Complications of anesthesia

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ABBREVIATIONS

ACh	Acetylcholine
AChR	Acetylcholine receptor
ASA	American Society of Anesthesiologists
BIS	Bispectral index
CBF	Cerebral blood flow
CMR	Cerebral metabolic rate
CPAP	Continuous positive airway pressure
CPP	Cerebral perfusion pressure
CPSP	Chronic postsurgical pain
DIC	Disseminated intravascular coagulation
DVT	Deep venous thrombosis
ETAG	End-tidal anesthetic gas
FRC	Functional residual capacity
GFR	Glomerular filtration rate
GI	Gastrointestinal
ICP	Intracranial pressure
ICU	Intensive care unit
LV	Left ventricle
MAC	Minimum alveolar concentration
MAP	Mean arterial pressure
NDMRs	Nondepolarizing muscle relaxants
NK_1	Neurokinin
NMJ	Neuromuscular junction
OSA	Obstructive sleep apnea
Pa_{CO2}	Arterial partial pressure of carbon dioxide
Pa_{O2}	Arterial partial pressure of oxygen
PACU	Postanesthesia care unit
PHBS	Pseudohypoxic brain swelling
POCD	Postoperative cognitive dysfunction
POI	Postoperative ileus
PONV	Postoperative nausea and vomiting
POPE	Postobstructive pulmonary edema
TOF	Train-of-four
TRALI	Transfusion-related acute lung injury
$5\text{-}HT_3$	Serotonin

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1. SUMMARY

Title: Complications of anesthesia
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Anesthesiology is a specialty in which the use of medications in gaseous or liquid form causes loss of consciousness, amnesia, analgesia, inhibition of autonomic reflexes, and skeletal muscle relaxation. It is one of the most challenging specialties in medicine. Anesthesia carries a certain risk, but with the expansion of knowledge, enhancement of technology, and new drugs the risk has been reduced dramatically. Mortality that can be ascribed purely to anesthetics is uncommon. Rather, perioperative risk is multifactorial, depending on patient factors such as age, physical status, and comorbid conditions. Likewise, the type of anesthesia, surgery, and skills and training of the individual medical provider contribute to the perioperative risk. Today, it is possible to operate on a patient at the extremes of age and with various comorbidities due to advancements in the field of anesthesiology. Without it, modern surgery, diagnostic procedures, intensive care, and even emergency care could not be performed. Complications are infrequent, but nevertheless should be discussed. Prevention of complications in this contemporary era is achievable with the introduction of extensive perioperative evaluation by the anesthesiologist, superior monitoring and equipment, and transfer to the postanesthesia care unit (PACU) for recovery after surgery. Additionally, variety of techniques used and individualization of anesthesia, so-called multimodal approach, contributed to the improvements in care for the patient.

Key words: anesthesiology, anesthetics, complications, risk

2. SAŽETAK

Naslov: Komplikacije u anesteziji

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Anesteziologija je specijalizacija u kojoj korištenjem lijekova u plinovitom ili tekućem stanju izazivamo gubitak svijesti, amneziju, analgeziju, inhibiciju autonomnih refleksa, i relaksaciju skeletnih mišića. Jedna je od najzahtjevnijih specijalizacija u medicini. Anestezija sa sobom nosi određeni rizik, ali širenjem znanja, napretkom tehnologije, te novim lijekovima taj rizik je dramatično smanjen. Mortalitet koji se isključivo može pripisati anesteticima je rijedak. Perioperativni rizik je multifaktoralan, ovisi o faktorima kod pacijenta kao što su dob, fizičko stanje, te prateće bolesti. Također, tip anestezije, operacije, vještina i znanje individualnih pružatelja zdravstvene zaštite pridonose perioperativnom riziku. Danas postoji mogućnost operacije na pacijentima u dubokoj starosti i sa različitim komorbiditetima uslijed napredovanja u polju anesteziologije, bez kojih suvremena kirurgija, dijagnostika, intenzivna skrb, pa čak i hitna medicina ne bi bile izvedive. Komplikacije su rijetke, međutim trebaju se razmotriti. Prevencija komplikacija u suvremenom dobu je ostvariva s uvođenjem opsežne perioperativne evaluacije od strane anesteziologa, superiornim monitoringom i opremom, te transferom u sobu za poslijeanestezijsku skrb (PACU) za oporavak nakon operacije. Nadalje, raznolikost tehnika koje se koriste i individualizacija anestezije, takozvani multimodalni pristup, su pridonijeli unapređenju o brizi pacijenta.

Ključne riječi: anesteziologija, anestetici, komplikacije, rizik

3. INTRODUCTION

The specialty of anesthesiology contributed greatly to advancement in health care, especially in the care of surgical patients, since its first successful use in 1846 (1,2). Early beginnings of anesthesia included many primitive techniques, from blows to patient's head or compression of carotid arteries to produce unconsciousness, squeezing the nerves or applying cold water and ice for pain relief, to introduction of ether as a first anesthetic agent. Later, introduction of chloroform and cocaine for general and regional anesthesia, respectively, as well as analyzing complications after anesthesia and surgery, paved the way to the specialty that we know today (2). The 1960s mark the beginning of modern era of anesthesia. Development of new drugs, monitoring, computer technology, and accumulation of knowledge facilitated complex procedures on patients at the extremes of age and with comorbidities (1–3). Since the beginning of the use of anesthesia, morbidity and mortality is at an all-time low. Overall mortality risk from anesthetic complications and adverse effects from anesthetic agents today is approximately 1 in 100 000 cases for Europe. Data on morbidity shows that complications remain frequent, but those related to only anesthesia are uncommon (3).

Tasks of the anesthesia professional are preoperative evaluation and planning, choice of the best anesthetic plan for the specific surgery and the patient, preparation and checking the equipment, checklists concerning the patient, execution, and adaptation of plans during the procedure (4). It is a unique specialty that can influence the safety and quality of patient care. For that particular reason, Helsinki Declaration on Patient Safety in Anesthesiology was developed. The Declaration has recommendations on practical steps which should be implemented to increase the level of protection to the patients (3,5). It is important not to forget that human factor and interactions within the team, organization of care and conditions in the system play crucial roles in the outcomes of anesthesia (4).

4. ANESTHETIC TECHNIQUES

4.1. General anesthesia

The American Society of Anesthesiologists (ASA) explains general anesthesia as “a drug induced loss of consciousness during which patients are not arousable, even by painful stimulation” (6). Primary effects produced by general anesthetics are unconsciousness, amnesia, analgesia, inhibition of autonomic reflexes, and skeletal muscle relaxation (7).

Since none of presently accessible anesthetic agents can accomplish all five of these desired effects, administration of different combinations of medications, such as hypnotics, neuromuscular blocking agents, and analgesics is a way of modernizing approach to general anesthesia (6,7).

Present-day practice relies on the use of combinations of intravenous and inhaled drugs, a concept known as balanced anesthesia, to exploit favorable properties of each agent while minimizing their adverse effects (7,8).

4.2. Regional anesthesia

Regional anesthesia involves infiltration of a peripheral nerve with an anesthetic agent and blocking transmission in order to avoid or relieve pain (9). Acts by selectively blocking a nerve or group of nerves supplying an area of the body such as a limb or an eye, using local anesthetics, allowing surgeon to operate without the need for full general anesthesia (10). Types of regional anesthesia include spinal anesthesia, epidural anesthesia, and nerve blocks (11).

With the introduction of ultrasound technology to help identify peripheral nerves and lower risks of adverse effects, regional anesthesia became increasingly more popular (10,12). Nowadays, neuraxial blocks are widely used for labor analgesia, cesarian section, orthopedic procedures, perioperative analgesia, and chronic pain management (13).

4.3. Local anesthesia

Local anesthesia acts by non-selectively blocking smaller area of the body, causing disruption of impulse generation or propagation, without any attempt to target particular nerve (10,14). Primary goal is loss of sensation or achievement of localized analgesia (15).

4.4. Monitored anesthesia care

Monitored anesthesia care is a specific anesthesia service used for diagnostic and therapeutic procedures during which anesthesia provider administers sedative, anxiolytic, or analgesic while continuously monitoring patient's vital functions, and converts to general anesthesia if necessary (16). Foundation of monitored anesthesia care is to provide safe sedation, control of patient's anxiety, and pain control (17).

5. TYPES OF ANESTHETICS

5.1. Inhaled anesthetics

Inhaled anesthetics cause central nervous system depression by influencing the electrical behavior of the nervous system. Augmentation of the function of inhibitory ion channels precipitates hyperpolarization of the neuron, whereas blocking of the function of excitatory ion channel hinders depolarization of the neuron (8). Inhaled anesthetics can be split into volatile and gaseous anesthetics. Volatile anesthetics include halothane, enflurane, isoflurane, desflurane, and sevoflurane, and considering they are in liquid form at room temperature, it is necessary that they are administered using vaporizers. Example of gaseous anesthetic is nitrous oxide (7,8). Characteristics of all inhaled anesthetics that can be measured include immobility and amnestic effects. Immobility is determined by the minimum alveolar concentration (MAC) of anesthetic that is required to suppress movement in 50% of patients at surgical incision. MAC is affected by certain drugs, age, electrolyte disturbances, but it remains unaffected by gender, duration of surgery and anesthesia (8).

Uptake of inhaled anesthetic into the body depends on alveolar concentration. Anesthesiologist can control how quickly alveolar concentration changes by controlling the inspired concentration or partial pressure, and alveolar ventilation. If there is increase in the inspired partial pressure it will lead to the increase of the gradient between inspired and alveolar partial pressure and result in acceleration of induction. Other factors affecting uptake are solubility characteristics of anesthetic and cardiac output (7). Primary intention of inhaled anesthesia is achievement of constant and optimal brain partial pressure of anesthetic. The brain and other tissues balance out the partial pressure of the inhaled anesthetic delivered by arterial blood, thus maintaining a constant and optimal partial pressure in arterial blood becomes a useful method of controlling the brain partial pressure of anesthetic (8). The recovery depends on the blood:gas partition coefficient, pulmonary blood flow, magnitude of ventilation, and tissue solubility of the anesthetic agent. Anesthetics with low blood:gas partition coefficient, meaning they are relatively insoluble in blood and brain, are eliminated faster than those with higher coefficient (7,8).

5.2. Intravenous anesthetics

Depression of the central nervous system through action on receptor-operated ion channels is the mechanism of action of intravenous anesthetics (18). Intravenous nonopioid anesthetics have a valuable role in the practice of modern anesthesia. Their ability to rapidly induce anesthesia made them preferable choice over inhalational anesthetics. They are also frequently used to provide sedation during monitored anesthesia care and in intensive care units (ICU). Lipophilic properties enable them to preferentially partition into highly perfused lipid-rich tissues, accounting for their rapid onset of action. Termination of the effect of a single bolus dose is a result of redistribution into tissues that are less perfused and active. Therefore, all anesthetic agents used for induction have a comparable duration of action when administered as a single bolus (7,19). Commonly used induction agents are propofol, etomidate, ketamine, and benzodiazepines (7,19,20). Propofol is frequently the agent of choice for induction and maintenance of anesthesia, as well as sedation in the operating room and ICU settings (76). Benzodiazepines are used in the perioperative period as premedication for anxiolysis and anterograde amnesia. Their action can be promptly terminated by administration of their selective antagonist flumazenil (7,19). Dose-dependent respiratory depression is produced by all intravenous induction agents, except for ketamine (20).

5.3. Opioids

Opioids have an extremely important role in the practice of anesthesiology, critical care, and management of pain. They react with opioid receptors producing primarily inhibitory effects that ultimately culminate in hyperpolarization of the cell and reduction of neuronal excitability (21). Opioids are principally used for analgesia, however they can also provide some degree of sedation, and general anesthesia when given in large doses (22). Most common clinical indication for opioid use is in so-called balanced anesthesia for their ability to decrease MAC. Basic principle is that drugs used in combination lessen the disadvantages of the individual drugs used in larger doses as single drug therapy. More recently developed and increasingly popular indication for opioids is total intravenous anesthesia (TIVA). Advantage of this technique is enhanced patient well-being in the early postoperative period. Clinical application of

opioids in treatment of postoperative pain is of prime importance, and in most other perioperative procedures they are used as adjuncts in combination with other drugs (21).

5.4. Skeletal muscle relaxants

Agents that affect muscle function include neuromuscular blockers, which are used during surgery and in intensive care unit (ICU), and spasmolytics used to reduce spasticity in an array of different painful conditions (23). Primary use is as adjuncts during general anesthesia to facilitate endotracheal intubation, assist with mechanical ventilation, and optimize surgical conditions (23,24). Muscle relaxants can be classified into depolarizing and nondepolarizing neuromuscular blockers. Depolarizing relaxants act as competitive agonists on neuromuscular junction (NMJ), whereas nondepolarizing relaxants act as competitive antagonists to ACh at the postsynaptic membrane (24). After administration of nondepolarizing neuromuscular blocking agents, it is imperative to ensure adequate return of neuromuscular function. Lingering effects of paralysis reduce upper esophageal tone, coordination of musculature during swallowing, and hypoxic ventilatory drive, and therefore increase morbidity and mortality (25). The best approach for terminating effects of relaxants is to use moderate doses and allow metabolization of the agent (24). However, cholinesterase inhibitors efficiently antagonize the effects of neuromuscular blocking drugs (23,24).

6. PHYSIOLOGY AND EFFECTS OF ANESTHETIC DRUGS

6.1. Cerebral physiology

Anesthetic drugs cause dose-related and reversible alterations in cerebral blood flow (CBF), cerebral metabolic rate (CMR), and electrophysiologic function. Anesthetic drugs and techniques have the potential to adversely affect the diseased brain, nevertheless their effects on CBF and CMR can be altered to improve surgical course and clinical outcome of patients with neurologic disease (26).

The brain receives 12-15% of cardiac output, which is the reflection of the brain's high metabolic rate. The brain's considerable demand for substrate, must be met by adequate delivery of oxygen and glucose, but space restriction from cranium and meninges require that blood flow is not excessive. CBF is regulated through various mechanisms, which include chemical, myogenic, neurogenic factors, as well as blood viscosity, vasoactive drugs used for hemodynamic manipulation, and age.

Chemical alterations consist of changes in CMR, arterial partial pressure of carbon dioxide (Pa_{CO2}), and arterial partial pressure of oxygen (Pa_{O2}) (26).

CMR increase is associated with proportional change in CBF. This flow-metabolism coupling is described as positive feedback mechanism in which increased neuronal activity results in a demand for energy that is met by increase in CBF. Newer data indicates that coupling is based on a mechanism where neuronal activity directly increases CBF which then leads to increased energy supply. The precise mechanisms that mediate flow-metabolism coupling have not been defined. CMR is influenced by functional state of nervous system (sleep, mental tasks, etc.), anesthetic drugs, and temperature (26).

Between respiratory gas tensions of 20-80 mm Hg, CBF is directly proportional to Pa_{CO2}. Correspondingly, anesthetic drugs that alter resting CBF cause changes in the response of the cerebral circulation to CO_2. Blood flow changes due to Pa_{CO2} are almost immediate, but not sustained, and are thought to be secondary to changes in pH in extracellular fluid of the brain. Only considerable changes in Pa_{O2} influence CBF (26,27).

Cerebral circulation has the capacity to adjust its resistance to maintain constant CBF over a broad range of mean arterial pressure (MAP) values, a mechanism termed autoregulation. Cerebral perfusion pressure (CPP), the difference between MAP and

intracranial pressure (ICP), is the main determinant of CBF. Below the lower limit (65-70 mm Hg) and above the upper limit of autoregulation (150 mm Hg), cerebral circulation is pressure dependent and CBF changes according to changes in MAP. Precise mechanisms are unknown, but it is suggested that changes in CPP lead to direct changes in vascular smooth muscle tone (26).

6.1.1. Effects of anesthetic agents on the brain

Most intravenous anesthetics cause parallel reduction in CMR and CBF, apart from ketamine which achieves the opposite effect. Furthermore, direct effects on cerebral vascular smooth muscle contribute to decrease in CMR and CBF (26).

All volatile anesthetics create a balance between decrease in CBF caused by CMR reduction and increase in CBF caused by direct cerebral vasodilation. At lower doses CMR suppression-induced decrease in CBF predominates and net CBF is less than in awake state. At 1 MAC, CMR suppression and vasodilatory effects are in balance. Lastly, at higher doses vasodilation predominates and CBF is increased. This means that CBF/CMR ratio is increased by increasing the dose of volatile anesthetics. The effect of nitrous oxide depends on whether it is administered alone or in combination with intravenous anesthetics. When administered alone it can significantly increase CBF and ICP, whereas when used in combination its vasodilating effect is weakened or even completely inhibited (26).

Singular effect of nondepolarizing muscle relaxants on the cerebral vasculature takes place via the release of histamine which can cause reduction in CPP due to simultaneous increase in ICP and decrease in MAP. This effect is presumably clinically insignificant unless large doses are administered to achieve conditions for rapid endotracheal intubation (26).

6.2. Neuromuscular physiology

Neuromuscular junction (NMJ) is a synaptic connection between a nerve and a muscle (28,29). Simply stated, physiology of neuromuscular transmission can be explained by using classic model of nerve signaling to muscle through the acetylcholine receptor (AChR). The nerve synthesizes and stores ACh in vesicles that migrate to the surface of the nerve, rupture, and discharge ACh into the cleft after nerve stimulation. AChR

respond by opening their channels for influx of sodium ions into the muscle, followed by depolarization of the muscle. Created end-plate potential continues along the muscle membrane by opening of sodium channels to initiate a contraction. ACh immediately detaches from the receptor and is destroyed by acetylcholinesterase.
Agonist drugs of the receptor, such as depolarizing muscle relaxants or nicotine and carbachol can act on these receptors and mimic the effect of ACh, causing depolarization of the end plate. Contrarily, antagonists also act on the receptor, but they prevent binding of ACh to the receptor, and thereby preventing depolarization (30).

6.2.1. Effects of nondepolarizing muscle relaxants (NDMRs)

NDMRs act by impairing or blocking neurotransmission by competitive binding to the muscle AChR, resulting in block or transmission, depending on relative concentrations of drugs and their comparative affinities for the receptor. Competitive binding to the receptor is biased in favor of the antagonist, since only one molecule of antagonist can prevent depolarization. Reversal with cholinesterase inhibitors is more difficult with high concentrations of relaxants, making cholinesterase inhibitors ineffective until the concentration of relaxant in the perijunctional area decreases to a lower level. (30) New concept in neuromuscular block reversal is chemical encapsulation by cyclodextrin (sugammadex), which takes place at any concentration of a steroid-based compound (30,31).

6.2.2. Effects of depolarizing muscle relaxants

Depolarizing relaxants are considered agonists because they initially stimulate the effect of ACh, followed by block of neurotransmission. Mechanism of action consists of initial contraction of the muscle, succeeded by relaxation because they are not susceptible to hydrolysis by acetylcholinesterase. Continuous depolarization is caused by almost immediate attachment to a receptor after separation from another and the time required for them to be cleared from the body is the principal determinant of how long the effects last (30).

6.3. Respiratory physiology

Respiratory function is tied to the practice of anesthesia. Even in the absence of adverse events, general anesthesia has substantial effects on respiratory function and physiology. Factors that influence respiratory physiology during anesthesia are age, obesity, preexisting lung conditions, body position, and spontaneous breathing.

Pulmonary function is impaired in an anesthetized individual, whether the patient is breathing spontaneously or is on mechanical ventilation. This is the reason why supplemental O_2 is almost regularly used (32).

Loss of muscle tone with ensuing alterations in the balance between inward and outward forces causes decrease in functional residual capacity (FRC), followed by reduction in compliance and increase in respiratory resistance. FRC is reduced with the change in the positioning and induction of anesthesia. Formation of atelectasis and airway closure precipitated by the reductions in FRC, alter the distribution of ventilation, ventilation-perfusion ratio, and impede oxygenation of blood and removal of carbon dioxide (32).

Atelectasis develops in majority of patients who are anesthetized. It is an important cause of hypoxemia and may form a focus of infection that can contribute to pulmonary complications. Greater degree of atelectasis is observed after thoracic surgery, cardiopulmonary bypass and in obese patients. For the most part, ventilation is distributed to the upper regions of the lung, with subsequent decrease toward the lower regions, and absence in the lowermost regions.

Hypoxemia and hypercarbia may be caused by hypoventilation, ventilation-perfusion mismatch, and shunt. For the optimal gas exchange, ventilation and perfusion must match. If ventilation-perfusion ratio is low, it will impede oxygenation to the degree of ventilation-perfusion mismatch. Elimination of CO_2 is even more limited by ventilation-perfusion mismatch because if alveolar ventilation is already impaired and cannot be increased, the addition of mismatch will increase Pa_{CO2} (32).

6.3.1. Effects of anesthetic agents on the respiratory function

Nitrous oxide causes tachypnea and decrease in tidal volume. End result is minimal change in minute ventilation and resting arterial CO_2 levels (33). Volatile anesthetics cause decrease in tidal volume and increase in respiratory rate, the outcome of which

is rapid and shallow breathing pattern. Furthermore, physiologic reaction to hypoxia and hypercarbia is blunted with the increase in dose of volatile anesthetics (34).
All intravenous induction anesthetics cause decrease in respiration which is manifested with decrease in tidal volume, minute ventilation, and decreased response to hypoxia. The only exception to this rule is ketamine (20).
Dose-dependent reduction in alveolar ventilation can be seen when using opioids. Periodic breathing or apnea can be caused by slow respiratory rate. Increase in arterial carbon dioxide will not induce an appropriate increase in ventilation (35,36).

6.4. Cardiac physiology

The heart is a pump that provides continuous delivery of essential metabolic substrates to tissues and removal of byproducts of metabolism. Effective and consistent electrical rhythm of the heart is imperative to its functioning (37). Cardiac function is regulated by autonomic nervous system. Sympathetic nervous system contributes positive chronotropic, inotropic, and lusitropic effects. Contrarily, parasympathetic nervous system has inhibitory effect in the atria and negative modulatory effect in the ventricles (38). Careful perioperative monitoring is one of the primary responsibilities of anesthesiologists (39).

6.4.1. Effects of anesthetic agents on the heart

In the healthy heart, volatile anesthetics cause depression of myocardial contractility, decrease in left ventricular (LV) diastolic function, and decrease in LV-arterial coupling related to the dose. The negative inotropic effects are related to changes in cardiac myocyte calcium homeostasis. These effects are exacerbated by hypocalcemia, calcium channel blockers, and $ß_1$-adrenoceptor antagonists. The issue may be reversed by administration of exogenous calcium and $ß_1$-adrenoceptor agonists.
Beneficial effects of volatile anesthetics have been observed during myocardial ischemia and reperfusion injury (40).
Nitrous oxide reduces myocardial contractility, but has little effect on blood pressure, heart rate, and cardiac output due to its stimulation of catecholamines (33).
Propofol, most commonly used intravenous anesthetic, causes dose-dependent reduction in blood pressure due to decrease in systemic vascular resistance, preload,

and myocardial contractility (41,42). Benzodiazepines and barbiturates produce mild and moderate decrease in blood pressure, respectively. In contrast to other intravenous anesthetics, ketamine produces increase in blood pressure, heart rate, and cardiac output due to stimulation of sympathetic nervous system (21,42). Since ketamine increases workload of the heart, it should be used carefully in patients with coronary artery disease, uncontrolled hypertension, congestive heart failure, and arterial aneurysms (21). Minimal effect on cardiovascular function separates etomidate from other rapid-onset anesthetics. It has been proven to be useful in patients with compromised heart function and hemorrhagic shock (42).

Most opioids decrease the effects of sympathetic nervous system and enhance vagal and parasympathetic tone. In patients that depend on high sympathetic tone, those receiving exogenous catecholamines, and in hypovolemia, administration of opioids predisposes them to hypotension. One of the effects dominating after the utilization of opioids is bradycardia (36).

6.5. Gastrointestinal physiology

The gastrointestinal (GI) tract serves primarily for the digestion and absorption of nutrients facilitated by digestive enzymes and secretions. The enteric nervous system consists of submucosal plexus that mainly controls absorption, and myenteric plexus that regulates tone and contractions within the intestinal wall (109).

6.5.1. Effects of anesthetic agents on the gastrointestinal tract

Nitrous oxide increases the risk of PONV, supposedly by activating the chemoreceptor trigger zone and the vomiting center in the medulla (33). Opioids, by binding to opioid receptors in the GI tract, slow GI motility and peristalsis (22,43). Postoperative ileus (POI) is a consequence of neuroimmune reaction. The base of this reaction is bidirectional communication of the immune system, within and outside of GI tract, and autonomic nervous system (44).

6.6. Hepatic physiology

The liver produces essential plasma proteins, it is responsible for metabolism and detoxification of drugs and harmful xenobiotics, absorbs critical nutrients, and is in charge of carbohydrate metabolism (45).

6.6.1. Effects of anesthetic agents on the liver

Inhaled anesthetics and regional anesthesia usually reduce hepatic blood flow in the absence of surgical stimulation, whereas intravenous anesthetics have minimal impact on the blood flow if the arterial blood pressure is maintained appropriately. Magnitude of the procedure determines the requirements of invasive monitoring (45).

6.7. Renal physiology

The kidneys are paired organs responsible for regulation of body fluid volume, acid-base balance, excretion of nonessential materials such as anesthetics and other medications, production of renin, as well as endocrine and metabolic functions (45,46). Excretion of drugs into urine depends on glomerular filtration, active secretion and passive reabsorption by tubules. Renal disease is relatively prevalent in surgical population and even mild renal dysfunction is associated with greater probability of postoperative complications (45).

6.7.1. Effects of anesthetic agents on the kidneys

General, spinal, and epidural anesthesia reduce renal function. It is measured by urine output, GFR, renal blood flow, and electrolyte excretion. Impairment of renal function associated with anesthesia is generally short-lived, reversible, and the effect can be decreased by maintenance of systemic blood pressure and preoperative hydration. (46) Patients with end-stage renal disease and comorbidities require more extensive monitoring, and agents or their metabolites that are eliminated through the kidneys, such as pancuronium, vecuronium, morphine, and meperidine, should be used tentatively or avoided (45).

7. COMPLICATIONS

7.1. Complications of the nervous system

7.1.1 Position-related injury

Patient positioning during surgery facilitates the procedure, nevertheless it can be a source of harm to the patient (47). Position-related injury can occur due to tissue compression, trauma, air embolism, and organ underperfusion. Identification of the problem related to positioning requires attentive awareness throughout and following surgery. Routine checks at regular intervals should be done in order to promptly identify malpositioning (48).

A. Nerve injury

Temporary arterial occlusion and interruption of nerve blood supply can be a cause of reversible conduction block. Mild stretching may result in small areas of nerve ischemia from disruption of vasa vasorum, and with more severe stretching it may cause tears in intraneural connective tissue leading to hemorrhage and necrosis. It can progress to intraneural edema and block of axoplasmic transport, causing nerve dysfunction that can last for several weeks. Predisposing conditions contributing to neurologic deficit, regardless of adequate positioning techniques, include peripheral vascular disease, diabetes, hereditary neuropathy, and anatomic variation (48). Nerve injury is a complication of peripheral regional techniques that may arise due to traumatic injury to the nerves during needle or catheter placement, infection, and choice or dose of local anesthetic solution. In theory, localization of neural structures with imaging would allow a high success rate without increasing the risk of neurologic complications, but it has not been confirmed (49).

B. Brain ischemia

The beach chair position is commonly used for shoulder arthroscopy. The patient is positioned 30° to 60° with head upward. There has been recent association of this position with hypotensive episodes and subsequent severe

neurologic dysfunction and loss of vision. Prophylaxis with metoprolol reduces the incidence of hypotension and bradycardia (48).

C. Pseudohypoxia

Pseudohypoxic brain swelling (PHBS) is a rare neurosurgical complication also known as postoperative intracranial hypotension-associated venous congestion (50). It is characterized by clinical and radiographic findings that resemble those of anoxic brain injury (51).

7.1.2. Delirium

Delirium is an acute clinical syndrome characterized by disturbed consciousness and cognitive function, irritability, anxiety, paranoia, and hallucinations that can present up to 3 days after surgery (52–54). Advanced age, certain procedures as repair of hip fracture and bilateral knee replacement, preoperative cognitive impairment, dementia, substance abuse, and severe illness are associated with higher risk of postoperative delirium (52,54,55). Blood loss, hematocrit less than 30%, and number of intraoperative blood transfusions are intraoperative elements that can be predictive of delirium following surgery (55). Early detection of delirium is essential to allow for supporting care and treatment of reversible causes such as inadequate hydration, perioperative medications, arterial hypoxemia, hypercapnia, pain, sepsis, and electrolyte abnormalities (52,55).

7.1.3. Cognitive dysfunction

Postoperative cognitive dysfunction (POCD) is an objectively measured deterioration of cognition after surgery compared with preoperative function (56–58). It should be distinguished from delirium and short-term cognitive disturbance, both of which have a shorter duration. Neuropsychological assessment is needed for verification and to objectively measure cognitive function (57). The cause is thought to be multifactorial and could possibly be related to inflammatory reactions, altered hormonal homeostasis, or direct anesthetic toxicity. It is more commonly observed after major surgery, cardiac surgery, and emergency surgery (58). POCD is associated with

higher mortality rate which could also be attributed to the older age, underlying health problems, and decreased compliance after surgery (59).

7.1.4. Awareness during anesthesia

Amnesia is one of the effects produced by general anesthesia, which refers to the absence of explicit and implicit memory. Awareness under anesthesia is represented with explicit memory or conscious recall of intraoperative events (60,61). Major causes are inadequate anesthesia, increased patient anesthetic requirements, and problems with anesthetic delivery systems (60). Insufficient anesthesia is characterized by motor responses and sympathetic activation which may be hindered with the use of neuromuscular blocking agents (60,62). Certain patient groups, such as those who are hypovolemic or have limited cardiac reserve are at increased risk. Alcohol, opioid, and amphetamine users, those with a past history of awareness, and children are another group of patients that are more likely to experience anesthetic awareness (60,62). Patients with ASA physical status III-V who are undergoing extensive surgery are more likely to experience awareness during operative procedure (60,61). Furthermore, use of nitrous oxide and administration of intravenous anesthetics during induction carries a greater possibility of intraoperative awareness, whereas with volatile anesthetics the risk is considerably decreased (60,61). Awareness under general anesthesia can be frightening experience. Roughly one third of patients will experience long-term psychological consequences with development of post-traumatic stress disorder (PTSD) (60,62–64). Recommendations for the prevention of awareness involve premedication with benzodiazepine, giving adequate doses of agents to induce anesthesia, avoiding muscle paralysis, and administering volatile anesthetics (65). Clinical signs such as patient movement, autonomic changes, tearing, perspiration, and end-tidal anesthetic gas (ETAG) may not be effective for measuring hypnotic component of anesthesia. Instead, monitors that collect spontaneous or evoked brain electrical activity may help decrease the incidence of intraoperative awareness with recall (60,66,67). Bispectral index (BIS) monitor is one of the most used and researched concerning the depth of anesthesia (60,62,66).

7.1.5. Body temperature and shivering

The body temperature is regulated almost exclusively through temperature regulating centers in the hypothalamus (68). Anesthetic agents interfere with hypothalamic reflex responses causing inhibition of central thermoregulation (69). If anesthetized patients are not actively warmed, the core temperature decreases 1-2°C within the first hour of general anesthesia due to redistribution of heat from central compartments to cooler peripheral tissues from anesthetic-induced vasodilation. Subsequently, the core temperature will continue to gradually decline in the following 3-4 hours because of continuous heat loss to the environment. Eventually steady state will be reached in which heat loss equals metabolic heat production (69).

Postoperative shivering is most commonly associated with hypothermia, volatile anesthetics, and procedures of long duration. Shivering may increase oxygen consumption, carbon dioxide production, and sympathetic tone causing increase in cardiac output, heart rate, systemic blood pressure, and intraocular pressure (55,69). Furthermore, hypothermia inhibits platelet function, coagulation factor activity, and drug metabolism which may lead to exacerbation of postoperative bleeding, prolongation of neuromuscular blockade, and delayed awakening. Increased incidence of myocardial ischemia and infarction, as well as increased perioperative mortality are long-term harmful effects of hypothermia (55).

7.1.6. Acute postoperative pain

Pain is defined as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage” (70). Postoperative pain can be classified as acute that typically lasts up to 7 days, or chronic continuing for more than 3 months (71,72). Pain is subjective, therefore it does not allow objective measurement (70,72). Nevertheless, a 0-10 numeric pain intensity scale is widely accepted (72,73). Perioperative pain is a consequence of surgical tissue injury with resultant release of histamine and inflammatory mediators (71,72). Continuous release of local inflammatory mediators can lead to sensitization of peripheral nociceptors characterized by a decreased threshold for activation, increased rate of discharge with activation, and increased rate of spontaneous discharge. These changes may contribute to development of functional alterations in

the dorsal horn of the spinal cord and subsequently cause postoperative pain to be perceived as more painful (71,72).

Uncontrolled postoperative pain has many negative short and long-term effects on a patient. Acute effects are enhancement of coagulation, inhibition of fibrinolysis, and increased platelet reactivity and plasma viscosity which may enhance the incidence of deep venous thrombosis (DVT), vascular graft failure, and myocardial ischemia. In addition to hypercoagulability, stress response may enhance postoperative immunosuppression and hyperglycemia. If pain is uncontrollable it could lead to activation of sympathetic nervous system which may increase myocardial oxygen consumption and decrease supply through coronary vasoconstriction. Sympathetic activation may likewise delay return of postoperative gastrointestinal motility. Poor control of acute postoperative pain is a predictive factor for development of chronic postsurgical pain (CPSP). CPSP is more common after certain procedures such as limb amputation, thoracotomy, sternotomy, breast surgery, and gallbladder surgery (71).

Some of the agents used for the management of postoperative pain are systemic opioids, nonopioid adjunctive medications, and regional techniques (72). Best way of managing postoperative pain is to begin treatment before the surgery, concept known as preventive analgesia (71,72). Prevention of central sensitization with thorough multimodal analgesic interventions could in theory lessen the intensity or completely eliminate acute and chronic postoperative pain (71).

7.2. Complications of the respiratory system

7.2.1. Laryngospasm

Laryngospasm is a sudden spasm of vocal cords characterized by high-pitched crowing noises or may be silent with complete glottic closure. Commonly occurs when the extubated patient is emerging from general anesthesia in the operating room. Jaw thrust maneuver with CPAP is often adequate to break the laryngospasm, but in case of failure, immediate skeletal muscle relaxation can be achieved with succinylcholine (55,74,75).

7.2.2. Upper airway obstruction

Upper airway obstruction requires prompt attention, preferably by noninvasive methods as jaw thrust maneuver with CPAP. If this is not effective, an oral, nasal, or laryngeal mask airway can be inserted. Lingering effects of neuromuscular blocking drugs can be reversed pharmacologically (55).

7.2.3. Residual neuromuscular blockade

Residual neuromuscular blockade should be considered in any patient that received neuromuscular blocking drugs during anesthesia presenting with upper airway obstruction. Measurement of the train-of-four (TOF) ratio that is routinely used for evaluation of neuromuscular function in anesthetized individuals is unreliable due to its subjectiveness. Research indicates increased risk of clinically meaningful postoperative respiratory complications associated with intermediate-acting neuromuscular blockade, despite of anticholinesterase reversal. The use of sugammadex, rather than neostigmine, could reduce the incidence of residual neuromuscular blockade (55).

7.2.4. Loss of pharyngeal muscle tone

Loss of pharyngeal muscle tone is the most frequent cause of airway obstruction in the immediate postoperative period. It is caused by persistent effects of inhaled and intravenous anesthetics, neuromuscular blockers, and opioids. Normally, contraction of pharyngeal muscles happens simultaneously with negative inspiratory pressure generated by the diaphragm, which facilitates opening of the upper airway by pulling the tongue and soft palate forward. This activity is depressed during sleep, and consequent decrease in tone can promote airway obstruction. Opening the airway with the jaw thrust maneuver or continuous positive airway pressure (CPAP) applied via facemask can assist airway obstruction caused by loss of pharyngeal tone and should be supported until the patient has adequately recovered from the effects of administered drugs (55).

7.2.5. Edema or hematoma

Postoperative wound hematomas following certain neck procedures can compromise the airway. In these cases, evaluation of airway patency must precede extubation

because mask ventilation may not be possible in a patient with severe upper airway obstruction (55,74).

7.2.6. Pneumonia

Pneumonia is one of the complications after major surgery performed under general anesthesia (76). The patient's protective airway reflexes are disrupted during tracheal intubation, putting the patient at risk of aspiration from the stomach, esophagus, mouth, or nose (75,77). Initial inflammatory response is defined as aspiration pneumonitis, which can progress to aspiration pneumonia (77). Furthermore, endotracheal intubation is associated with the development of ventilator-associated pneumonia (VAP) in a patient after 48 hours of mechanical ventilation (78).

7.2.7. Pulmonary edema

Pulmonary edema can be either cardiogenic or noncardiogenic in nature. Noncardiogenic edema can occur due to airway obstruction, transfusion during surgery, and sepsis. Postobstructive pulmonary edema (POPE) is a consequence of acute upper airway obstruction such as laryngospasm, or relief of chronic partial airway obstruction (55,79). Transfusion-related acute lung injury (TRALI) is a clinical syndrome characterized by noncardiogenic pulmonary edema with hypoxia (80).

7.2.8. Obstructive sleep apnea

"Obstructive sleep apnea (OSA) is a condition caused by repeated episodes of upper airway collapse and obstruction during sleep associated with arousal from sleep with or without oxygen desaturation" (81). A lot of patients are undiagnosed at the time of the procedure. This presents a problem because patients with OSA are particularly prone to airway obstruction. Extubation should not be performed until the patient is fully awake and able to follow commands. These patients are sensitive to opioids, and when combined with benzodiazepines could cause significant episodes of hypoxemia and apnea. Regional anesthesia and multimodal analgesia techniques should be used to provide analgesia after surgery. CPAP should be provided in the immediate postoperative period (55,82).

7.3. Complications of the cardiovascular system

7.3.1. Hemodynamic instability

A. Systemic hypertension

Systemic hypertension may lead to unfavorable perioperative outcomes and patients with known history of hypertension require pharmacologic control of blood pressure (55,83,84). Postoperative hypertension is frequently associated with carotid endarterectomy and intracranial procedures (55).

B. Systemic hypotension

Systemic hypotension may be caused by decrease in preload, afterload, or intrinsic pump failure. Hypovolemic systemic hypotension is most commonly due to decrease in intravascular volume and preload caused by third-space loss, major intraabdominal procedures with inadequate intraoperative fluid replacement, and loss of sympathetic nervous system tone produced by neuraxial blockade (55).

Distributive shock is characterized by systemic vasodilation leading to hypoperfusion of brain, heart, and kidneys (85). Notable cause of hypotension in the perioperative period is iatrogenic sympathectomy resulting from the use of regional anesthesia. If this is not treated with phenylephrine and ephedrine immediately it could lead to cardiac arrest. Critically ill patients are extremely sensitive to even minimal doses of inhaled anesthetics, opioids, or sedative-hypnotics, which can produce significant systemic hypotension.

Cardiogenic systemic hypotension can be a cause of myocardial ischemia and infarction, cardiomyopathy, cardiac tamponade, and cardiac dysrhythmias (55).

7.3.2. Myocardial ischemia

Depending on the patient's cardiac history and risk index, they are divided into those at low and high risk of myocardial ischemia. Postoperative ST-segment changes in patients at low risk are usually benign unless they are accompanied by cardiac rhythm disturbances or hemodynamic instability. In patients at high risk, ST-segment and T-wave changes that are consistent with myocardial ischemia should be further evaluated immediately (55). Cardioprotection is a strategy of myocardial injury prevention that occurs during and after inadequate blood supply. This can be achieved

with volatile anesthetics, opioids, propofol, dexmedetomidine, and phosphodiesterase inhibitors, however continuing research in the field of cardioprotection is needed (86).

7.3.3. Cardiac dysrhythmias

One of the most common cardiac complications that may occur during anesthesia is arrhythmia (87). Cardiac dysrhythmias in the perioperative period are usually transient and multifactorial (55). During surgery, arrhythmia is clinically significant due to consequent influence on cardiac pumping mechanism and hence hemodynamic stability (87). Physiologic consequences of dysrhythmia will determine the urgency of treatment. Tachydysrhythmias reduce coronary perfusion time and increase myocardial consumption of oxygen, and therefore have most harmful effects in patients with coronary artery disease. Bradycardia is more damaging in those with a fixed stroke volume, namely infants, patients with restrictive pericardial disease or cardiac tamponade. In most cases treatment relies on identifying and correcting underlying cause such as hypoxemia, hypoventilation with hypercapnia, electrolyte abnormalities, acidemia, fluid overload, and anemia (55).

7.4. Miscellaneous complications

7.4.1. Allergic reactions and anaphylaxis

Allergic or hypersensitivity reactions are excessive responses of the immune system to an antigen in already sensitized person (88). Minor allergic reactions, such as rash, are not unusual to see in an operating room, whereas anaphylactic shock is less often, but life-threatening (89). Anaphylaxis is immediate hypersensitivity reaction that is produced by IgE-mediated release of pharmacologically active substances. This clinical syndrome is characterized by urticaria, bronchospasm and upper airway edema, vasodilation, increased capillary permeability and alterations in inotropy (88,90,91). Onset of signs and symptoms is for the most part immediate, although it may be delayed for a couple of minutes to as long as 2.5 hours (91). Latex, ß-lactam antibiotics, neuromuscular blockers, and intravenous contrast are associated with anaphylaxis (88,89,91,92). Immediate management consists of removing the offending agent, administration of epinephrine, oxygen, and intravenous fluids (89,90).

7.4.2. Postoperative nausea and vomiting

Postoperative nausea and vomiting (PONV) are most common adverse effects after surgery ranging from 30% in general population, up to 80% in high-risk groups. Risk factors are female gender, younger age, non-smoking, history of PONV or motion sickness, certain surgical procedures, and use of opioid analgesia. It is associated with longer stay in PACU, unanticipated hospital admission, increased health care costs, increased incidence of pulmonary aspiration, and significant discomfort. (55,93) There is no agent that is generally used for prophylaxis and treatment of PONV. Use of multimodal prophylaxis is recommended in patients with one or more risk factors (55). Types of drugs used can be subdivided into gastrointestinal prokinetic drugs, phenothiazines, butyrophenones, anticholinergics, antihistamines, NK_1-antagonists, serotonin receptor antagonists, and steroids (94). Patients with PONV who did not receive prophylaxis should get 5-HT_3 receptor antagonists such as ondansetron and ramosetron, or if prophylaxis has failed, they should receive antiemetic treatment from a different pharmacological class (55).

7.4.3. Renal dysfunction

Postoperative renal dysfunction can be classified into prerenal, intrarenal, and postrenal causes. Often, the etiology is multifactorial, with exacerbation of preexisting renal insufficiency during surgery. Oliguria is a common cause of postoperative renal dysfunction. It could be due to intravascular fluid volume depletion, postoperative urinary retention, radiographic contrast dyes, rhabdomyolysis, injury or obstruction of ureters, and mechanical obstruction or malposition of urinary catheter (55).

7.4.4. Malignant hyperthermia

Malignant hyperthermia (MH) is one of the most devastating complications associated with anesthesia. It is an autosomal dominant condition of increased skeletal muscle metabolism triggered with the administration of volatile halogenated alkane such as halothane, and depolarizing muscle relaxant succinylcholine (8,95–97). Before exposure to the triggering agent, MH has practically no characteristic phenotype (96–98). Potential triggers include ether, halothane, enflurane, isoflurane, desflurane, sevoflurane, and succinylcholine. Onset of symptoms is extremely variable, so that

diagnosing in a clinical setting is quite difficult (96). Early symptoms are unexplained tachycardia, elevated end-tidal CO_2, and rigidity even with the administration of nondepolarizing relaxants (8,96,98,99). The patient can develop numerous metabolic abnormalities including metabolic acidosis, respiratory acidosis, hypoxemia, hyperthermia, rhabdomyolysis, hyperkalemia, hypercalcemia, acute renal failure, cardiac dysrhythmias, disseminated intravascular coagulation (DIC), and can even cause death if left unrecognized and untreated (96,99). Acute management consists of discontinuation of all anesthetic agents, hyperventilation with 100% O_2, administration of dantrolene, controlling fever, monitoring acid-base balance and urinary output, and analyzing coagulation studies (96).

8. PREVENTION

8.1. Risk of anesthesia

Prerequisite for making an informed decision when preparing for anesthesia and surgery is getting accurate information on the probability of specific perioperative complications. The risk of anesthesia has been dramatically decreased over the past decades and death exclusively attributed to anesthesia is rare. Perioperative risk is multifactorial. It depends on factors specific to the patient, type of anesthesia, and surgery (100). Risks may vary from common and minor, to rare and serious complications (101). Coexisting diseases in a patient increase perioperative morbidity and mortality. Noteworthy risk markers for increasing mortality are advanced age, male gender, increasing physical status score, major or emergency surgery, complications in the surgical unit, and use of narcotic anesthetic techniques. Additionally, skills and training of the anesthesiologist may affect the risk (100).

8.2. Perioperative evaluation

Perioperative assessment includes preoperative evaluation of the patient, intraoperative management, and postoperative assessment to determine if there are any consequences of anesthesia care that patient experienced. The purpose is to identify patients in need of more extensive evaluation and management of underlying conditions (102). Preoperative evaluation should include medical history with all medications used in recent past, allergies, reactions to previous anesthetics, and physical examination. Physical examination should include vital signs, examination of anatomy, auscultation, palpation, percussion, and guides further laboratory testing if needed (103). The ASA Physical Status Classification (*Figure 1.*) is traditionally used for the purpose of assessment of patient's comorbidities before anesthesia. It does not predict perioperative risks when used alone, but in combination with other components, such as the type of surgery and patient's status, can be helpful in anticipation of perioperative risks (104).

Communication between the staff, implementation of checklists, and routine briefing before surgery have been successful in reducing intraoperative complications and improving patient safety (102).

ASA PS Classification	Definition	Adult Examples, Including, but not Limited to:
ASA I	A normal healthy patient	Healthy, non-smoking, no or minimal alcohol use
ASA II	A patient with mild systemic disease	Mild diseases only without substantive functional limitations. Current smoker, social alcohol drinker, pregnancy, obesity (30<BMI<40), well-controlled DM/HTN, mild lung disease
ASA III	A patient with severe systemic disease	Substantive functional limitations; One or more moderate to severe diseases. Poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, history (>3 months) of MI, CVA, TIA, or CAD/stents.
ASA IV	A patient with severe systemic disease that is a constant threat to life	Recent (<3 months) MI, CVA, TIA or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, shock, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis
ASA V	A moribund patient who is not expected to survive without the operation	Ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	

Figure 1. ASA Physical Status Classification. Available at: https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system [accessed 12 Jun, 2022]

8.3. Postanesthesia care unit

The postanesthesia care unit (PACU) is intended for monitoring and care of patients recovering from immediate physiologic effects of anesthesia and surgery. Standards for postanesthesia care are continuously updated to keep up with changing practice

parameters and advances in technology. There are various discharge criteria which assess activity, respiration, circulation, and mental status (55,105).

8.4. Monitoring

Obligation of the anesthesiologist is a continuous assessment of status, influence of surgery and anesthetics on the patient's physiology. Monitoring permits repeated evaluation of the patient during surgery and correction of any abnormalities (106). Standard practice is to monitor patient's oxygenation, ventilation, circulation, and temperature (107). Anesthesia management factors that have been associated with decreased risk of perioperative mortality are equipment check with protocol and checklists, anesthesiologist and anesthesiology nurse that were present throughout the whole procedure, and reversal of muscle relaxants and opioids (108).

9. CONCLUSION

In the present-day, complications of anesthesia have been diminished due to guiding principles of patient safety, collection of knowledge, analyzing errors, critical incident reporting, checklists, and communication protocols amongst others. Statistical data shows that an overall incidence of minor perioperative events related to anesthesia are at 18-22%, more serious complications are at 0.45-1.4%, and complications resulting in permanent damage are at 0.2-0.6%. Hypotheses behind the improvement of morbidity and mortality in anesthesia is better monitoring and equipment, new anesthetic agents, better training, availability of postanesthesia care unit for the recovery, and improved airway management (3).

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