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SPECIAL ARTICLE

Premedication with midazolam prior to caesarean section has no neonatal adverse effects[☆]

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KEYWORDS

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Abstract Like all surgical patients, obstetric patients also feel operative stress and anxiety. This can be prevented by giving patients detailed information about their operation and with preoperative pharmacological medications. Because of depressive effects of sedatives on newborns, pharmacological medications are omitted, especially in obstetric patients. The literature contains few studies concerning preoperative midazolam use in Caesarian section (C/S) patients. Our aim in this study was to help patients undergoing C/S surgery. One group scheduled for elective C/S received midazolam 0.025 mg kg⁻¹ intravenously, the other received saline. Maternal anxiety was evaluated using Amsterdam Preoperative Anxiety and Information Scale (APAIS) scores, and newborns were evaluated using Apgar and the Neonatal Neurologic and Adaptive Capacity Score (NACS). In conclusion, patients receiving midazolam 0.025 mg kg⁻¹ as premedication had significantly low anxiety scores, without any adverse effects on the newborns. Midazolam can therefore safely be used as a premedicative agent in C/S surgery.
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Introduction

Anxiety is a natural reaction arising in response to entering a different environment, such as an operating theater. Like all patients scheduled for surgery, obstetric patients may also feel operative stress and anxiety, and an autonomic stress response can develop in association with this. This stress response leads to vasoconstriction in the uter-

ine arteries and may cause fetal distress.^{1,2} This can be prevented by giving patients detailed information about their operations and also with preoperative pharmacological medications such as benzodiazepines or narcotics. Because of the depressive effects of sedatives on newborns, pharmacological medications are omitted, especially in obstetric patients. Many case reports have been published concerning low motor tonus at birth among newborns and pregnant women given diazepam, especially in the 1960s.^{3,4} These events led to a widespread antipathy to benzodiazepines, and as a result, there is an insufficient number of studies on this subject in the literature. The literature contains few studies concerning the use of the fast-acting and short-term agent midazolam in Caesarian section (C/S) patients.

[☆] Study conducted at Universidade Federal de São Paulo, São Paulo, Brazil.

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	Not at all	1	2	3	4	5	Very much
1. I am worried about the anesthetic.							
2. The anesthetic is on my mind continually.							
3. I would like to know as much as possible about the anesthetic.							
4. I am worried about the procedure.							
5. The procedure is on my mind continually.							
6. I would like to know as much as possible about the procedure.							

Figure 1 Amsterdam Preoperative Anxiety and Information Scale.

The aim of this study is to determine the ability of midazolam premedication to reduce stress in obstetric patients. We compared anxiety scores in obstetric patients scheduled for elective caesarian surgery who were undergoing regional anesthesia.

This study was intended to compare anxiety scores in obstetric patients scheduled for elective Caesarian surgery with the regional anesthesia technique in groups administered sedation using midazolam or without sedation and to compare Apgar and Neurologic and Adaptive Capacity Score (NACS) scores between newborns in these groups.⁵

Materials and methods

We conducted this study with 50 cases aged between 18 and 40 indicated for elective Caesarian surgery for their first baby. The subjects were briefed about the study beforehand and provided written consent and consisted of American Society of Anesthesiologists (ASA) groups 1 and 2 after we obtained Ethical Committee approval.

The exclusion criteria were non-elective cases, multiple pregnancies, preterm pregnancies, cases with fetal anomalies and retarded fetal development, pathologies that might affect the acid-alkaline balance, patients with diabetes mellitus, hypertensive patients, cases with obstetric complications such as antepartum hemorrhage and congenital malformations, infants with a birth weight below 2,500 g or at risk of meconium/amniotic fluid aspiration and cases contraindicated for regional anesthesia or refusing a regional technique. During the study, we excluded four pregnant women on whom spinal anesthesia could not be performed and one baby with meconium.

We allocated patients randomly into two groups of 25 members each. The first group was given iv. premedication with 0.025 mg kg⁻¹ midazolam (Group I), while the control group was given an equal quantity of SF (Group II) in the waiting room thirty minutes before surgery.

We evaluated patient anxiety with the Amsterdam Preoperative Anxiety and Information Scale (APAIS), and measured newborn well being using the Apgar and NACS scales. We visited patients scheduled for surgery in their rooms for APAIS evaluation. One such scale is the Amsterdam Preoperative Anxiety Information Scale (APAIS)⁶ (Fig. 1). Developed by a Dutch group in 1996, APAIS contains six questions enquiring into patients' concerns and anxieties. We elected to use APAIS for the objective analysis of anxiety in patients scheduled for Caesarian surgery since it is short and easy to administer.

On the day of surgery, we administered midazolam 0.025 mg/kg i.v. to Group I patients in the preoperative waiting room when they arrived at the theater for elective surgery. Group II patients were given an equal volume of SF. The same anesthesia assistant, who was not one of the authors, applied both. A researcher repeated APAIS 5 min later. Patients were then taken into the operating theater.

Thirty minutes before surgery, all patients received crystalloid fluid replacement at a speed of 15 mL kg⁻¹ per hour via two 20 gauge intravenous cannulae through the back of the hand or the antecubital region. We applied standard monitoring to patients taken for surgery. We performed non-invasive arterial tension, ECG monitorization and pulse oximetry throughout the operation. We enabled all patients to receive 2 L min⁻¹ oxygen by mask throughout surgery.

For spinal anesthesia, 12.5 mg intrathecal levobupivacaine was given using a 25-G spinal needle with patients in the decubitus position. We determined level of sensory block with hot-cold and pinprick tests. Surgery commenced when a sufficient level of sensory block was achieved. Following spinal anesthesia, we maintained systolic arterial blood pressure above 90 mmHg. We administered a 10 mg iv. bolus of ephedrine to cases falling below this level.

Once the baby had been removed, we performed basic neonate examination, and recorded Apgar scores at minutes 1 and 5 (Fig. 2). Following basic neonate care and the severing of the cord by clamping, we measured and recorded NACS at minute 15 (Fig. 3).

Postoperatively, we evaluated patients in terms of complications: convulsion, nausea, vomiting, vertigo, headache, trembling, ringing in the ears, confusion, a metallic taste in the mouth, itching, hallucination or respiratory depression (respiratory rate less than 10/min and SpO₂ below 91%). Patients were kept in the recovery room for 30 min and then sent to the ward.

We analyzed demographic data means and standard deviation using the t test. We analyzed correlation between Apgar, APAIS and NACS scores using the chi square test. $p < 0.05$ after analysis was regarded as significant and $p > 0.05$ as insignificant.

Results

Weight, average age and ASA values of the obstetric patients in the study are shown in Table 1.

We determined no significant difference between the patient groups in terms of age ($p = 0.93$), weight ($p = 0.54$) or ASA ($p = 0.63$). The APAIS results significantly differed between the two groups, but there was no difference

Sign	Score 0	Score 1	Score 2
Heart rate	Absent	< 100•min ⁻¹	> 100•min ⁻¹
Respiration	Absent	Weak	Good cry
Muscle tone	Flaccid	Some flexion	Well flexed
Reflexes	No response	Grimace	Cough/Sneeze
Colour	Pale/Blue	Blue éxtremities	Completely pink

Figure 2 Apgar scoring.

		0	1	2
Adaptive capacity	1 Response to sound	Absent	Mild	Vigorous
	2 Habituation to sound	Absent	7-12 sitimuli	< 6 sitimuli
	3 Response to light	Absent	Mild	Blinking, startle
	4 Habituation to light	Absent	7-12 sitimuli	< 6 sitimuli
	5 Consolability	Absent	Difficult	Easy
Total adaptive capacity				
Passive tone	6 Scarf sign	Angling the neck	Elbow slightly passes midline	Elbow does not reach midline
	7 Recall of bowel	Absent	Slow weak	Reproducible
	8 Popliteal angle	> 110	100-110	< 90
Active tone	9 Recall of lower limbs	Absent	Slow weak	Reproducible
	10 Acitive contraction of neck flexors	Absent or abnormal	Difficult	Good; head is maintained
	11 Active contraction of neck extensors from leaning forward position	Absent or abnormal	Difficult	Good; head is maintained
	12 Palmar grasp	Absent	Weak	Excellent; reproductable
	13 Response to traction following palmar grasp	Absent	Lifts parts of the body weight	Lifts all of the body weight
Primary reflexes	14 Supporting reaction (upright position)	Absent	Incomplete transitory	Strong; supports all body weight
	15 Automatic walking	Absent	Difficult to obtain	Perfect reproducible
	16 Moro reflex	Absent	Weak; incomplete	Perfect; complete
General assessment	17 Sucking	Absent	Weak	Perfect; synchronous with swallowing
	18 Alertness	Coma	Lethargy	Normal
	19 Crying	Absent	Weak	Normal
	20 Motor activity	Absent or grossly Excessive	Diminished or mildly Excessive	Normal
Total neurological				
Total score 15. Minutes of life				

Figure 3 Neonatal Neurological and Adaptive Capacity Scoring.

between the groups in terms of the newborn Apgar or NACS values (Table 2).

Discussion

Anxiety is a particularly natural reaction for an individual about to be operated on for the first time. However, pre-operative anxiety leads to pathophysiological responses in the body. The success of a surgical procedure depends on very many somatic and medical variables, among which the

patient's psychological state occupies a prominent position. Thus, preoperative anxiety has been the subject of much research.⁷⁻¹⁰ Many researchers have reported that increased preoperative anxiety means the use of more anesthetic agent and more peri- and postoperative analgesic and longer hospitalization.^{11,12} While there are several studies concerning the use of midazolam in regional anesthesia, the number of studies regarding its use in C/S is limited.¹³⁻¹⁸

The most important objectives in anesthesiologists' administration of premedication are the suppression of

Table 1 Groups' age, weight and ASA values.

	Group I (25)	Group II (25)	p
Age (years)	28.8 ± 4.40	29.8 ± 4.09	0.93
Weight (kg)	76.4 ± 5.82	75.6 ± 4.36	0.54
ASA	88% ASA I 12% ASA II	92% ASA I 8% ASA II	0.63 0.63

ASA, American Society of Anesthesiologists.

Table 2 Group Amsterdam Preoperative Anxiety and Information Scale (APAIS), Apgar and Neonatal Neurologic and Adaptive Capacity Score analyses.

	Group I	Group II	p
APAIS 1st min	18.24 ± 4.23	17.84 ± 3.77	0.725
APAIS 5th min	10.84 ± 3.51	15.00 ± 3.29	0.0001
Apgar 1st min	7.28 ± 1.11	7.32 ± 1.51	0.91
Apgar 5th min	9.12 ± 0.58	9.16 ± 0.73	0.83
NACS	31.24 ± 5.01	30.60 ± 5.22	0.66

APAIS, Amsterdam Preoperative Anxiety and Information Scale; NACS, Neonatal Neurologic and Adaptive Capacity Score.

feelings of fear and anxiety and the establishment of a light state of sleep and amnesia.¹⁹⁻²²

Anxieties such as worry over anesthesia, regarding the risk of death, fear the baby may be disabled, fear of pain and worries over loss of bodily control are likely in patients due to undergo surgical procedure. Studies have reported that 60%-80% of patients are anxious in the preoperative period.^{23,24} The patient speaking with relatives before surgery and being prepared psychologically for the operation by being given information about it represent the psychological component of premedication. The pharmacological component in premedication involves overcoming anxiety with pharmacological agents and the establishment of amnesia and analgesia.²⁵⁻²⁷

While sedation has a wide sphere of use in today's regional anesthesia procedures, its probable depressant effect on the newborn in Caesarian operations explains its rare or non-existent employment. The role of sedation is even more important in an operation such as the C/S in which the mother-to-be's anxiety and preoperative stress are intense. Vasoconstriction develops in the uterine arteries as a result of the mother developing stress and autonomic response, where fetal distress can ensue.

Midazolam is a lipophilic drug and can pass through the placenta by passive diffusion. In one experimental animal study on the use of midazolam in pregnancy, midazolam and its metabolite 1-hydroxymethyl midazolam passed through the placenta, and the plasma concentration level was measured. Studies have shown the circulation distribution and half-life of midazolam and its metabolites in both maternal and fetal circulation.²⁸

Kanto et al. administered 0.075 mg/kg iv. midazolam to mothers following baby removal through C/S performed under epidural anesthesia, and patients were exceedingly cooperative when taken into the recovery room.³¹ This

shows the superiority of midazolam over other benzodiazepines as a fast-acting and short-term agent.

In one study on the subject, Frölich et al. administered a single dose of 0.02 mg/kg midazolam and 1 mcg/kg fentanyl iv. to patients undergoing C/S. It was administered during the skin-cleaning step prior to spinal anesthesia. The newborn Apgar scores were not reported to differ between the group administered the midazolam and fentanyl combination and the control group.¹⁸ The dose selected in this study was determined as the dose that would not lead to maternal depression or impair respiration but that would have a clinical effect on anxiety.

The dosage and timing of the pharmacological agents used for premedication are very important. For that reason, we administered 0.025 mg kg⁻¹ midazolam i.v. while the patients were still in the operating theater waiting room. We chose this time to suppress increased anxiety in pregnant women - a patient group with particular characteristics - before entering the theater. We believe that the weak point of Frölich et al.'s 2006 study was that they administered fentanyl and midazolam immediately before the spinal anesthesia procedure. We planned this study with the intention of being able to administer routine premedication in our clinic to this special patient group in which the pre-caesarian emotion is very intense. In addition, we determined the dose selected in that study (midazolam 0.02 mg kg⁻¹ and fentanyl 1 mcg kg⁻¹) as one that would not lead to maternal depression or impair respiration but would still have a clinical effect. We therefore selected a 0.025 mg kg⁻¹ dose that was close to theirs and which we considered effective in our own clinical practice.

In a study published by Fung et al. in 1992, 90% of mothers reportedly fell asleep before surgery with midazolam administered iv. for sedation purposes in C/S performed under spinal anesthesia. They reported no difference in

these operations between newborn Apgar scores and umbilical vein pH values compared to those of the control group.²⁹

One of the main reasons for sedation being declined prior to Caesarian surgery under regional anesthesia is reported as the mother's desire to see her baby being born and remember that moment.³⁰ The dose used in our study was regarded as meeting our criteria of not causing amnesia in the mother or preventing her from seeing the baby being born and remembering "that moment." Heyman and Salem recommended in 1987 that anxiety in this period could be overcome by talking with the patient or playing music after the extraction of the baby, rather than administering midazolam, and that the amnesic characteristics of midazolam could thus be avoided.³¹ However, this is not intended to reduce the patient's preoperative anxiety. In our opinion, it is more useful for anxiety to be eliminated or at the very least minimized during the period when anxiety is at its peak, when entering the operating theater and before the emergence of the baby, rather than during the period after the emergence of the baby when the mother is emotionally relaxed.

We also employed the Apgar scoring system, another area of evaluation frequently used for determining a newborn's well being. This scoring system developed by Apgar is an easily applied method that suggests whether the baby needs to be resuscitated at birth and how it responds to resuscitation efforts which permits rapid evaluation of the newborn's clinical condition. We selected the NACS scoring system to allow for evaluation of potential effects that can appear in a newborn exposed to any drug. We considered NACS, a scoring system established for the purpose of distinguishing opiate-dependent newborn depression from secondary depressive states such as asphyxia, suitable for this study. Contrary to previously reported studies, these evaluations demonstrated that midazolam premedication had no adverse effect on newborns.

The limitation of our study is sample size. New studies with higher sample size must be performed to enable greater conclusions with minimum side effects but greater dose of midazolam.

In conclusion, the 0.025 mg kg⁻¹ dose and timing of midazolam we used led to a decrease in anxiety in mothers and caused no negative effects to be observed in newborn babies.

Conflicts of interest

The authors declare no conflicts of interest.

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