A single dose of fentanyl and midazolam prior to Cesarean section have no adverse neonatal effects

[Une seule dose de fentanyl et de midazolam administrée avant la césarienne n'a pas d'effet néonatal]

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Purpose: Analgesia and sedation, routinely used as adjunct medications for regional anesthesia, are rarely used in the pregnant patient because of concerns about adverse neonatal effects. In an effort to obtain more information about maternal analgesia and sedation we studied neonatal and maternal effects of iv fentanyl and midazolam prior to spinal anesthesia for elective Cesarean section.

Methods: In this double-blinded, randomized, placebo-controlled trial, 60 healthy women received either a combination of $1 \mu\text{g}\cdot\text{kg}^{-1}$ fentanyl and $0.02 \text{ mg}\cdot\text{kg}^{-1}$ midazolam intravenously or an equal volume of iv saline at the time of their skin preparation for a bupivacaine spinal anesthetic. Sample size was based on a non-parametric power analysis (power > 0.80 and alpha = 0.05) for clinically important differences in Apgar scores. Fetal outcome measures included Apgar scores, continuous pulse oximetry for three hours, and neurobehavioural scores. Maternal outcomes included catecholamine levels, and recall of anesthesia and delivery.

Results: There were no between-group differences of neonatal outcome variables (Apgar score, neurobehavioural scores, continuous oxygen saturation). Mothers in both groups showed no difference in their ability to recall the birth of their babies.

Conclusions: Maternal analgesia and sedation with fentanyl ($1 \mu\text{g}\cdot\text{kg}^{-1}$) and midazolam ($0.02 \text{ mg}\cdot\text{kg}^{-1}$) immediately prior to spinal anesthesia is not associated with adverse neonatal effects.

Objectif: L'analgésie et la sédation, complément habituel à l'anesthésie régionale, sont rarement utilisées chez la femme enceinte parce qu'on craint les effets néonataux indésirables. Pour en savoir davantage sur l'analgésie et la sédation de la mère, nous avons étudié les effets sur la mère et l'enfant du fentanyl et du midazolam iv administrés avant la rachianesthésie pour césarienne.

Méthode : Pour l'étude randomisée, à double insu et contrôlée contre placebo, 60 femmes en santé ont reçu une combinaison intraveineuse de $1 \mu\text{g}\cdot\text{kg}^{-1}$ de fentanyl et $0,02 \text{ mg}\cdot\text{kg}^{-1}$ de midazolam ou un volume égal de solution saline iv au moment de préparer à la rachianesthésie avec bupivacaine. La taille de l'échantillon reposait sur une analyse de puissance non paramétrique (puissance > 0,80 et alpha = 0,05) pour des différences cliniquement importantes d'indices d'Apgar. Les mesures de l'évolution du fœtus comprenaient l'indice d'Apgar, la sphymo-oxymétrie continue pendant trois heures et les scores neurocomportementaux. L'évaluation de la mère incluait les niveaux de catécholamine et la présence de souvenir de l'anesthésie et de l'accouchement.

Résultats : Il n'y a pas eu de différence intergroupe des variables mesurées chez le nouveau-né (indice d'Apgar, comportement neurologique, mesure continue de la saturation en oxygène). Les mères des deux groupes ont montré la même capacité à se rappeler la naissance de leurs enfants.

Conclusion : L'analgésie et la sédation maternelles avec du fentanyl ($1 \mu\text{g}\cdot\text{kg}^{-1}$) et du midazolam ($0,02 \text{ mg}\cdot\text{kg}^{-1}$) administrées immédiatement avant la rachianesthésie ne sont pas associées à des effets néonataux indésirables.

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THE study of drugs used during pregnancy is one of the most neglected areas in the field of clinical pharmacology and drug research.¹ Considering the amount of pharmacological research in the general population, data available on drug biodisposition and effect of orally and intravenously administered drugs in the pregnant patient are scarce, fragmentary and frequently contradictory. The anesthesia literature on drug effects in pregnancy, although more comprehensive, focuses on the pharmacology of epidural or spinally administered opioids and local anesthetics, rather than adjuvant *iv* medication. Few reports discuss the *iv* administration of midazolam during pregnancy without providing much information about its use close to delivery.²⁻⁴ Because pregnant women may benefit from *iv* analgesia and sedation in preparation for medical or surgical procedures, we designed a study to compare maternal and neonatal effects of two common anesthetic drugs, midazolam and fentanyl when compared to placebo (saline control) in pregnant women. Both drugs are routinely used as premedication for a significant portion of surgical procedures performed annually, an estimated 42 million in the United States of America alone.⁵ As premedication for regional anesthesia in pregnancy, *iv* analgesia and sedation is the exception rather than the rule. Although benzodiazepines and opioids have stood the test of time, physicians are still hesitant to administer them to term pregnant patients because information on transplacental pharmacology and fetal safety is scarce.⁶ To provide more information regarding procedural premedication in term pregnancy, we tested whether a small *iv* dose of fentanyl and midazolam in combination was associated with adverse neonatal effects or maternal amnesia. We hypothesized that premedication as used in this study does not have a demonstrable clinical effect on the neonate.

Methods

Design and sample size

This study was a randomized, prospective, placebo-controlled clinical trial. Our power analysis was based on Apgar scores. We estimated that a sample size of 49 subjects would be required to detect a 6% difference in normal five-minute Apgar scores (8 and 9) with 80% power, and an alpha error of 0.05. For this analysis normal Apgar scores were compared to Apgar scores ranging from 4 to 7, and less than 4 (Chi-square, DF = 5). We recruited 60 patients to compensate for incomplete data. The Institutional Review Board of the Health Science Center and the Review Board of the General Clinical Research Center of the University of Florida approved this study.

Recruitment

Study subjects were patients scheduled for an elective Cesarean section. We introduced this study and obtained written informed consent from patients after they had been admitted to the preoperative area on the day of their scheduled Cesarean section. After being informed of a new study participant, our satellite pharmacy prepared the study medication (either midazolam and fentanyl or an equal volume of normal saline) according to a concealed randomization list. Exclusion criteria were significant pre-existing maternal or fetal medical problems, chronic pain, insulin-dependent diabetes mellitus, hypertensive disease of pregnancy and a body mass index > 39 kg·m² (morbid obesity). Typical indications for the scheduled Cesarean section were a history of prior Cesarean delivery or fetal malpresentation.

Anesthesia

Patients underwent spinal anesthesia with 12 mg hyperbaric bupivacaine, 10 µg fentanyl and 300 µg preservative-free morphine in the sitting position. Mothers received oxygen at a rate of 2 L·min⁻¹ via nasal cannula. Maternal monitoring included non-invasive blood pressure measurement, pulse oximetry and electrocardiography. Fetal heart rate was recorded until mothers were placed supine.

Study drug administration and blinding

Study drugs were prepared by the operating room satellite pharmacy according to the randomization protocol, and consisted of either a mixture of fentanyl (1 µg·kg⁻¹) and midazolam (0.02 mg·kg⁻¹) or an equal volume of normal saline (placebo). No individual other than the pharmacist preparing the study medication had access to the randomization protocol. Study drugs were administered at the time of skin preparation for the spinal anesthesia. The time interval from drug administration to delivery was recorded.

Fetal outcome measures

The pediatrician on duty recorded fetal Apgar scores at one and five minutes. Arterial and venous cord blood was collected to assess the fetal acid-base status immediately after the umbilical cord was clamped. One of two study nurses with expertise in neonatal medicine recorded fetal pulse oximetry for three hours and obtained two newborn neurobehavioural scores three hours after birth; the neurologic and adaptive capacity score (NACS) and the early neonatal neurobehavioural scale (ENNS). Fetal oxygen saturation was recorded manually every ten to 15 min and continuously, using a Nellcor N-595 pulseoximeter, for three hours after

birth. The Score™ Analysis Software (version 1.1a, Mallinckrodt Inc., St. Louis, MO, USA) was used for analysis of oxygen saturation data. Within the Score™ Analysis program, criteria for the detection of desaturation episodes are customizable. We used two criteria for the electronic identification of desaturation episodes: (a) pulse oximetry reading less than 90% for more than ten seconds or (b) pulse oximetry reading less than 95% for more than ten seconds. Presumed desaturation episodes associated with a lost fetal heart rate tracing were identified as electronic artefacts and discarded. No supplemental oxygen was administered to neonates during the three-hour observation period.

Maternal outcome measures

To assess the potential effect of analgesia and sedation on the maternal stress response, we measured catecholamine plasma levels at the time of delivery using high performance liquid chromatography (HPLC). Venous blood samples were separated in a refrigerated centrifuge, frozen immediately and sent on dry ice individually for analysis at the Quest Diagnostics Nichols Institute. The HPLC assay used to analyze samples had greater than 98% reliability; detection limits were $< 20 \text{ pg}\cdot\text{mL}^{-1}$ for both epinephrine and norepinephrine. Mothers were also asked questions to assess recall of their birth and anesthesia while in the recovery room. The three questions asked were: “how do you remember the placement of your spinal anesthetic?”, “how do you remember the birth of your child?” and “did you find the medication which was given to help you relax helpful?”

Statistical analysis

Continuous data, such as cord pH, are summarized as means and standard deviation, and were compared between the two groups with a two-sided, independent-sample t test. Ordinal data are summarized as median and range and analyzed with the Chi-square test or Mann-Whitney test if assumptions for the Chi-square analysis were violated. Frequency responses to questions about maternal recall were compared using the Chi-square test. To meet the Cochran criterion for Chi-square tests, counts for desaturation episodes were collapsed into five levels. Multiple comparisons of blood gas values were performed with the Bonferroni t test. A probability level < 0.05 was considered significant.

Results

Subject characteristics

Women did not differ with respect to their weight, height or age (Table I).

TABLE I Subject characteristics

	<i>Placebo</i>	<i>Midazolam / Fentanyl</i>
Height (cm)	159.3 (16.3)	163.1 (7.4)
Weight (kg)	93.5 (18.4)	87.5 (23.8)
Age (yr)	27.2 (6.4)	27.4 (6.1)

Subject characteristics are displayed in SI units. There are no significant group differences ($P < 0.05$, paired t test).

Fetal outcome measures

The results of fetal outcomes are displayed in Table II. There were no significant differences in either one-minute or five-minute cord gas values, ENNS and NACS scores. None of the neonates showed clinically significant oxygen desaturation. Eight neonates, four neonates from the placebo and four from the fentanyl/midazolam group, were admitted to the level III nursery for temporary observation (one-on-one nursing care). Clinical details regarding these neonatal intensive care unit (NICU) admissions is provided in Table III. These infants were included in the analysis.

Maternal outcome measures

We did not observe a difference with respect to maternal birth recall, whereas more mothers in the fentanyl/midazolam group perceived their anesthesia as being pleasant and the study medication as helpful (Figure 1). Maternal catecholamine levels were similar in the two groups (Figure 2). One participant received an unintended high dose of 4 mg of midazolam and 200 μg of fentanyl. This subject was included in the analysis and individual data are provided in Table III. Another participant required supplemental *iv* anesthesia because of inadequate spinal anesthesia. Because of the added maternal stress and increased *iv* narcotic administration during the procedure, the study protocol was discontinued and this subject could not enter the analysis.

Discussion

The use of fentanyl and midazolam as a method of labour pain relief has been the subject of many studies.^{7,8} Many opioids are used routinely for labour pain relief if neuraxial analgesia is relatively contraindicated such as in the thrombocytopenic patient.⁹ The use of opioids and/or benzodiazepines as adjunct anesthetic medication for operative procedures during pregnancy is rare, but has been described as part of general anesthesia.^{10,11} Reports have also documented the successful use of *iv* sedation during pregnancy and the use of *iv* narcotics during labour as an alternative to

TABLE II Neonatal data

		<i>Placebo</i>	<i>Drug</i>	<i>P-value</i>
<i>Apgar</i>	One-minute	9 [0-9]	9 [2-9]	0.66 *
	Five-minute	9 [8-9]	9 [7-9]	0.97 *
<i>ACBG</i>	pH	7.23 [0.10]	7.26 [0.04]	0.08 †
	CO ₂	60.08 [11.55]	54.31 [5.79]	0.01 †
	pO ₂	16.52 [5.25]	17.65 [4.88]	0.76 †
	HCO ₃	23.64 [2.33]	23.7 [2.32]	0.98 †
	Base deficit	4.85 [4.60]	3.65 [2.35]	0.21 †
<i>VCBG</i>	pH	7.28 [0.10]	7.32 [0.04]	0.08 †
	CO ₂	49.41 [8.94]	47.14 [4.88]	0.17 †
	pO ₂	24.39 [5.26]	27.88 [6.46]	0.03 †
	HCO ₃	22.46 [2.59]	23.54 [1.48]	0.08 †
	Base deficit	4.33 [4.25]	2.39 [1.40]	0.04 †
<i>ENNS</i>	Pin prick	3 [1-3]	3 [1-3]	0.84 *
	Tone	8 [7-10]	7 [4-10]	0.54 *
	Rooting	2 [0-2]	2 [1-3]	0.84 *
	Sucking	2 [0-3]	2 [1-3]	0.87 *
	Moro response	2 [0-3]	2 [1-3]	0.55 *
	Reaction to light	2 [1-3]	2 [1-3]	0.6 *
	Response to sound	2 [1-3]	1 [1-3]	0.58 *
	Placing	2 [1-3]	2 [1-3]	0.29 *
	Alertness	1 [1-3]	1 [1-3]	0.51 *
	General	1 [0-1]	1 [0-1]	0.98 *
<i>NACS</i>		32.7 (5.2)	33.6 (3.7)	0.44 *
Desat.	SpO ₂ < 95%	12 [0-60]	15 [0-34]	0.2 *
	SpO ₂ < 90%	4 [0-15]	4 [0-14]	0.43 *
DD-time		46.9 (18.9)	45.3 (16)	0.76 *

ACBG = arterial cord blood gas; VCBG = venous cord blood gas. ENNS = early neonatal neurobehavioural scale; NACS = neurologic and adaptive capacity score. *Not significant at α -level of 0.05; †not significant at Bonferroni adjusted α -level of 0.005. Neonatal data are summarized as median and range is denoted in square brackets or mean and standard deviation round brackets as appropriate. The statistical test used to compare groups was the Wilcoxon rank-sum test for non-normally distributed data and the paired t test for normal data. Adjustments for multiple comparisons were not performed. Alpha values are Bonferroni-adjusted for the comparisons of the multiple, partially related blood gas values.

epidural analgesia, but midazolam and fentanyl as premedication for spinal anesthesia have not been studied prospectively.¹²⁻¹⁴ Premedication to facilitate neuraxial blockade remains the rare exception in pregnant patients, based on concerns about potential untoward effects of fetal drug exposure. The most worrisome adverse fetal effects are over sedation, decreased motor tone, and respiratory compromise. In fact, in the 1960's several case reports described decreased motor tone in infants born to mothers who had been treated with diazepam during their pregnancy.^{15,16} Another reason for the relative infrequent use of benzodiazepines during pregnancy is probably related to their putative association with facial malformations in animals when given during the teratogenic period of

pregnancy, although, in a recent review, the alleged association of benzodiazepine use during pregnancy with facial malformations has been completely dismissed.^{17,18} Therefore, women in some cases may endure a great deal of anxiety and discomfort when undergoing placement of a spinal or epidural block for Cesarean delivery.

In an effort to address these concerns, we decided to study the effect of a single bolus dose of midazolam and fentanyl prior to elective Cesarean section. We chose a single dose based on weight, rather than multiple doses, to ensure uniform treatment of patients in both study arms. We also chose a concentration likely to achieve a clinical effect without causing excessive maternal sedation or respiratory compromise. We

TABLE III Subjects admitted to level III nursery

Reason for intensive care unit admission	Randomization group
Respiratory (“grunting”)	Midazolam & fentanyl
Respiratory (“grunting”)	Placebo
Metabolic (hypoglycemia)	Midazolam & fentanyl
Respiratory (“grunting”)	Midazolam & fentanyl
Metabolic (hypoglycemia)	Placebo
Respiratory (“tachypnea”)	Placebo
Respiratory depression not responsive to naloxone	Placebo
Medication error (200 µg fentanyl and 4 mg midazolam)	Midazolam & fentanyl

Maternal data: body mass index: 37 kg·m², birth recall: pleasant.
Fetal data: umbilical vein pH = 7.34, APGAR = 9/9.
This table describes all unanticipated neonatal intensive care unit III admissions involving study patients. Each of these admissions was promptly reported to the Institutional Review Board and additional precaution implemented as needed. These events, with one exception, were considered unlikely to be related to study interventions.

realize however, that individual responses to a single weight-based bolus dose may vary considerably, and that in clinical practice one may prefer to titrate *iv* drugs to effect. Thus, the findings of our study may not be applicable if higher or repeated doses of *iv* analgesia and sedation are chosen.

Apgar scores are routinely measured because of the clear physiological correlation of this scoring system to characterize neonatal well being.¹⁹ Our sample size was therefore based on this parameter. We also recorded umbilical cord blood gas values and noted no significant difference. The reliability of either Apgar scores or fetal cord gas values to detect respiratory depression and hypoxia has been questioned.^{20,21} Therefore, we decided to record and analyze pulse oximetry in the neonate as well. We noted that the analysis of continuous pulse oximetry revealed a surprisingly high median number of 3.5 and 4 desaturation episodes (oxygen saturation < 90% for more than ten seconds) in the study groups. However, these episodes went unnoticed by the clinical observer (research nurse). We also recorded and reported to the Institutional Review Board on a case-by-case basis whenever a newborn was assigned to the level III (neonatal intensive care) nursery for closer observation, even if assigned for a brief time period. Given the healthy study population, the NICU admission rate may appear high, but is consistent with our overall conservative NICU admission policy followed by the pediatric house officer called to evaluate term new-

FIGURE 1 Questions about recall were asked in the recovery room prior to discharge to the postpartum floor. The categories assessed were the general perception of pre-medication, recall of birth and recall of spinal anesthetic placement. The label “neutral” substitutes the response “something I can deal with” for the “anesthesia recall” question and “concerned with other things” for the “birth recall” question. Significant differences within each group are marked with an asterisk (Pearson Chi-square, $P < 0.05$).

borns. The apparent non-reassuring clinical condition of some neonates in both of our study groups reflects the physiologic instability during this transition period of neonatal life.²²

Other fetal outcome measures used were the NACS and the ENNS.^{23,24} These two neurobehavioural scales are not universally accepted, but both have been used to assess the potential effects of neonatal drug exposure.^{25,26} Both tests are designed to differentiate drug-induced neonatal depression from depression secondary to asphyxia, and were found to have good interobserver reliability.²³ While the ENNS concentrates on the infant’s habituation ability, the NACS emphasizes motor tone as a key indicator of drug-induced abnormal behaviour. The mean NACS in our study (33 in both groups, Table II) are somewhat lower than what was originally proposed for normal newborns (35–40). These scores probably reflect the individual application of the scoring system by the two blinded pediatric research nurses trained in biophysical evaluation of newborns, rather than an overall abnormal group of infants. This finding gives more sup-

FIGURE 2 Box plots show concentrations of catecholamines on a logarithmic scale. Boxes mark the 25th, 50th (median) and 75th percentile, whiskers extend from the 5th to the 95th percentile, individual data points are represented by dots. The two study groups were similar with respect to maternal norepinephrine and epinephrine concentrations (Wilcoxon rank-sum test).

port to the view of Brockhurst and Littleford, which indicate its poor reliability in obstetric anesthesia research.²⁵ Because of these concerns, we use a combination of these neonatal measures to make predictions about neonatal drug effects.

As part of this study, we also assessed maternal recall of anesthesia and birth. This topic is relevant since the ability of the mother to experience the birth of her baby during Cesarean delivery is one of the foremost rewards of regional anesthesia. Active recall of the spinal anesthetic placement on the other hand is not desirable by most patients. We asked three simple questions while patients were still in the recovery room to address recall. Maternal responses demonstrate that

premedication as used in our study is not associated with maternal amnesia and that mothers in the premedication group have a more pleasant memory of the spinal anesthetic administration. The main intent of our questions was to assess maternal amnesia in a concrete fashion. We therefore inquired about specific events, the placement of the spinal anesthetic and the actual birth event. More patients in both groups had a pleasant recall of the birth, an event with positive emotional content. More patients in each group had neutral responses when asked about the anesthetic, most likely because this event, unlike the birth is associated with anxiety in most patients. We also note with interest that several participants in the placebo group did not remember birth or anesthesia. This is an important observation as it reminds us that factors other than medication such as the patient's level of interest in experiencing the birth, the patient's level of anxiety and other situational factors may have an impact on a mother's ability to recall intraoperative events. We did not repeat our question at a later time and one should consider that the effect on memory at later time points may be different.

One approach to assess the maternal response to stress is the quantification of plasma catecholamine concentrations. Maternal catecholamine levels have been proposed as indicators for the maternal stress response associated with labour and delivery by Shnider *et al.*²⁷ We compared plasma epinephrine and norepinephrine concentrations between the sedation and placebo groups and observed the results to be similar. This negative finding may be explained by the attenuating effect of regional anesthesia on the excretion of circulating catecholamines noted by Shnider *et al.*,²⁷ a factor that was present in both study groups. The effect of *iv* analgesia and sedation may, by comparison, have a very small or no impact on circulating catecholamines.

The results of this double-blinded, placebo-controlled study of maternal premedication illustrates that a combination of a modest dose of fentanyl and midazolam improves patient comfort, without inducing adverse affects in the newborn, or maternal amnesia during the peripartum period. However, we do caution that fetal or maternal effects may develop if large or repeated doses of fentanyl and midazolam are given, or the *iv* administration is closer to delivery and that continuous cardiorespiratory monitoring is essential.

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