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Case Report

Bupivacaine-Fentanyl Induced Anaphylactic Reaction in Cesarean Delivery Undergoing Spinal Anesthesia: A Case Report

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Abstract

Background : Incidences of anaphylaxis during pregnancy are unreported but high risks to both infant and mother due to pharmacokinetic profile changes of local anesthesia agents in pregnancy.
Case : A 36-year-old woman (G4P2A1) delivered an infant at 40 weeks of her gestation using a cesarean surgical procedure with spinal anesthesia technique. The spinal anesthetic was administrated bupivacaine 15 mg and adjuvant analgesic (fentanyl 25 mcg). The delivery proceeded seamlessly. The patient was experiencing itching, swelling, and erythema in almost every part of her body, including her face, neck, arm, thigh, and leg in 43 minutes after drugs administration. This anaphylaxis reaction resolved after 22 minutes using 2 ampoules of intravenous dexamethasone 5 mg/ml and 1 ampoule of intravenous methylprednisolone 125 mg/ml. No data on second phase allergy was reported from the patient and infant who are born healthy and have a good response, indicated by an Apgar score 8–9.
Conclusion : The alterations pharmacokinetic profile of local anaesthesia in pregnancy can cause adverse effects such as anaphylaxis reactions. Anaphylaxis reactions require suitable therapeutic intervention (adrenaline and glucocorticoids) to ensure the safety of both the mother and infant during the delivery operation.

Keywords : *anaphylaxis, bupivacaine, fentanyl, pregnancy, spinal anesthesia*

INTRODUCTION

Spinal anaesthesia is a regional anaesthesia procedure or technique by injecting a local anaesthetic into the subarachnoid which is often used in various surgical procedures, especially in the lower body area. In Indonesia, spinal anaesthesia is commonly used for a variety of surgical operations. In one of Bekasi's hospitals, 99.4% of the population receives spinal anaesthetic during caesarean section operations.[1] The most widely used anaesthetic agent in spinal anaesthesia procedures is bupivacaine.[2]

Bupivacaine is a potent local anaesthetic that suppress action potential in the nerve cell. There are unique components of an aromatic ring structure with an amide group linkage.[3] In recent studies on the effects of using spinal anaesthesia was associated with a decrease in intraoperative blood pressure.[3,4] An earlier study, using of another local anaesthetic in pregnancy caused anaphylactic shock during delivery.[5]

Articles of anaphylactic/immunologic reaction during pregnancy are still lacking. Some incidents of anaphylaxis during pregnancy are unreported, so are in Indonesia. Anaphylactic reactions are becoming more common as time passes. In this study, we discuss anaphylaxis reaction as an adverse event of bupivacaine-fentanyl and management therapy of anaphylaxis reaction undergoing bupivacaine-fentanyl as a spinal anesthetic in pregnancy, especially cesarean delivery.

CASE PRESENTATION

A 36-year-old woman who was four times pregnant, with twice cesarean delivery and once aborted (G4P2A1). She was scheduled for a cesarean operation underlying spinal anesthesia at 40 weeks of her gestation. She had an asthma history but no allergy to the drug. She consistently carries an inhaler to alleviate asthma attacks. In the operating room, she had started hydroxyethyl starch intravenous and crystalloid intravenous fluid (CaCl2, KCl, NaCl, sodium acetate) using a transfusion set. At 10.45 a.m., spinal anesthetic was administrated bupivacaine 15 mg and adjuvant analgesic fentanyl 25 mcg in the sitting position, at the L3-L4 interspace. Observation was conducted for 10 minutes to confirm the patient's experience of foot numbness. The caesarean section operation was initiated by the obstetrician and surgical team at 11:03 a.m. The infant was delivered safely after five minutes, accompanied by loud wailing. Apgar score evaluation of the infant's health status and response is shown in Table 1.

At 11.28 a.m., the patient was experiencing itching, swelling, and erythema in almost every part of her body, including her face, neck, arm, thigh, and leg (Figure 1). The patient's blood pressure, heart rate, and respiratory rate were maintained at 126/65 mmHg, 78 pulses per minute, and 22 times per minute, respectively. The anaesthesiologist administrated 2 ampoules of intravenous dexamethasone 5mg/ml and the patient was observed for15 minutes. Section caesarean operation finished at 11.50 a.m. and the patient was moved to the recovery room.

In the recovery room, the patient continues to experience itching and increased burning sensations. Then, the anaesthesiologist administrated 1 ampoule of intravenous methylprednisolone 125mg/ml. It was observed in 20 minutes, the patient no longer experienced itching, and the redness had resolved. Vital signs remained stable, including blood pressure 138/87 mmHg, heart rate 76 pulses per minute, and respiratory rate 22 times per minute. Maternal breathing also remained stable at 99% of saturation oxygen.

DISCUSSION

This case describes an anaphylactic reaction during cesarean delivery induced by a bupivacaine-fentanyl combination. This combination was administered using a spinal anesthesia procedure. The selection of spinal anesthesia procedures is based on safety and health

TABLE 1
The Apgar Score Evaluation

Details	Time measurement		
	1st minute	5th minute	10th minute
Appearance	2	2	2
Pulse	1	2	2
Grimace	2	2	2
Activity	1	1	1
Respiration	2	2	2
Total Apgar Score	8	9	9

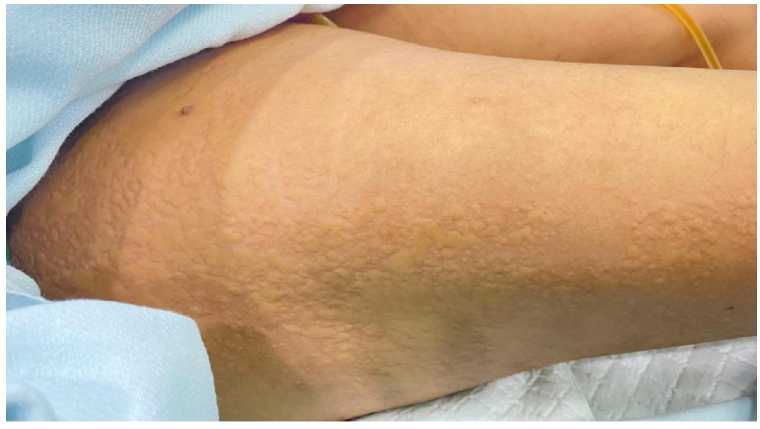

Figure 1. Anaphylactic reaction

TABLE 2
The characteristics of previous case report published

Study	Age	Type of anesthesia	Technique of administration	Side effects	Treatment	Prognosis
Takahashi M, *et al* [5]	42 years old	Mepivacaine	Combination of spinal and epidural anesthesia	Anaphylactic shock	Phenylephrine intermittent, Methylprednisolone 500 mg to prevent second phase of allergic	Resolved immediately
Browne I, *et al* [25]	43 years old	Lidocaine	Spinal anesthesia	Anaphylactic reaction	Not mentioned	Resolved
Iwasaki M, *et al* [26]	33 years old	Bupivacaine, Morphine	Spinal anesthesia	Anaphylaxis: hypotension, decreased saturation, hoarseness, breathlessness, skin flushing	Phenylephrine (total dose 0.4 mg), ephedrine (total dose 25 mg), hydrocortisone and famotidine.	Resolved after 23 minutes

advantages for both the mother and the infant.[6] Spinal anesthesia has been the best choice and effective for cesarean delivery with minimal complications such as low blockade respiratory, immediate patient feedback when evaluating the proximity of surgical instruments to neural elements, and reduced respiration of stomach content.[6–8]

In this case, the bupivacaine-fentanyl combination was used during the spinal anaesthesia procedure, these were injected into the spinal space to induce numbness and weakness in the lower extremities.[2] Bupivacaine was most often utilized due to its prolonged local anaesthetic mechanism of action; it also has special characteristics from amide group and is categorized as a strong local anaesthetic.[9] Fentanyl is an opioid that was co-administered to improve the efficacy of local anaesthetic. The Synergistics analgesic effect of fentanyl has given benefits such as reducing visceral pain that enhanced the efficacy of the block, and reducing the necessary dosage of local anaesthetic, thereby ensuring hemodynamic stability.[10,11]

Structure amide group and ester group of local anesthetics can cause another complex phenomenon is the cross-reactivity hypersensitivity, although patterns vary significantly among patients.[12] Amide derivates e.g. lidocaine, mepivacaine, bupivacaine, ropivacaine, prilocaine. Ester derivates e.g. procaine and tetracaine. Recent studies have shown that inconsistent patterns in cross reactions, variable reactivity factors play a major role in cross reactions. Variable reactivity occurs when a patient is allergic to one local anesthetic of the amide group and shows cross-reactions with other amides but is still tolerated with other amides. For example, a patient had allergies to mepivacaine, cross-reactivity to lidocaine

and ropivacaine but tolerated bupivacaine and levobupivacaine.[12,13] This reaction necessitates the utilization of a skin prick test to confirm cross-reactivity. The limitation of this study is its inability to demonstrate any cross-reactions occurring in patients.

The anaphylactic incident in this case has been investigated by the medical team with considering the patient's anamnesis since exposure to bupivacaine-fentanyl. The physical examination showed notable findings, namely vital signs indicative of bradycardia leading to hypotension if not promptly addressed. The assessment of the skin and mucosal membranes demonstrated itching, swelling, and erythema. This is deemed to have fulfilled the criteria for in determining the incidence of anaphylactic reactions. Recent guideline recommends supporting examinations including skin prick tests, Ig E, serum tryptase levels, and plasma histamine levels to determine etiology of anaphylaxis.[14] However, the patient declined to undergo a skin prick test due to concerns that her skin condition would worsen. The examination of serum tryptase was not conducted due to inadequate equipment and unavailability in the hospital laboratory, representing a limitation of this study. The immunological supporting examination used in this case is an increase in eosinophils up to 2 times (5.3%, normal 1–3%), although eosinophils are not primary effectors, Eosinophils contribute to allergic inflammation and immunological modulation by releasing various mediators, such as cytokines, histamine, and granule proteins, which enhance the manifestation of allergic responses.[15]

The study team has hypothesized the presence of additional causal factors. The investigation's findings indicated that intravenous hydroxyethyl starch and crystalloid fluids administered to patients did not elicit allergic responses. It is confirmed that there is no allergic reaction associated with the administration of intravenous fluids during the pre-operative and post-operative procedures. Recent studies have shown rare cases of anaphylactic reactions caused by intravenous fluids e.g. hydroxyethyl starch and crystalloid.[16] Another suspected causative agent is latex, but no evidence indicates that latex allergies have arisen following the patient's hospitalization.

Pharmacokinetic profile of bupivacaine and fentanyl

Bupivacaine had high lipid solubility which impacted the pharmacokinetic profile of bupivacaine. Lipophilic of bupivacaine determines the potency, duration of action, and plasma protein binding of local anaesthetics.[17] A recent study about the pharmacokinetic profile of bupivacaine changes in the pregnancy population showed higher AUC $_{(0-\sim)}$. AUC $_{(0-\sim)}$ describes the amount of active drug present in systemic circulation, if the AUC $_{(0-\sim)}$ value increased the amount of active drug that has an effect will also be higher.[18] That effect can be therapeutic effects or adverse effects. It's possibly can cause an anaphylactic reaction in the patient in this case. It was substantiated in the interview process; the patient reports no history of allergy to bupivacaine and screening of adverse effects monitoring using the Naranjo algorithm result probably scored (above 6 points).

Fentanyl as a strong opioid had selectively bound to gamma receptors in the peripheral and central nervous system which impacted on pharmacokinetic profile especially the metabolism of fentanyl.[19] Recent study on the pregnancy population, the metabolic ratio of fentanyl significantly was higher than non-pregnant (*p-value* = 0.001), that shown the conversion rate to major metabolite in pregnancy was faster than non-pregnant.[20] Secretion of fentanyl inactive metabolites occurs 48–72 hours by urine, probably plasma fentanyl concentrations are expected to remain elevated because an anaphylactic reaction in this case occurred 25 minutes after fentanyl administration.[21]

The combination of bupivacaine and fentanyl has been studied for pharmacokinetic interactions. Synergistic interactions of analgesic effect showed in randomized controlled studies that these combinations given fast onset duration of sensory blockade, an elevated sensory level, and extended postoperative analgesia.[22] Accumulation of the amount of drug combination in blood serum also increased and led to elevating adverse effects.[23] Other conditions have been studied, especially impaired liver and kidney function would change pharmacokinetic profile, leading to slower metabolism and excretion of these drug.[22,24]

Case study of incidence anaphylactic caused by local anaesthesia

Although anaphylactic reaction after local anaesthetic administration is unpredictable, our study found that it occurred in other pregnancies (Table 2). The patients are between 22 and 43 years old, occurring in Asia (70%). Spinal anaesthesia is a technique administration used in all the case study. The local anaesthetics involved are mepivacaine, lidocaine, and bupivacaine in combination with morphine. High lipid solubility such as mepivacaine and bupivacaine had a potential anaphylactic shock reaction in a pregnancy population.[2]

Takahashi M, *et al* showed mepivacaine as local anaesthesia can cause anaphylactic shock. It was clarified by examination of the causative agent of the anaphylaxis reaction after the operation. Mepivacaine has been reported to cause hypersensitivity reaction (redness) in the hand area instead of the others (lidocaine, procaine, bupivacaine).[5] Iwasaki M, *et al* found a shock anaphylactic reaction after bupivacaine and morphine administration in L3–L4 interspace. The manifestations are hypotension, decreased saturation, shortness of

breath, and skin flushing.[26] It's similar to this patient study. The dose of bupivacaine is 12,5 mg and 15 mg, based on theory, these doses are within the therapeutic dose range. However, pharmacokinetic profile changes during pregnancy such as higher active drugs in plasma and elevated active metabolite can cause adverse effects.[18,26]

Management treatment of anaphylactic reactions

International guidelines of anaphylactic management treatment claim adrenaline agents as first-line and glucocorticoids as adjuvants/second line.[27] Recent study, phenylephrine as adrenaline was used to resolve anaphylactic and glucocorticoids (methylprednisolone, hydrocortisone) as the second line to prevent the second phase of allergy. The results achieved good outcomes not more than 30 minutes.[5,26] However, adrenaline was not administered to treat the adverse effects in this patient. It is because the medical team's investigation indicated that the reaction was not severe. Furthermore, this patient had a history of asthma and pre-hypertension, and using adrenaline could elevate risk adverse effect of uncontrol blood pressure. So, the medical team considered intravenous glucocorticoids dexamethasone and methylprednisolone have been given to achieve therapeutic outcomes.

Glucocorticoids are potent immunosuppressant and anti-allergy agent which reduce the inflammatory process. Glucocorticoids mechanism action reduced activation mass cell and decreased maturation mass cell in central role of anaphylaxis reaction. Glucocorticoid receptors bind specific elements such as activating protein-1 nuclear factor to provide anti-inflammatory effects. Action of glucocorticoids in mast cell reduced transcription cytokines of inflammatory, arachidonic acid molecule, so promptly block the release of histamine from mast cell surface and increased inflammatory mediators.[27,28]

Effective management of anaphylaxis in pregnant women is crucial. Maternal anaphylaxis, although rare during pregnancy, presents a serious threat to both maternal and fetal health condition. Without prompt and effective intervention, it can result in critical complications such as fetal distress, neurological impairment, and even death. During pregnancy, an anaphylactic reaction can induce maternal hypoxemia, potentially leading to intrapartum asphyxia. Additionally, maternal hypotension and vasoconstriction may reduce uterine blood flow, significantly increasing the risk of severe fetal brain injury.[29]

Corticosteroids may be utilized in the management of anaphylactic reactions during pregnancy; however, several critical considerations must be considered regarding their effects during the antenatal period. Synthetic corticosteroids, when administered antenatally, readily cross the placenta and can expose the fetus to supraphysiological concentrations. While the primary therapeutic target is fetal lung maturation, other organ systems––particularly the developing neurological and immune systems––may also be affected. Emerging evidence from observational cohort studies indicates a potential association between antenatal corticosteroid exposure and long-term neurodevelopmental impairments in offspring.[30] Additionally, concerns have been raised regarding an increased risk of rare but serious infections in children exposed to antenatal corticosteroids. Recent large-scale studies conducted in the United States and Taiwan have reported a higher incidence of infections such as sepsis and pneumonia following short-term use of oral corticosteroids in the general population. However, in this case, the infant was not exposed to any medications, as the mother received treatment only after delivery.[31] Therefore, the therapeutic interventions did not affect the baby.

All the infants in these cases were delivered safely after anaphylactic problem was resolved, and the mother did not suffer from recurrent anaphylactic episodes, including the infant in present case was born safely. It is shown in the APGAR (Appearance, Pulse, Grimace, Activity, Respiration) score evaluation. The Apgar score is an assessment that indicates the health and response of infant after birth. The Apgar score for the infant in this case is 8 at first minute, 9 at five minutes, and 9 at ten minutes. A score range of 7–10 indicates that the baby is healthy and able to good respond.

A potential limitation of this case report was unreported data of allergy skin tests to detect specific allergies from some local anaesthesia and inability to demonstrate any cross-reactions occurring in patients in this patient.

CONCLUSION

This research highlights the alterations pharmacokinetic profile of local anaesthesia in pregnancy that can cause adverse effects such as anaphylaxis reactions. This s issue requires suitable therapeutic intervention (adrenaline and glucocorticoids) to ensure the safety of both the mother and infant during the delivery operation.

CONFLICT OF INTEREST

All authors declare no conflict of interest and this research did not receive specific funding. This research had ethical approval number: KE/FK/1883/EC/2024 from The Medical and Health Research Ethics Committee "Faculty Medicine, Public Health and Nursing Universitas Gadjah Mada Dr. Sardjito General Hospital".

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