Low-dose midazolam for aniolysis for pregnant women undergoing cesarean delivery: a randomized trial

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Abstract

Introduction: Anxiety and fear are common among pregnant women undergoing cesarean delivery. In addition to psychologically unpleasant, they can elicit endocrine and metabolic changes. Administration of benzodiazepines in this patient group is uncommon and investigation focusing on the topic is rare. This study aimed to determine anxiolysis efficacy of low-dose midazolam administered preoperatively, right before cesarean delivery, and to evaluate whether its administration impacts neonatal vitality, maternal consciousness, and recall of the moment the baby was born.

Methods: Fifty pregnant women with indication for cesarean delivery were included in this randomized, double-blind, placebo-controlled clinical study and allocated into two groups of 25 participants each (Midazolam and Control group). Midazolam (0.0125 mg.kg⁻¹) or a placebo solution was administered immediately before spinal anesthesia and the anxiolytic effect was assessed using a visual analogue scale before and after administration. We registered the Apgar score at 1 and 5 minutes, the Ramsay scale and recall of the moment of birth, that was assessed 90 minutes after birth.

Results: Pregnant women from the Midazolam group presented a 1.3-point reduction in anxiety on the visual analogue scale, while the Control group showed virtually no change (p = 0.027). We observed no statistically significant changes in Apgar scores, level of maternal consciousness and recall of the moment of delivery.

Conclusions: Low-dose midazolam can provide anxiety management in pregnant women undergoing cesarean delivery with no significant undesirable effects.

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Introduction

Anxiety and fear are common among patients before surgery, notwithstanding considerable scientific and technological progress related to surgery and anesthesia safety. Likewise, pregnant women undergoing cesarean delivery, the most frequently performed surgery worldwide, present a high incidence of anxiety of up to 72%, although the procedure does not commonly occur in a scenario including illness. In addition to psychologically unpleasant, anxiety and fear can promote worse perioperative outcomes. Anxious pregnant women are prone to higher plasma cortisol levels, as are their newborns, as revealed by the analysis of blood samples collected from umbilical cords. In addition, there is a higher prevalence of postoperative pain, requiring higher doses of analgesics postoperatively, and a higher risk of chronic pain occurrence. Commonly, anxious patients have worse surgical recovery, higher infection rates, loss of appetite, insomnia, and lengthier hospital stays. A study revealed that hypotension related to spinal anesthesia is also influenced by anxiety in the immediate prenatal period and can promote higher levels of acidemia for the newborn, either due to hypotension itself, or more vasopressor requirements.

The circumstances explaining the anxiety in this group of patients are the concerns about their own health and that of their fetus, fear of feeling pain, temporary separation from family members, in addition to the fact that they stay awake throughout the procedure in an unfamiliar environment. Some pregnant women may prefer general to spinal anesthesia so as to not remain awake during surgery.

Strategies have been proposed to attempt reduction in preoperative anxiety with pharmacological and non-pharmacological approaches. Audiovisual resources, verbal information and leaflets with instructions explaining the perioperative process can improve satisfaction of surgical patients, and when properly employed can adequately reduce anxiety. Benzodiazepine use as preanesthesia medication for surgical patients is widespread due to the anxiolytic and amnestic effects that promote comfort to patients. Notwithstanding, they are rarely used in cesarean delivery patients due to concerns shared by anesthesiologists, obstetricians, and pediatricians. Given pregnant patients already have delayed gastric emptying, sedation offers a higher risk for broncho aspiration. Likewise, transplacental drug passage may be associated with lower vitality at birth. Moreover, the amnestic effect of benzodiazepines would be undesirable, as it could interfere with the mother’s recollection of the moment of birth. Despite the importance of the topic, clinical trials focusing on the topic are still rare and, we did not find any systematic reviews while searching the literature.

This clinical study aimed to assess whether low-dose midazolam effectively reduces anxiety in these pregnant women to be submitted to cesarean delivery, and to verify whether the drug impacts the newborn’s wellbeing, maternal awareness and recall of the moment of birth.

Methods

This prospective, parallel, randomized, double-blind, placebo-controlled clinical study assessed pregnant women with obstetric indication for cesarean delivery. The study is based on the context of non-inferiority studies, as we administered a dose of midazolam that is lower than the dose used in previous studies, aiming to provide a better safety profile both for the mother and the fetus. The primary outcome of the study was change in anxiety in the groups after intravenous solution administration, while the assessment of Apgar score, Ramsay scale, and recall of the moment of birth were defined as secondary outcomes. Data collection started after approval by the Research Ethics Committee of the Pontificia Universidade Católica de Campinas (PUC-Campinas), under CAE no. 73249617.0.0000.5481, opinion 2326760 of 11/OCT/2017, and complied with the requirements of Resolution 466/12 of the National Health Council, in addition to the Declaration of Helsinki of the World Medical Association. The study was registered in the Brazilian Registry of Clinical Trials (ReBEC) under the code RBR-23/x2s and complied with Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Data were collected at a general tertiary care university hospital, which provides care to patients from the public health system and private health insurance, located in the city of Campinas, state of São Paulo, Brazil. We included in the study patients between 18 and 40 years of age, ASA (American Society of Anesthesiologists) physical status II, and full-term pregnant. The criteria for exclusion from the study were emergency procedures, underdeveloped fetus or with malformation, acute fetal distress, multiple pregnancy, pregnant women presenting cardiac disorder, moderate to severe lung disorder, moderate to severe psychopathologies, patients presenting pain or initial scores on the anxiety Visual Analogue Scale (VAS) of 0 or 1.

While patients were waiting in the pre-delivery room at the delivery unit, they were invited to participate in the study by one of the researchers, received information about the study, and read and signed the Informed Consent Form. The following data were acquired from the medical chart or from the interview: age, weight, height, parity, number of previous cesarean deliveries, gestational age, and indication for cesarean delivery. After this first step, patients remained for different periods before being sent to the delivery room by nursing staff.

Once in this room, patients were monitored with continuous ECG, pulse oximeter, and non-invasive blood pressure device. The same researcher presented a VAS with drawings to the patient, and subsequently a standardized question was asked: From zero to ten, how anxious are you right now? Zero being no anxiety and ten the worst anxiety you can imagine. Soon after, while the attending anesthesiologist was preparing the material and drugs for spinal anesthesia, the researcher outside the operating room and without the presence of the anesthesiologist, randomly allocated the patient to one of the study groups, Midazolam group or Control group, and prepared the solution to be administered. Then, after entering the operating room the researcher administered the solution without interacting
with the patient or anesthesiologist. Patients in the Midazolam group received a single intravenous bolus dose of midazolam of 0.0125 mg.kg⁻¹. Patients in the Control group also received intravenously an identical volume of 0.9% NaCl saline placebo solution. The randomization method was performed using an application for smartphones provided by RANDOM.ORG.¹⁷

The administration of the solution occurred in the time interval between randomization and positioning the patient for the spinal anesthesia puncture. Spinal anesthesia was performed with the patient in a sitting position, a 26G or 27G Quincke-type needle and a standardized spinal injection of 12 mg 0.5% hyperbaric bupivacaine, 20 μg fentanyl and 80 μg morphine. Hypotension resulting from sympathetic blockade was controlled with co-loading approximately 10 mL.kg⁻¹ of crystalloid fluids via an 18G venous cannula, manual or Crawford wedge uterine displacement and bolus infusions of 0.25 to 0.5 mg of metaraminol, targeting to keep arterial blood pressure at pre spinal anesthesia values.

VAS assessment of level of anxiety was repeated at the short interval between sterile draping by the surgeon and skin incision. At that time, the question was posed by the anesthesiologist who was unaware of the group the patient was allocated to. Shortly after, using the Ramsay scale, the same professional verified the level of sedation of the patient.¹⁸

The pediatrician, who was also blind to randomization, collected anthropometric and vitality data of the newborn, comprising weight, length, and Apgar score of the first and fifth minutes.¹⁹,²⁰

Finally, patients to whom the newborn was presented immediately after birth were asked about their recall of that moment with the question: Do you remember if your baby was shown to you soon after birth? This step of the study took place in the postpartum room, 90 minutes after the time of birth.

Descriptive statistics of categorical variables were performed using simple and accumulated frequencies, while means and standard deviations were used for continuous variables. Groups were compared regarding fetal vitality assessed by the first- and fifth-minute Apgar score, using an ANOVA model, Student t-test, and Mann-Whitney test. A significance level of 5% was chosen. Sample size was calculated based on previous studies¹⁵,²³-²⁵ and by repeated analysis of the hypothesis tests performed during data collection. Calculations were performed using the Statistical Analysis System software for Windows (SAS Institute Inc. Cary, NC, USA – version 9.4) and Minitab Statistical Software (version 16).
The criteria were presented to patients, wherein Ramsay size was used for the pre-administration VAS from the pre-administration VAS. The mean decrease in anxiety for the Midazolam group was 1.3 points, whereas the Control group showed practically no change (Table 2). This difference between groups was statistically significant, p-value of 0.0274, using an ANOVA model. The boxplot (Fig. 2) also depicts anxiety variations. When comparing times and groups, the effect size for the VAS was 0.73 favorable to the experimental group.

Progress of anxiety for each patient was calculated by subtracting the value of the post-administration VAS from the pre-administration VAS. The mean decrease in anxiety for the Midazolam group was 1.3 points, whereas the Control group showed practically no change (Table 2). This difference between groups was statistically significant, p-value of 0.0274, using an ANOVA model. The boxplot (Fig. 2) also depicts anxiety variations. When comparing times and groups, the effect size for the VAS was 0.73 favorable to the experimental group.

First- and fifth-minute Apgar scores are shown in Table 3. No significant differences were found between groups. Two patients in the Midazolam group had a first-minute Apgar below 8. One of them was a cocaine user (first-minute Apgar = 7) and the other had well-controlled gestational diabetes mellitus and hypothyroidism (first-minute Apgar = 2).

Among the Midazolam group patients to whom their newborns were presented immediately after birth, only one patient did not recall that moment when questioned 90 minutes after delivery. This showed an atypical consciousness level decrease, as will be explained below. In the Control group a larger number of patients had their newborn presented after birth, but this difference was not statistically significant for the study sample, as Table 4 reveals.

All patients in the study had a consciousness level of 2 on the Ramsay scale immediately prior to the beginning of the surgical procedure. Interestingly, one patient in the Midazolam group had a drop in level of consciousness approximately ten minutes after drug administration, at which point the assessment recommended by the study had already taken place. She remained unconscious until the end of the surgical procedure but responded to verbal stimuli. We believe that this situation was not related to the administration of midazolam, given the disproportionality of the effect at the significantly low dose of the drug. Although we cannot provide an accurate diagnosis of what happened, we suggest that it may be related to some psychological factor or the context of a possible unwanted pregnancy.

We observed that 14 women desired to undergo surgery, seven from each group. Interactivity was the second most frequent indication, with 11 women, nine from the Experimental group (Fig. 3).

Discussion

In the present study the most relevant finding was that midazolam at a dose of 0.0125 mg.kg⁻¹ is efficacious to provided anxiolysis in pregnant women undergoing cesarean delivery without promoting significant undesirable effects. We believe methodological biases were mitigated in the present study to better represent the studied population, because the design was double-blind, placebo-controlled, randomized, and maintained standardized procedures for the anesthetic procedure.

As anxiety is a subjective feeling, measuring its intensity is challenging. In the literature, we find tools aiming to quantify perioperative anxiety. The ideal tool for this purpose must be effective, simple, quick to apply, and possible to be performed by professionals who are not psychologists or psychiatrists. The anxiety-dedicated Visual Analogue Scale (VAS) is a tool extensively used in several studies, as it allows fast, sequential, and convenient assessment by different health professionals. In this study, the use of this scale enabled us to quantitatively assess anxiety, which did not happen in most earlier studies. In addition, we were able to use it at two moments, before and after administering the solution. In our study, we also emphasized the moment of administration of the solution before periods of greater concern for patients, such as spinal block, start of the cesarean delivery and birth of the newborn.

Prior studies on the subject are scant and tools vary significantly. Danielak-Nowak et al. compared midazolam with propofol, using an induction dose followed by continuous infusion after birth. Advantage regarding action onset and lower incidence of amnesia has been shown for propofol, although some patients complained of pain during propofol infusion. Jiang et al. assessing the level of sedation in patients receiving different doses of dexmedetomidine, reported deep sedation and bradycardia, dependent on the administered dose. In that study, data related to maternal satisfaction, postpartum recall and neonatal vitality were not acquired. In the study by Mokhtar, Elsakka and Ali, a study dose of midazolam higher than ours (0.035 mg.kg⁻¹) was administered 30 minutes before delivery. Although the results of that study showed a reduction in anxiety in the experimental group, the administration timing of the drug may have caused less predictable midazolam plasma concentration upon delivery of the newborn, either due to
Table 1  Maternal and newborn parameters according to the groups (mean ± SD).

| Parameter                     | Midazolam group (n = 25) | Control group (n = 25) |
|-------------------------------|---------------------------|------------------------|
| Age (years)                   | 28.9 ± 5.5                | 28.2 ± 5.6             |
| BMI (kg.m⁻²)                  | 32.9 ± 7.0                | 32.5 ± 4.8             |
| Number of previous pregnancies| 2.5 ± 1.3                 | 2.2 ± 1.0              |
| Number of previous cesarean deliveries | 1.0 ± 0.9                | 0.8 ± 0.7              |
| Gestational age (weeks)       | 39.1 ± 1.1                | 39.3 ± 1.2             |
| Newborn weight (kg)           | 3.3 ± 0.4                 | 3.3 ± 0.6              |
| Newborn height (cm)           | 47.7 ± 1.7                | 47.9 ± 2.3             |

BMI, Body Mass Index.

Table 2  Comparison of anxiety scale scores according to the time the evaluation occurred and groups.

| Group               | VAS | Mean | SD | Minimum | Median | Maximum | p    |
|---------------------|-----|------|----|---------|--------|---------|------|
| Midazolam (n = 25)  | Pre-solution | 6.7  | 2.0| 2.0     | 7.0    | 10.0    | 0.004|
|                     | Post-solution | 5.4  | 1.5| 2.0     | 5.0    | 8.0     |      |
|                     | Dif (Post- - -Pre) | -1.3 | 2.1| -5.0    | -2.0   | 3.0     |      |
| Control (n = 25)    | Pre-solution | 6.6  | 1.8| 3.0     | 7.0    | 10.0    | 0.862|
|                     | Post-solution | 6.6  | 2.8| 1.0     | 7.0    | 10.0    |      |
|                     | Dif (Post- - -Pre) | 0.0  | 2.3| -5.0    | 0.0    | 5.0     |      |

Dif, difference; SD, Standard Deviation.

Table 3  First- and fifth-minute Apgar score according to the group (mean ± SD).

| Apgar score | Midazolam group (n = 25) | Control group (n = 25) | p    |
|-------------|---------------------------|------------------------|------|
| First-minute| 8.9 ± 1.6                 | 9.4 ± 0.6              | 0.169|
| Fifth minute| 9.8 ± 0.4                 | 9.8 ± 0.4              | 0.746|

a Mann-Whitney test.

Table 4  Comparison between groups regarding the presentation of the newborn to the mother and recall of this moment after 90 minutes.

| Parameter              | Category | Midazolam group (n = 25) | Control group (n = 25) | p    |
|------------------------|----------|--------------------------|------------------------|------|
|                       | n | % | n | % | n  | % | n  | % |
| Presentation to mother | No | 6 | 24 | 1 | 4 | 0.098\a |
|                       | Yes | 19 | 76 | 24 | 96 |      |
| Recall after 90 minutes| No | 1 | 5 | 0 | 0 | Not calculated\b |
|                       | Yes | 18 | 95 | 24 | 100 |      |

a Fisher exact test.
b Due to low variability.

Figure 3  Indications for cesarean delivery according to the groups.
inter-individual variations in liver metabolism or due to the unpredictability of the time of delivery.

A study that resembled our design administered a combination of midazolam 0.02 mg.kg⁻¹, and fentanyl 1 μg.kg⁻¹ during skin preparation prior to spinal anesthesia. The fetus was evaluated by both umbilical arterial and venous blood gas analysis, pulse oximetry, neurobehavioral scores, and Apgar score. Despite this, maternal satisfaction assessment was performed posing only a single question postoperatively, not controlling for the impact of other external factors. We also suggest that those doses have greater potential to promote amnesia or change in consciousness of patients.¹³ The dose used in our study was associated with a statistically significant decrease in anxiety, revealed by a reduction of 1.3 points (13%) on the visual analogue scale. It is noteworthy that, as the dose used is considerably low, it provides a better safety profile both for mother and fetus. However, whether such level of anxiety relief is enough to improve maternal comfort is arguable. Hence, we consider that this midazolam dose should be considered as the minimum or initial dose to be administered in this group of patients.

Midazolam did not reduce fetal vitality after birth similarly to the study by Frolich et al.⁵ The fifth-minute Apgar score was very similar between groups. Regarding the first-minute Apgar score, although there were no statistically significant differences between groups, the Midazolam group revealed lower mean values. Investigations assessing larger samples might better establish the trend of this variable.

Although the Ramsay scale is very suitable for use in intensive care units, we think it might be an insensitive tool for assessing more subtle consciousness level variations, as its grades present a large discrepancy. All patients in our study remained conscious and collaborative, or Ramsay grade 2, at the moments of assessment established by our study design. Despite this, one of the patients showed an atypical response, catatonia-like, approximately 10 minutes after midazolam was administered, sustaining closed eyes, and not interacting verbally, but without seeming to be asleep. The patient was the only one who did not recall being introduced to her newborn. We did not detect error in the administered dose and were unable to explain her response, as such low doses do not tend to cause such response, whether in pregnant or non-pregnant patients. We suggest that some external psychosocial explanation may be involved. This case seems to be isolated, and we believe that it should not be used against midazolam use.

One of the limitations of this study was the small size of the sample. In part, this was related to the large number of patients who refused to participate in the study. We believe that patients, when reading the Informed Consent Form, were afraid to be informed that, although midazolam is a widely used medication and that it would be administered in low doses, it could cross the placental barrier and reach the bloodstream of the fetus. Other limitations were not being multicenter, the care provided by other health professionals involved with patient care was not standardized, and the absence of control regarding characteristics of the environment to which the patient was exposed, such as noise and the number of patients sharing the same prepartment room. Conversely, some of these factors may have had less interference on the study, as the priority in our analysis was data referring to the progress of anxiety pre- and post-surgery, and not just analyzing its final score.

In view of the high prevalence of anxiety in pregnant women undergoing cesarean delivery, low-dose midazolam has been shown to be effective and safe in a controlled population and may be an alternative for anxiolysis, by duly weighing the risk-benefit ratio.

Conclusion

Low doses of midazolam reduce anxiety in pregnant women undergoing cesarean delivery without promoting significant adverse effects. Future studies may confirm these findings.

Contribution statement

All authors declare to have extensively contributed to all items described in the section Instruction for Authors of the journal.

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Conflicts of interest

The authors declare no conflicts of interest.

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