

Original Article

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Analysis of suspected adverse reactions to anesthetic drugs during cesarean delivery in a cohort of women from a teaching maternity hospital in Ceará (Brazil)

Ingredi Gabrieli SILVA¹, Rannyella Saldanha DIÓGENES¹, Igor Gomes ARAÚJO²,
Alisson Menezes LIMA³, Arlandia Cristina MORAIS¹

¹Universidade de Fortaleza, Brasil; ²Universidade Estadual do Ceará, Brasil; ³Universidade Federal do Ceará, Brasil

Corresponding Author: Araújo IG, igorg.araujo7@gmail.com

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Abstract

Objective: To analyze and describe post-surgical adverse events in pregnant women treated at a teaching maternity hospital in the city of Fortaleza, Ceará. **Methods:** Cross-sectional, quantitative study. Medical records and interviews of women in the postpartum cesarean section were used, in a teaching maternity hospital, in the city of Fortaleza, in the state of Ceará. All patients submitted to the anesthesia application technique were selected. The materials used for this research and the specific data were determined such as variables, education, complications, habits, allergies, pre-existing diseases, medications, reactions and applied procedures. **Results:** The research included 88 patients. Most patients are aged between 20 and 29 years, 46.59% (n= 41), and 30 to 39 years, 42.05% (n= 37). The predominant type of anesthesia was the spinal epidural used in 93% (n= 82) of the patients. Post-anesthetic reactions were: flatulence 22.63% (n= 55), itchy face 17.69% (n= 43) and vomiting 10.29% (n= 25). Bupivacaine was the only anesthesia used in all women who underwent cesarean section, 100% (n=88). Adjunctive drugs were used, such as morphine 97.72% (n= 86) and fentanyl 55.68% (n= 49). The patients' adverse events were mild 62.50% (n= 55) to moderate 37.50% (n= 33). **Conclusion:** The pregnant women received the same anesthetic (bupivacaine), and presented some reactions such as headache, flatulence, facial itching and vomiting. These data reinforce the importance of follow-up by the pharmacist to minimize possible adverse reactions and drug interactions. Furthermore, it is important to use pharmacovigilance resources as a tool for adverse pharmacological events. It is suggested to deepen the analysis for a longer period of time and cover the population of high-risk pregnant women in Ceará.

Key words: anesthetics, caesarean, pregnant women, pharmaceutical, pharmacovigilance.

Análise de suspeitas de reações adversas a medicamentos anestésicos no parto do tipo cesariano em uma coorte de mulheres de uma maternidade-escola do Ceará (Brasil)

Resumo

Objetivo: Analisar e descrever eventos adversos pós-cirúrgicos em gestantes atendidas em uma maternidade escola do município de Fortaleza, Ceará. **Métodos:** Estudo transversal, quantitativo. Utilizaram-se prontuários e entrevistas de mulheres no pós-parto do tipo cesáreo, numa maternidade escola, no município de Fortaleza, no estado do Ceará. Foram selecionadas todas as pacientes submetidas à técnica de aplicação de anestesia. Os materiais utilizados para esta pesquisa e os dados específicos foram determinados como variáveis, escolaridade, complicações, hábitos, alergias, doenças pré-existentes, medicamentos, reações e procedimentos aplicados. **Resultados:** Na pesquisa foram incluídos 88 pacientes. A maioria das pacientes tem uma faixa etária entre 20 a 29 anos, 46,59% (n= 41), e 30 a 39 anos, 42,05% (n= 37). O tipo de anestesia predominante foi a raquiepidural utilizada em 93% (n= 82) dos pacientes. As reações pós-anestésicas foram: flatulência 22,63% (n= 55), prurido no rosto 17,69% (n= 43) e vômito 10,29% (n= 25). A bupivacaína foi a única anestesia utilizada em todas as mulheres que realizaram cesárea, 100% (n=88). Foram utilizados medicamentos coadjuvantes, como morfina 97,72% (n= 86) e fentanil 55,68% (n= 49). Os eventos adversos das pacientes foram leves 62,50% (n= 55) a moderados 37,50% (n= 33). **Conclusão:** As gestantes receberam o mesmo anestésico (bupivacaína), e apresentaram algumas reações como cefaleia, flatulência, prurido facial e vômitos. Esses dados reforçam a importância do acompanhamento pelo profissional farmacêutico para minimizar possíveis reações adversas e interações medicamentosas. Além disso, é importante utilizar os recursos de farmacovigilância como ferramenta para eventos farmacológicos adversos. Sugere-se aprofundar a análise por um período maior de tempo e abranger a população de gestantes de risco no Ceará.

Palavras-chave: anestésicos; cesariana; gestantes; farmacêutico; farmacovigilância.



Introduction

Cesarean delivery (C-section) emerged as an innovation for mothers and infants, contributing a new perspective of reducing complications arising from pregnancy and labor¹. C-sections have presented a high rate in the world, causing an increase in the budgets of health services and in the perils of maternal and perinatal morbidity and mortality. Maternal mortality is a serious public health problem and worldwide, the prevalence in underdeveloped countries records 99% of all cases².

In 2018 and according to the Ministry of Health, the Maternal Mortality Ratio (MMR) indicator was 59.1 deaths per 100,000 live births (LBs), an alarming figure. Between 1996 and 2018, 28,919 maternal deaths were reported in the Mortality Information System (*Sistema de Informações sobre Mortalidade*, SIM). It should be noted that nearly 830 women die worldwide every day due to problems during delivery that are considered preventable³.

There are several complications in cesarean deliveries, such as the following: increasingly advanced maternal age, which increases the probability of the onset of some diseases such as diabetes, hypertension, overweight and embolic episodes, among others^{3,4}. In this context, the World Health Organization (WHO) highlights the objective of reducing the risk of maternal mortality worldwide by 2.5% per year. It also considers that cesarean deliveries grow above 15% annually and that 230 million obstetric surgeries are performed⁵.

At the time of hospitalization, intravenous drugs are used to provide analgesia; however, the analgesia degree is subjected to some side effects. These drugs require safety and efficacy in the care of patients during the preoperative period, being related to the deployment of care samples, thus designating stimuli for health professionals due to the high development in technology, current clinical systems and new surgical procedures⁶. In addition, the risks of adverse events (AEs) need to be monitored. It is worth noting that they are defined by the WHO as any incident that results in harms to the patient⁷.

Epidural analgesia is also used, that is, an anesthetic technique used in the introductory stage of labor, with cervical dilation less than 4 cm, if the patient does not have sufficient expansion, it is associated with an increase in the cesarean section rate, which makes it contraindicated in a way that corresponds to its performance in that period⁸.

The anesthesia technique to be applied is the epidural block, which provides anesthesia during delivery. The drug to be used is introduced into the epidural space, usually a local anesthetic agent such as ropivacaine, bupivacaine or lidocaine, associated or not with an opiate (fentanyl or sufentanil). The most commonly used local anesthetic agent is bupivacaine 2.5 mg at a concentration of 0.5% associated with sufentanil (from 2.5 to 5.0 µg) or fentanyl (from 10 to 20 µg). These drugs are lipophilic, and there is the possibility of also improving intensity of the analgesia, as they have a short latency time, although they present shorter action. Bupivacaine is found in the racemic form and can reach toxic plasma concentrations, producing some effects on the Central Nervous System (CNS), mainly seizures, and cardiovascular effects, which may evolve to cardiorespiratory arrest and death⁹.

Delivery is a painful and visible process. The reactions reported contribute to worsening of the complaints, which brings to the

research questions and answers about what can be corrected in the use of these inputs in parturients. In addition to that, there are few studies investigating the safety of anesthetic agents in epidural, spinal-epidural and general deliveries.

For this reason, the current study aims at analyzing and describing post-surgical adverse events caused by epidural, spinal-epidural and general anesthetic agents used in cesarean deliveries, in pregnant women treated at a teaching maternity hospital in the city of Fortaleza, Ceará.

Methods

This is a cross-sectional, observational, quantitative and prospective study, in which medical charts and interviews with women in the postpartum of cesarean sections were used, at a tertiary teaching maternity hospital in the city of Fortaleza, state of Ceará. This maternity hospital has specialties such as Gynecology, Obstetrics and Mastology, with a record of 42,959 emergency visits, with 4,999 deliveries performed in 2020.

The study and data collection were carried out from March to April 2022. The patients selected were all those subjected to the technique of application of epidural, spinal-epidural and general anesthesia in the lower spine vertebral space.

The materials used for this research were medical charts and the data collected were the following variables: age group, schooling, complications, habits, allergies, pre-existing diseases, medications, reactions to the anesthesia and anesthetic agents applied.

No parturient woman was excluded from this research. In order to carry out the interviews with the parturients, the Free and Informed Consent Form (FICF) was applied and a questionnaire formulated by the researchers was used. The parturients' follow-up was of mutual interest, as the participating patients were curious to know about the adverse effects of the anesthesia. However, when approaching post-abortion women, given that most delicate moment, an even more careful conversation was sought.

The reactions observed were classified according to severity as mild, moderate, severe and lethal, as recommended by the WHO¹⁰ and the Naranjo algorithm¹¹ was used. Mild reaction – Does not require specific treatments or antidotes and it is not necessary to suspend the medication; Moderate – Requires therapeutic change, but the offending drug does not need to be suspended. It may be necessary to extend the hospitalization time and the use of a specific treatment; Severe – Potentially lethal and requires interruption of drug administration and adoption of a specific treatment for the adverse reaction; Lethal – Directly or indirectly contributes to the death of the patient.

Identification of the Adverse Drug Reaction (ADR) was in charge of a pharmacist.

The results were expressed as absolute (n) and relative (%) frequencies using Excel, version 2010.

The research complies with the ethical aspects, having been approved by the Ethics Committee involving human beings of the University, under opinion No. 5,262,084 and CAAE: 55785722.5.0000.5050.



Results

The individuals included in the research were 88 patients subjected to anesthesia: spinal-epidural, epidural or general. Table 1 shows the distribution of the patients according to age, schooling, complications, habits and allergies. Most of the patients analyzed are aged between 20 and 29 years old (46.59% [n=41]), followed by the age group from 30 to 39 years old (42.05% [n=37]). The predominant type of anesthesia was spinal epidural and was used in 93% (n=82) of the patients.

Table 1. Characteristics of the puerperal women (n=88) hospitalized post-anesthesia in a maternity teaching hospital, from March to April 2022 (Ceará, Brazil).

Age group	N (%)
14-19 years old	6 (6.82)
20-29 years old	41 (46.59)
30-39 years old	37 (42.05)
40-49 years old	4 (4.54)
Schooling	N (%)
Incomplete/Complete Elementary School	23 (26.14)
Incomplete/Complete High School	55 (62.50)
Incomplete Higher Education	10 (11.36)
Complications	N (%)
Yes	55 (62.50)
No	33 (37.50)
Habits	N (%)
Smoking habit	2 (2.27)
Alcoholism	2 (2.27)
Illicit drugs	3 (3.41)
Does not use	81 (92.05)
Comorbidities	N (%)
No comorbidities	40 (32.8)
Gestational Diabetes Mellitus	20 (16.4)
Systemic Arterial Hypertension	21 (17.2)
Severe Pre-eclampsia	14 (11.5)
Others	13 (10.7)
AIDS	6 (4.9)
Syphilis	4 (3.3)
Obesity	4 (3.3)
Allergy	N (%)
Yes	19 (21.59)
No	69 (78.41)

Source: Research data, 2022.

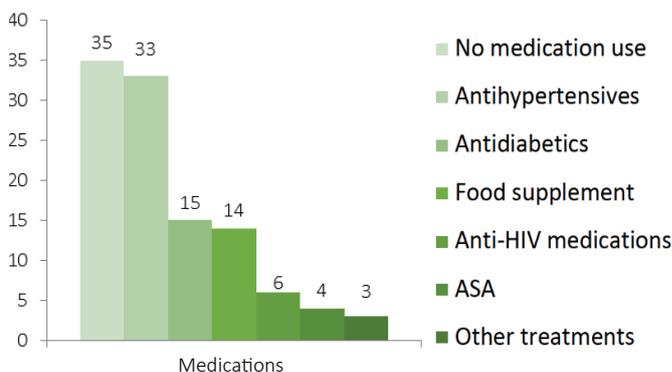
Based on the data from the medical charts, still in Table 1, it is possible to observe the comorbidities that the patients presented during their pregnancies or pre-existing comorbidities. Diabetes mellitus (16.4% [n=20]), Arterial hypertension (17.2% [n=21]) and Severe pre-eclampsia (11.5% [n=14]) were the most frequent ones.

Regarding the medications used in the treatment of comorbidities and other diseases, it was observed that there are patients that are not using any medications (31.8% [n=35]), antihypertensives appear next with 30.0% (n=33), followed hypoglycemic agents with 13.6% (n=15), according to Figure 1.

It was observed that bupivacaine was the only anesthesia used in all women who underwent cesarean sections (100% [n=88]).

It should be noted that, along with the anesthesia, coadjuvant medications were also used, such as the morphine (97.72% [n=86]) and fentanyl (55.68% [n=49]) opioids. Morphine is indicated for pain relief and supplementation of general anesthesia, while fentanyl is used for pain and sedation in more severe surgeries.

Figure 1. Medication use or not by pregnant women at the maternity hospital, from March to April 2022 (Ceará, Brazil).

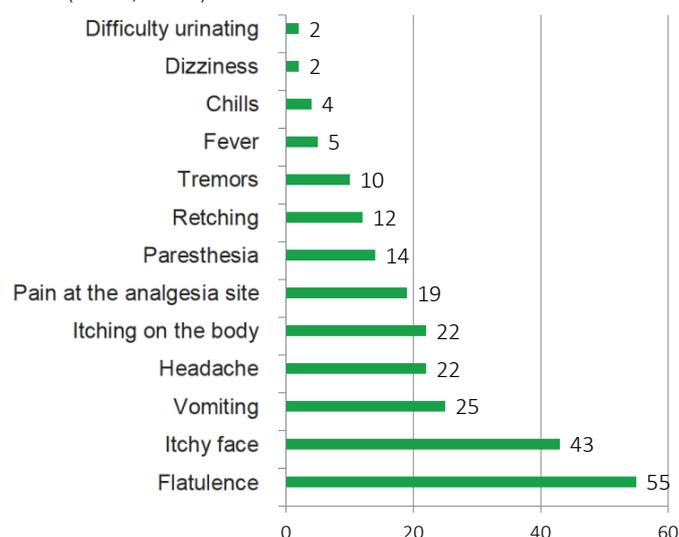


Source: Research data, 2022.

The post-anesthetic reactions in post-operative women who underwent spinal-epidural, epidural and general anesthesia already mentioned were as follows: flatulence (22.63% [n=55]), itchy face (17.69% [n=43]) and vomiting (10.29% [n=25]), as shown in Figure 2. The anesthetic agents suspected for the reactions were the following: (i) fentanyl- flatulence; (ii) morphine- itchy face; and (iii) bupivacaine- vomiting and headache.

The patients' adverse events were classified from mild in 62.50% (n=55) to moderate in 37.50% (n=33). In the current study, no adverse event culminating in death was observed. The adverse event data were not included in the hospital's medical charts; therefore, the questionnaire used by the researchers was the strategy that enabled such investigation.

Figure 2. Adverse reactions to the anesthesia in the parturient women at the maternity teaching hospital, from March to April 2022 (Ceará, Brazil).



Source: Research data, 2022.

Discussion

The study allowed analyzing and describing suspected ADRs caused by anesthetic agents in a population of women admitted to a public maternity teaching hospital.

There are several factors that can worsen these events, such as some comorbidities. Among the most associated with ADRs are diabetes mellitus, systemic arterial hypertension and severe pre-eclampsia. Gestational diabetes is due to hyperinsulinemia, as it reduces insulin sensitivity¹². Hypertension is related to fetal compromise and, with that, it has meant increased risks during pregnancy and delivery¹³. Severe pre-eclampsia is a genetic and immunological failure or a placenta inversion, which occurs due to problems in the development and fixation of the placenta blood vessels, having an endothelial lesion as an exacerbated inflammatory reaction to stress, which contributes to severe pre-eclampsia (SPE), resulting in increased vascular permeability¹⁴.

The most used medications were antidiabetics, antihypertensives and food supplements, among others. Antihypertensives used during pregnancy are important to avoid complications such as SPE. In the study, it was observed that SPE was present in 14 patients and that all of them used antihypertensive medications with more than one drug combination, namely: methyldopa, nifedipine, amlodipine and others. It should be noted that these medications can cross the placental barrier, reaching fetal circulation and favoring reactions to the fetus, with the possibility of drug interactions¹⁵.

Acetylsalicylic acid plays an important role, as it acts in cardiovascular prophylaxis and, thus, can prevent some disorders related to pregnancy, such as SPE¹⁶.

Among the antidiabetics, the most frequently used were metformin, insulin and gliclazide. Metformin is considered a safe medication to treat early gestational diabetes mellitus (GDM), representing the main treatment choice⁹. Food supplements are important for the health of the fetus and for replenishment of nutrients¹³. The use of antiretroviral therapy was observed in some patients to reduce transmission of the HIV virus from mother to fetus¹⁷.

The most frequently observed reactions were as follows: post-anesthetic headache, vomiting and retching, itching on the body and face, and pain at the anesthesia site, among others. Headache represents a very significant percentage: of all 88 women, 25% (n=22) experienced postpartum headache. This pain is characterized by being located in the cervical region or shoulder, which can last from cesarean delivery to days or weeks after the anesthesia; this headache can be primary or secondary¹⁸. The reactions observed were expected and are described both in the anesthetic package inserts and in the literature.

Postoperative vomiting and retching do not pose any risk; they are complications that are frequently observed in patients. When anesthesia adheres to the body, the patients tend to vomit immediately after application or after a while, although always in the first 24 hours postpartum¹⁹. Itching on the face and body was mild and bearable by the patients, not requiring any pharmacological therapy. These reactions were caused by the association of morphine with bupivacaine, used in surgeries²⁰.

The pain at the anesthesia site reported by the patients is caused by tissue damage and inflammatory processes, due to insertion of the needle at the application site. The patients reported pain that bothered them when lying down, getting up, walking and doing other activities considered of everyday life²¹.

It is observed that bupivacaine was the anesthetic agent with the highest rate of choice among 88 cesarean deliveries. Its choice seeks to reduce induced side effects, as it is less toxic for the cardiovascular system and more selective for sensory fibers, producing less motor blockage. The association of epidural fentanyl with morphine shows an improvement in the quality of the duration of analgesia²².

Bupivacaine has some latency time from epidural puncture until the patient complains about a paresthesia sensation. The type of alteration is referred by the patient as a sensation of heaviness, tingling and numbness²¹. Duration of spinal anesthesia not only depends on the choice of the local anesthetic agent, but also on the dose administered. Isobaric 0.5% bupivacaine is a long-acting local anesthetic²³.

Opioid analgesics bind to the receptors both in the Central Nervous System and in other tissues. The levorotatory form has agonist activity. Presence of the ionized form is required for interaction with the receptor's anionic ligand. Fentanyl is a synthetic opioid of the phenylpiperidine group. Its analgesic potency is nearly 80 to 100 times that of morphine. Its main advantage is the absence of histamine release and that it retains the characteristics of little action on the hemodynamic parameters²².

In view of the results, the importance of pharmacovigilance in activities related to the identification, evaluation, understanding and prevention of adverse effects is observed. Pharmacist are an essential figure in this process, as they hold the technical knowledge and fundamental skills in identifying possible adverse drug reactions and suspected drug interactions. It is emphasized how necessary the role of hospital pharmacists is for the evaluation of prescriptions, particularly in the surgical center and beds, in the context of multiprofessional monitoring.

The literature indicates an interest in deepening on this topic, which is so vast and important for women's health and generates curiosity among the patients interviewed, who question the reactions, which cause a lot of discomfort and about what can be improved and avoided. Health professionals are important actors in this context, investigating possible adverse reactions/drug interactions, such as those observed in this study, thus contributing to performing notifications through pharmacovigilance.

This study has limitations such as data collection from the patients' recall and the restricted data collection period. However, the results obtained on the frequency of suspected ADRs described by the patients contributed to the discussion of this topic, which is still quite scarce in the literature.

Conclusion

The pregnant women received the same anesthetic agent (bupivacaine) and had some reactions such as headache, flatulence, itchy face and vomiting. Although the reactions were classified as mild (mostly) and moderate, both presented significant discomforts.

These data reinforce the importance of monitoring by pharmaceutical professionals to minimize and manage possible adverse reactions and drug interactions. In addition to that, it is important to use pharmacovigilance resources as a tool to monitor adverse events in pregnant women undergoing epidural, spinal-epidural and general anesthesia.

It is suggested to deepen the analysis for a longer period of time and encompass the population of pregnant women at risk in Ceará, so that pharmacovigilance protocols and routines of obstetrics and pharmacovigilance services can be developed. The use of Standard Operating Procedures (SOPs) in the early detection of risk to pregnant women becomes fundamental in the safety of this high-risk population.

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Collaborators:

Conception and design (AMA and ACL); Data analysis and interpretation (IGA); Writing of the article (IGP AND RSD).

Conflict Of Interest Statement

The authors declare no conflicts of interest in relation to this article.

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