

At 6 weeks postpartum, there were 11 women (18%) who were not breast-feeding. More women who were randomly appointed to acquire epidural sufentanil were not breast-feeding (35%) than women who were randomly appointed to acquire either sonophoretic transdermal sufentanil (10%) or no sufentanil (10%) ($P = 0.004$). The small number of patients must be borne in mind.

In all situations, stopping breastfeeding was reported by the mother to be due to the infant having breastfeeding difficulties. Generally, when a patient reported a difficulty at 24 h, she was more prone not to be breast-feeding at 6 weeks (29%) than if she did not report a difficulty at 24 h (10%) ($P = 0.005$).

Newborn status was favorable and mostly comparable in all groups at all timings, with the exclusion of a lowest NACS at 24 h in Group III receiving the epidural sufentanil ($P = 0.04$). The infant's NACS median scores encountered at 24 h were 34, 32, and 31 in the no sufentanil, sonophoretic transdermal sufentanil and epidural sufentanil groups, respectively. The 24-h and 6 weeks postdelivery differences were also statistically identified among studied patients when assessed in relation to the total amount of sufentanil received epidurally.

Positive correlation was found between the maternal assessment of problematic breast-feeding at 24 h and NACS score ($P = 0.0005$), but this association was not found between NACS score and the breastfeeding consultant's assessment of difficultness in breast-feeding ($P = 0.55$) or between NACS score and breast-feeding failure at 6 weeks ($P = 0.57$). No positive relationship was revealed between lactation success at 6 weeks and the breast-feeding consultant's evaluation at 24 h or with the NACS. In addition, neither the duration of labor nor the period when the initial dose of sufentanil was administered until delivery did bear any relationship to the occurrence of breast-feeding problems at 24 h or 6 weeks postpartum.

5. Discussion

In this study 60 healthy parturient women receiving labor epidural analgesia were enrolled. They were administered epidural bupivacaine (12-ml bolus then 10 ml/h of 0.125%) solely (Group I, $n = 20$) or with sonophoretically transdermally administered sufentanil (Group II, $n = 20$) or with epidurally administered sufentanil (Group III, $n = 20$). Sufentanil was detected in 5 umbilical arterial (UA) samples in Group III versus in 2 UA samples in Group II.

Neonatal Neurologic and Adaptive Capacity Score (NACS) at 24 h was lowest in Group III ($P = 0.04$).

On postpartum day 1, Group III women reported breast-feeding difficultly (25%) more oftentimes than Group II women (10%), or Group I women (5%) ($P = 0.05$). There was 45% breast-feeding difficulty in each group according to lactation consultant's assessment ($P = 1.0$).

At 6 weeks postpartum, more Group III women were not breast-feeding (35%) than Group II women (10%) or Group I (10%) ($P = 0.004$).

Several studies investigated the relation between peridural analgesia and breastfeeding, as breast milk is considered the first and best newborn nutrition [2,6].

The use of transdermal route for drug delivery by sonophoresis is a promising technique [7].

The principal revelation of the present contemplate was regarding previously successfully breast-feeding mothers receiving epidural analgesia in vaginal deliveries. Those who received epidural sufentanil were more difficult in starting breast feeding on post-partum day one and were least probably breast-feeding 6 weeks postpartum as compared with women who acquired sonophoretic transdermal sufentanil or no sufentanil.

Recent studies discovered that sonophoresis is an effective technique in delivering proteins, hormones, vaccines, and other nanoparticles. Moreover, It is already clinically widely used for topical anesthetics [7].

It was also proved that low frequency ultrasound (LFS) increases trandermal transport of several drugs up to 1000 times even higher than therapeutic ultrasound [12].

Ueda et al. in 2009, revealed that the cavitation properties of low frequency ultrasound is the enhancing mechanism of LFS for transdermal drug delivery [13].

Moreover, Tezel et al. revealed successful transdermal delivery of anti-sense oligonucleotides by the use of low-frequency ultrasound [14].

It was previously been revealed that those who acquired peridural and intravenous analgesia during childbirth did not breast-feed as considerably during the initial post delivery period but with no alteration on breast-feeding capability at 6 weeks post delivery as evaluated by breastfeeding consultants through phone conversations [15].

The easiness and non-invasive nature of LFS makes its use more save when compared with an invasive route for analgesia such as the epidural route.

Using LFS as a route of drug delivery through the skin in addition to its safety and easiness, it avoids first pass gut and hepatic metabolism, maintains constant drug levels in bloodstream for longer times and decreases potential side effects [8,16].

Ultrasound sonophoresis for analgesic drugs delivery was also used in the treatment of carpal tunnel syndrome, teeth extraction, and topical analgesia [17].

LFS increases skin accumulation of Cyclosporine A helping the targeting of the drug without a concomitant increase in its side effects [18].

Halpern et al. performed phone conversations at 6–8 weeks postpartum to check whether women were consistently lactat-

ing. They found no relation between delivery analgesia and lactation problems [19].

Similar tools were used for evaluation of success of lactation in the current study. Individual variables as well as the woman and breastfeeding consultant judgment regarding if the newborn was experiencing lactation problems were both assessed.

Baumgarder et al. studied breastfeeding in the first 24 h in 231 mothers if they managed to deliver a minimum of two lactation sessions. They administered peridural analgesia 115 mothers and compared them with the other 116 control women who were not given peridural analgesia. It was revealed in mothers who with peridural analgesia lactation sessions were fewer by (70%) than the mothers with no peridural analgesia (90%).

Epidural analgesia with narcotics carries the risk of increased complications such as nausea, vomiting, itching, hypotension and urinary retention.

Nevertheless, the study was not randomized and there was not any statement of the drugs used epidurally. Moreover, no evaluations were done anywhere later than twenty-four hours [20].

It was obvious that the women who suffered problems at the first day postpartum were more prone to stop lactation at 6 weeks, which is well more than the period required by the infant and the mother to develop lactation skills and breast milk amount is considerably enough [21].

There is no single optimal drug or mixture of drugs for childbirth peridural analgesia. The tendency among anesthetists is using minute concentrations of regional anesthetics during childbirth peridural analgesia to prevent lower body motor blockade. This is mostly established by adding opioids like fentanyl or sufentanil via different delivery routes [22].

This contemplate did not study the relation between epidurals and breast-feeding, but exclusively the interferences of various delivery routes of sufentanil among women who acquire an epidural. The frequency of lactation problems was considerable among groups at 24 h and at 6 weeks post delivery. According to the results of the present contemplate, it is advised to have a consensus regarding the safe use of labor sufentanil and to build up more consciousness on the potentiality of lactation problems that can be related to its use and that may be well minimized using alternate novel routes of drug administration and solved by early management and training.

To conclude, it was revealed that multiparous mothers, who previously breast-fed and acquired epidural sufentanil had a significantly inferior lactation success rate at 24 h and at 6 weeks postpartum as compared with the corresponding mothers who acquired sonophoretic transdermal sufentanil or no sufentanil.

Therefore, this does not entail any recommendation concerning abandoning using labor sufentanil as this may arise other complications as increasing instrumental deliveries.

Sonophoretically administered sufentanil is an effective non-invasive route for pain relieve during normal vaginal delivery with comparable analgesic results to that of epidural sufentanil with less adverse effects. Further studies need to be performed on larger number of patients and on other modalities of painful conditions.

Conflict of interest

No conflict of interest.

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