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INTRAOPERATIVE HYPOTENSION DURING GENERAL ANESTHESIA AFTER METAMIZOLE ADMINISTRATION: A CASE REPORT AND LITERATURE REVIEW

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A – study design, **B** – data collection, **C** – statistical analysis, **D** – interpretation of data, **E** – manuscript preparation, **F** – literature review, **G** – sourcing of funding

ABSTRACT

Background: Multiple factors often cause hypotension in patients undergoing operations. The simultaneous presence of several detrimental factors tends to lower arterial pressure.

Aim of the study: To investigate the specificity of intraoperative hypotension during general anesthesia after metamizole administration and describe this phenomenon based on a literature review.

Case report: This report describes a patient who experienced a sudden drop in blood pressure after receiving metamizole, an agent commonly used for intraoperative pain management during general anesthesia. However, the drop in blood pressure was not accompanied by other symptoms, indicating that it was unlikely caused by additional factors. The patient was treated with a sympathomimetic agent.

Conclusions: Metamizole is a relatively safe drug commonly used for optimal pain control in anesthesia practice. The occurrence of hypotension after its administration is an infrequent phenomenon, but proper monitoring and observation of patients' vital signs during infusions of this drug are essential.

KEYWORDS: blood pressure, ephedrine, isolated hypotension, dipyrone

Background

Despite substantial advances in medicine, intraoperative hypotension remains one of the most common side effects in patients undergoing anesthesia for surgery [1]. Indeed, a multicenter observational study with a sample of over 22,000 people showed that there was at least one episode of hypotension, defined as mean arterial pressure (MAP) <65 mm Hg lasting for 1 minute, in 88% of cases [2].

The pathophysiological basis of hypotension is not simple [3]. A 2009 study, described as groundbreaking, found that the occurrence of intraoperative hypotension was not related to annual mortality [4]. Thirteen years later, reports on the phenomenon have not brought us closer to an international consensus on the exact definition of intraoperative hypotension [3]. Wesselink et al. investigated which MAP values and their duration are associated with the risk of complications such as death, myocardial infarction, and acute kidney damage. Their analysis showed a slight increase in the risk of complications with MAP <80 mm Hg for ≥10 minutes or ≤70 mm Hg for <10 minutes. Furthermore, an elevated risk of complications was observed when MAP was <65 mm Hg for ≥20 min, <50 mm Hg for ≥5 min, or <40 mm Hg for any length of time. The analysis also revealed that the MAP thresholds associated with the risk of adverse events vary depending on the organ system [5]. In addition to defining the level of blood pressure that can be considered hypotension, it is necessary to account for the many possible causes of the phenom-

enon during surgery and introduce effective treatment after identifying the cause.

Based on the following case report, the authors attempted to address the differential diagnosis and proper management of intraoperative hypotension.

Aim of the study

This case study aimed to present a clinical case of a patient experiencing intraoperative hypotension during general anesthesia after metamizole administration and to describe this phenomenon based on a literature review.

Material and methods

Study design and setting

A case study was conducted in March 2022 at the Klinika-Hospital Zum Heiligen Geist in Fritzlar. Data was obtained by analyzing medical documentation and an anesthetic monitoring chart. The patient was informed of the study's intention and provided informed consent.

Participant

A 75-year-old male was admitted to the Department of Orthopedics for a planned endoprosthetic procedure on the right hip joint. The patient was being treated for left ventricular heart failure, hypertension, and type II diabetes. In addition, he had second-degree obesity (38.31 kg/m2) and an implanted pacemaker. Medications for his co-morbidities included a fixed combination of angiotensin-converting enzyme inhibitors (ramipril), statins (atorvastatin), and acetylsalicylic acid. Before the procedure, he had taken all medications except ramipril and did not report any drug allergies.

Data sources/measurements

After bringing the patient to the operating room, perioperative monitoring began, which included electrocardiography, non-invasive blood pressure monitoring, determination of functional oxygen saturation, and body temperature measurement. The patient was then oxygenated passively for three minutes with 100% oxygen through a face mask. Induction of anesthesia used sufentanil (10 μg), propofol (200 mg), atracurium (20 mg), and dexamethasone (4 mg). The patient was intubated with an 8.5 mm tube, and its correct location was confirmed by auscultation and capnometry.

Anesthesia was maintained by sevoflurane (minimum alveolar concentration of 0.9-1.0) in air, with a fraction of inspired oxygen of 0.5 and a fresh gas flow rate of 1 L/min. Ventilation was conducted in volumetric mode with a positive end-expiratory pressure of 5 cm H_2O. A drip infusion of 500 ml of multielectrolyte fluid was administered, and the patient was connected to a time of flight (TOF) neuromuscular blockade monitoring device, which indicated 0% after induction. A solution of 1.5 g of cefuroxime was used for prophylactic antibiotic therapy. After 20 minutes of intubation, a bolus of sufentanil (10 μg) was administered intravenously to optimize analgesia. A downward trend in the patients' pressure measurements was noticed approximately 25 minutes after intubation, so a 9 mg bolus of ephedrine was administered and had the expected adrenergic effect.

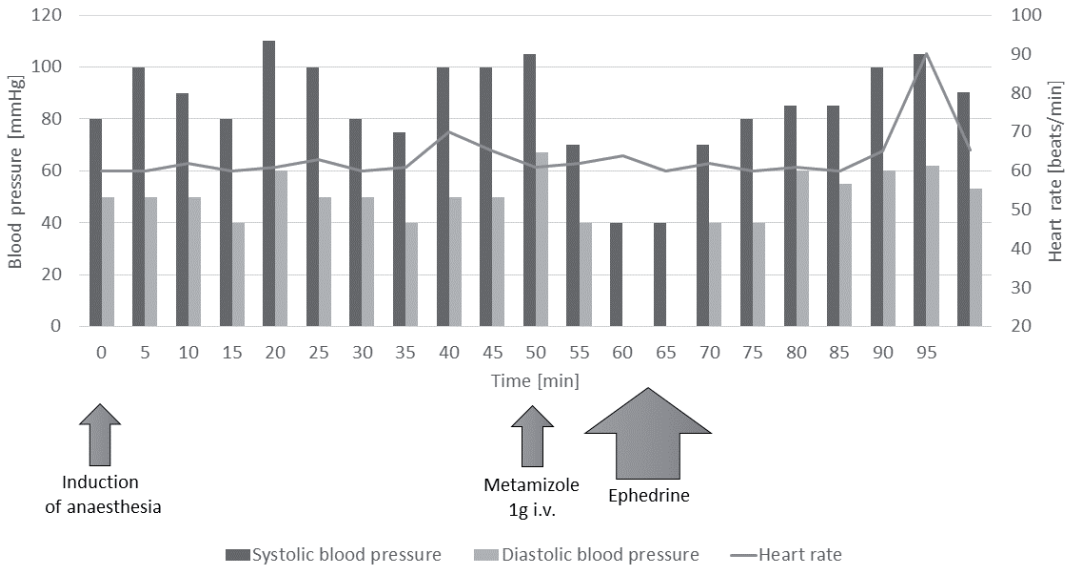

Figure 1. Monitoring of hemodynamic parameters. Abbreviations: i.v. – intravenous

Results

Fifty minutes after intubation, 1 g of metamizole in a 0.9% sodium chloride (NaCl) solution and a 5 μg bolus of sufentanil were administered intravenously. Approximately five minutes after the patient's last supply of drugs, there was a drastic drop in blood pressure to unquantifiable values, and he developed tachypnea (27 breaths/minute) (Figure 1).

A total of 54 mg of ephedrine was administered (four 9 mg boluses and one of 18 mg), with short intervals of a few minutes between doses, which allowed the blood pressure to return to a value observed before the episode of hypotension. The non-standard (for Polish conditions) dosage of ephedrine is due to the fact that it is available in 30 mg/ml ampoules in hospitals in Germany, where this event occurred. General endotracheal anesthesia lasted for 95 minutes, and the extubation and awakening of the patient went without further complications. No unexpected blood loss was recorded, and the patient scored 10 points on the Aldrete scale after waking up. The postoperative course was without complications.

Discussion

Key results

The issue of intraoperative hypotension is complex, and there is no single correct definition of this clinical condition. Furthermore, low blood pressure during anesthesia can have various causes. Therefore, the patient's clinical profile, medical procedures, and drug side effects should be considered during treatment management. However, it should also be noted that removing the direct cause of hypotension may not always be the best solution.

Interpretation

Intraoperative hypotension always requires an immediate response from the anesthesia team because prolonged episodes of low blood pressure or very low MAP values, regardless of duration, are associated with a higher risk of complications such as death, myocardial injury, myocardial infarction, cardiogenic shock, acute renal failure, hallucinations, and stroke [6].

The absolute values defining hypotension are generally considered as MAP <60 mm Hg and/or systolic arterial pressure (SAP) <90 mm Hg. However, these values are used as cut-off points in clinical trials but are not included in official guidelines. The literature describes hypotension as any reduction in blood pressure requiring a therapeutic intervention that increases the volume of the vascular bed or employs vasoconstrictors. On the other hand, other researchers consider hypotension to be a decrease in blood pressure values by 10-60% compared to baseline [6].

The causes of intraoperative hypotension are preoperative, intraoperative, and postoperative. For a better illustration, they are detailed in Table 1.

Table 1. Causes of perioperative hypotension [2, 6-8]

Causes of perioperative hypotension			
Preoperative	**Intraoperative**		**Postoperative**
Patient-related	**Anesthesia-related**	**Operation-related**	**Complications-related**
• Advanced age • Low blood pressure before anesthesia • Hypovolemia • High ASA score • Long-term hypotensive treatment • Diabetes mellitus • Hypothyroidism • Alcohol abuse • Low BMI	• Too-deep anesthesia • Too high a dose of painkillers • Anaphylactoid response • Sympathetic blockade (if indicated – consider paravertebral blockade) • Measurement error • Adverse drug reactions and/or interactions • Other drugs – nitroprusside, nitroglycerine, histamine-releasing agents	• High-risk operations • Long-term surgery • Intraoperative bleeding	• Myocardial ischemia • Hypovolemia • Dysrhythmia • Dynamic left ventricular outflow tract (LVOT) stenosis • Pneumothorax • Cardiac tamponade • Embolism • Sepsis • Hemorrhage

Abbreviations: ASA – American Association of Anesthesiologists; BMI – body mass index.

Recently, several interesting studies have emerged assessing artificial intelligence (specifically a machine learning model) for estimating the risk of perioperative hypotension in real time [9-11]. However, despite promising results, some researchers recommend caution and a more pragmatic approach to this new technology [12].

The intervention procedure used during intraoperative hypotension consists of increasing vascular bed filling using fluids or blood preparations and plac-

ing the patient in the Trendelenburg position. However, these are very general recommendations, and the primary aim is to conduct a quick and accurate differential diagnosis to determine the most probable cause of the hypotension. Some causes, such as sepsis, pulmonary embolism, and arrhythmias, necessitate using appropriate protocols or guidelines. Meanwhile, other situations require the supply of fluids and drugs such as ephedrine, norepinephrine, adrenaline, and phenylephrine.

An undoubtedly vital issue to consider in intraoperative hypotension is the supply of anesthetic drugs. Indeed, anesthesia being too deep is one of the primary causes of intraoperative hypotension. However, the Position of the Consultation Council of the Polish Society of Anesthesiology and Intensive Therapy is that interventions for hemodynamic instability should initially aim to optimize the circulatory system, if possible, and shallow anesthesia combined with the parallel administration of amnestics (benzodiazepines) and analgesics (opioids) should be a last resort. Their position is justifiable given that intraoperative hypotension is a significant risk factor for unintentional intraoperative return of consciousness [6, 13].

The authors of the international consensus of the Perioperative Quality Initiative do not explicitly state which therapy is most suitable for use in intraoperative hypotension. As such, the choice of therapeutic interventions is the subject of ongoing debate, and it remains unclear which treatment strategies significantly affect outcomes [13]. However, Meng et al. proposed a scheme for the differential diagnosis and treatment of perioperative hypotension, as shown in Figure 2 [14].

Prevention of undesirable drops in blood pressure is most difficult when the occurrence of factors related to the patient prevails. In the case of hypotension prevention and stabilization of the circulatory system, volume loss should be replaced with fluids while avoiding harmful leakages [6, 15], with a maximum volume of shunted fluids of less than 2 ml/kg/h [15]. In addition, if the patient is taking ACE-I/ARBs (angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers), they should be suspended during the perioperative period (minimum ten hours of withdrawal), as their use is associated with prolonged and refractory hypotension [16]. Also, episodes of hypotension caused by excessive medication doses can be prevented by monitoring the depth of anesthesia using indicators such as the Bispectral Index (BIS). The literature also emphasizes the role of intraoperative transoesophageal echocardiography in detecting changes in myocardial contractility, which indicates that ischemia may result from a decrease in blood pressure [6].

In the current case, the patient had several preoperative, non-modifiable risk factors for hypotension, including old age, hypertension, left ventricular heart failure, and an American Association of Anesthesiologists (ASA) classification of III. Nonetheless, attention should be paid to any dangerous episode of low blood pressure immediately after administering metamizole and sufentanil. However, the authors rule out the possibility of the opioid provoking such a severe event because a small dose was adminis-

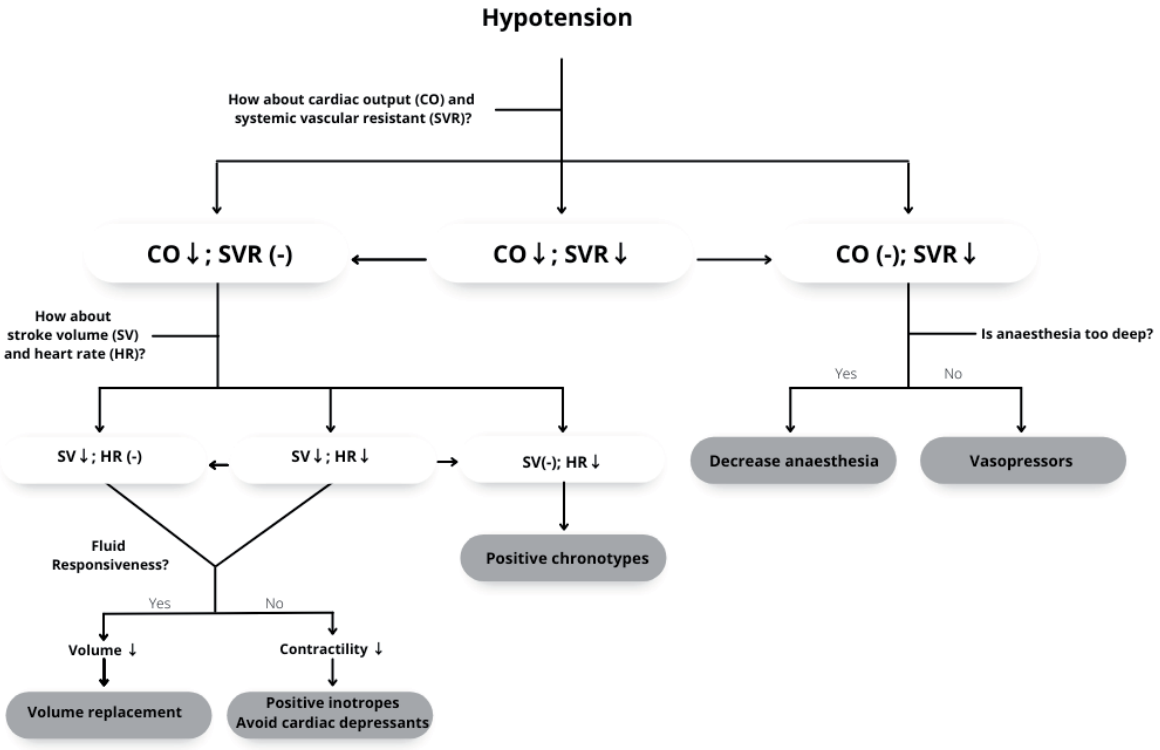

Figure 2. Differential diagnosis and treatment of hypotension in perioperative care [14]

tered, and previous boluses did not cause significant fluctuations in blood pressure.

In this case, the principal cause of intraoperative hypotension was metamizole, which can cause isolated hypotension of unknown prevalence after intravenous administration, according to the Summary of Product Characteristics [17]. In addition, retrospective studies from the 1990s demonstrated that severe hypotension occurred at a frequency of 1:300 after parenteral administration of the drug [18, 19]. Also, pharmacological factors indicate that metamizole was responsible for the episode of hypotension, as the drug relaxes smooth muscle cells. Moreover, metamizole obtained a value of 3 on the Naranjo scale, indicating that an adverse reaction is possible when the drug is used [20, 21].

Metamizole intake significantly affects the expression and function of certain drug-metabolizing enzymes belonging to the cytochrome P450 (CYP) family, with studies showing that metamizole can induce human CYP2B6 and CYP3A4 [22]. Furthermore, metamizole increases the risk of severe hypothermia when used in combination with neuroleptic and phenothiazine derivatives. Additionally, metamizole can increase the serum concentration of methotrexate, which exacerbates its toxicity [23]. However, it is highly unlikely that the hypotonia resulted from an interaction between metamizole and any drugs we administered or that the patient had taken before the procedure [24].

Therapeutic intervention in the current case may be debatable. According to the Product Characteristics, ephedrine should only be administered to a maximum dose of 30 mg. If this does not produce the expected effect, another drug should be considered (a continuous infusion of norepinephrine would be most appropriate in this situation). Indeed, continued use of ephedrine without adequate breaks leads to tachyphylaxis, with the loss response caused by decreased sensitivity to the agent [17, 25].

A review of the literature using PubMed/Medline and Google Scholar did not provide definitive answers on the characteristics of the metamizole-induced intraoperative hypotension phenomenon. Using anesthetics in older patients increases the risk of hypotension and cardiovascular collapse. However, an initial dose of up to 10 mg of metamizole per kg of body weight is recommended for all patient groups before commencing continuous drug infusion [16, 26]. As such, attention should be paid to anaphylactic reactions, and blood pressure should be monitored regularly [26]. Before the end of the procedure, metamizole should be administered as a fifteen-minute infusion of 1.0 g/100 ml of 0.9% NaCl solution, although the maximum daily dose suggested by the manufacturer is 5 g intravenous [17, 26]. Nonetheless, it should be noted that the therapeutic index of metamizole is very high [27].

Generalizability

An appropriate response by doctors to patient complaints allows for quick diagnosis, identification of underlying causes, and implementation of optimal treatment and care procedures.

Study limitations

The study was limited to only one patient, which should be expanded to include additional subjects in the future. Furthermore, subsequent research should focus on the frequency of intraoperative hypotension during general anesthesia after metamizole administration.

Recommendations

It is important to be aware of all causes of perioperative hypotension and the protocols or guidelines for managing such cases to improve the level of care provided. Additionally, it is crucial to consider that each patient requires an individualized approach.

Conclusions

There is no officially accepted definition of intraoperative hypotension. However, any lowering of blood pressure values of concern to a physician should be carefully analyzed regardless of which of the available values we accept as valid. Such scrutiny is warranted given the range of causes of hypotension and the many direct consequences of this phenomenon. Metamizole is a safe drug commonly used for optimal pain control in anesthesiology practice, and hypotension does not appear to be a frequent phenomenon after its administration. However, proper monitoring and meticulous observation of patients' vital signs during infusions of this drug is mandatory. Indeed, even drugs that are commonly used, and are considered safe, have side effects.

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