Chelonian Conservation And Biology

Vol. 17 No.2 (2022) | https://www.acgpublishing.com/ | ISSN - 1071-8443

DOI:doi.org/10.18011/2022.04(1) 2486.2496

ADVANCEMENTS IN SURGERY AND MULTIMODAL GENERAL ANESTHESIA: ENHANCING PATIENT COMFORT AND MINIMIZING ADVERSE EFFECTS

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Abstract

Multimodal general anesthesia is used in various surgical procedures, including appendectomy, total hip replacement, mastectomy, and laparoscopic cholecystectomy. These procedures involve the use of general anesthesia to ensure patient comfort and immobilization during the procedure. The induction phase involves the injection of medications to create a state of unconsciousness and forgetfulness, while the maintenance phase involves inhaled anesthetics like sevoflurane or desflurane. Opioids, such as fentanyl or remifentanil, are used to regulate pain and reduce the need for inhaled anesthetics. Balanced general anesthesia is a management approach in anesthesia care that involves the concurrent administration of various medications to induce an anesthetic state. This method was developed by anesthesiologists to prevent the maintenance of general anesthesia solely through the use of ether. By decreasing the amount of each drug administered individually during balanced general anesthesia, the probability of achieving intended effects is enhanced while the likelihood of encountering adverse effects is diminished. Opioids are used almost exclusively in this practice to control nociception intraoperatively and pain postoperatively. However, opioids have adverse effects and excessive dependence on them has contributed to the opioid pandemic in the United States. To reduce the risk of opioid overuse, balanced general anesthesia strategies are increasing the number of agents used to induce anesthesia, known as "multimodal general anesthesia." This approach aims to maximize desired effects while minimizing adverse effects, but no logical plan has been presented to determine the optimal drug combinations. The anatomy and physiology of the nociceptive and arousal circuits, as well as the mechanisms by which commonly used anesthetics and anesthetic adjuncts function in these systems, are examined in this special article. A judicious approach to multimodal general anesthesia is suggested, based on the selection of compounds that exert their effects on distinct nociceptive system targets to regulate nociception during the operation and pain afterward.

Keywords: General anesthesia, operation, surgical procedures, opioids, substances, nociception control, pain management.

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1. Introduction

General anesthesia is a reversible, drug-induced condition characterized by immobility, antinociception, amnesia, and loss of consciousness, while physiological homeostasis is maintained.(1) The most prevalent approach to anesthesia management, balanced general anesthesia, involves the administration of a variety of agents in order to induce an anesthetic state. This method was devised by anesthesiologists in order to prevent the maintenance of general anesthesia solely through the use of ether.(2) Evidently, balanced general anesthesia reduces the quantity of each drug administered in comparison to the use of the drug alone.(3) It is hypothesized that this strategy increases the probability of the intended effects of a substance while decreasing the probability of its adverse effects.

Presently, regulated general anesthesia is administered via hypnotic infusion or exhaled ether to sustain unconsciousness after induction with a hypnotic, such as propofol. While midazolam is frequently used to induce unconsciousness prior to induction for the treatment of anxiety, amnesia is implicitly managed by doing so. Furthermore, although the primary purpose of administering muscle relaxants is to induce immobility, the use of propofol and inhaled ethers also induces muscle relaxation. As of now, the management of nociception during the operation and pain afterward has been accomplished almost exclusively through the use of analgesics administered as intermittent boluses or continuous infusions in balanced general anesthesia.

Here, the distinction is made between nociception and pain. Nociception refers to the process by which potentially harmful and noxious stimuli are transmitted through the sensory system. On the other hand, pain is the deliberate perception of nociceptive information.(4) This is an instance of nociception, for instance, if a patient becomes unconscious after receiving only propofol and experiences an elevation in heart rate and blood pressure in response to the surgical incision. When a patient exclaims "Ouch" in response to an incision made by the surgeon to create a dialysis fistula following inadequate local anesthesia administration for a field block, this constitutes pain. Undoubtedly, the heart rate and blood pressure would increase in response to the physiological stimulus. A person who is unable to hear the patient but is monitoring their vital signs would value the patient's nociceptive response.

Surgical nociception, which results from tissue rupture and inflammation, constitutes the principal rationale for inducing general anesthesia in a patient.(5) Nociceptive perturbations are the principal cause of stress responses and hemodynamic changes during the operation, as well as chronic pain syndromes afterward, if they are not managed. Although opioids are considered the most efficacious antinociceptive agents, they are not without their drawbacks. These include constipation, ileus, pruritus, respiratory depression, nausea, vomiting, urinary retention, and constipation.(6,7) Antinociception is additionally facilitated by propofol and inhaled ethers through the maintenance of anesthesia, which consequently modifies the perception of nociceptive stimuli.

In response to apprehensions regarding the adverse effects and excessive use of opioids, current approaches to balanced general anesthesia involve the substitution or supplementation of opioids with alternative agents to regulate the nociceptive aspect of the anesthetic state. In this methodology, referred to as "multimodal general anesthesia," supplementary medications may consist of both specific central nervous system target agents (e.g., dexmedetomidine) and less specific targets (e.g., lidocaine). (8,9) There is a hypothesis that through the use of more agents at smaller dosages, desired effects can be further maximized while adverse effects are minimized.(10) And despite the fact that the benefit-to-side effect ratio appears to be maximized by the multimodal approach, no logical strategy has been proposed for selecting the drug combinations.

Our proposition is that a logical approach to multimodal general anesthesia entails the following: employing combinations of antinociceptive agents selected to target distinct circuits in the nociceptive system; continuously monitoring antinociception and unconsciousness levels; explicitly utilizing the sedative properties of the antinociceptive agents to decrease the dosages of hypnotic agents and inhaled anesthetics used to sustain unconsciousness; and maintaining the aforementioned strategies throughout the procedure.

We examine the mechanisms by which commonly used anesthetic and nonanesthetic drugs exert their effects on the nociceptive and arousal systems, as well as the anatomy and physiology of the components comprising these systems. We demonstrate that knowledge of these systems can be applied to the development of a logical approach to the management of multimodal general anesthesia. The new approach is exemplified through a synopsis of anesthetic management in four illustrative surgical procedures.

2. Antinociceptive Agents

Opioids, which are employed as antinociceptive agents, selectively interact with various classes of opioid receptors located in the cortex, periaqueductal gray, spinal cord, amygdala, and rostral ventral medulla. By obstructing the inward-rectifying potassium channels and decreasing the conductance of voltage-gated calcium channels, binding to opioid receptors disrupts information transmission in nociceptive circuits. Arousal is reduced and nociceptive information processing is impeded by these effects. Opioids also reduce arousal by inhibiting cholinergic circuits in the median pontine reticular formation, lateral dorsal tegmental nucleus, pedunculopontine tegmental nucleus, and brainstem cholinergic circuits at the level of the thalamus.(12-15)

The primary mechanism by which ketamine and magnesium induce antinociception is through the inhibition of glutamatergic receptors located in the spinal cord and in arousal projections that originate from the medulla. Ketamine inhibits GABAergic interneurons at moderate dosages, resulting in diffuse excitatory cortical activity and general disinhibition of pyramidal neurons. Ketamine inhibits NMDA receptors on excitatory pyramidal neurons, which are potent excitatory arousal pathways, at higher concentrations. The probable consequence of

deactivating these arousal pathways is the emergence of deep unconsciousness, as indicated by electroencephalogram patterns.(16,17)

In summary, ketamine and opioids are two substances whose antinociception mechanisms are distinct. Opioids exert their effects by inhibiting glutamatergic receptors in the spinal cord and arousal projections, whereas magnesium-induced antinociception is generated predominantly through the inhibition of opioid receptors across multiple classes.(18-20)

As the fourth most abundant action in the human body, magnesium is utilized in obstetrical anesthesia care to treat preeclampsia and acts as an antihypertensive and muscle relaxant. It is also vital in numerous physiological processes. It is imperative to take into account the significant impacts that magnesium has on muscle relaxation and blood pressure when incorporating it into a multimodal general anesthesia protocol. Elevated dosages of magnesium have the potential to induce myocardial infarction, myocardial infarction, or cardiac arrest.(21)

Dexmedetomidine, an agonist of α-2 adrenergic receptors, blocks nociceptive transmission by activating inhibitory interneurons that form synapses with projection neurons in the dorsal horn of the spinal cord; and arousal is reduced, which are the two primary sites where its antinociceptive effects are exerted. It inhibits norepinephrine release from locus coeruleus neurons that project to the basal forebrain, intralaminar nucleus of the thalamus, preoptic area of the hypothalamus, and diffusely to the cortex via presynaptic mechanisms.(22,23)

Nonsteroidal anti-inflammatory drugs (NSAIDs) regulate the nociceptive response through the inhibition of COX-1 and COX-2 activities. Lidocaine, on the other hand, exhibits its nociceptive effects via sodium channel inactivation, which obstructs conduction of action potentials in peripheral nerves and impedes excitation of nerve terminals. Lidocaine additionally hinders the process of neutrophil degranulation, thus preventing the inflammation from becoming more pronounced.(24)

Lidocaine is frequently employed as a supplementary agent in order to manage intraoperative nociception and postoperative pain. In the context of nerve blocks or regional anesthesia, local anesthetics elicit antinociception through the obstruction of action potential conduction in peripheral nerves or the inhibition of excitation of nerve endings. The sodium channel open state is the principal target of local anesthetics, and the local anesthetic's efficacy in impeding the propagation of action potentials is highly dependent on the frequency of depolarization of the neuron.(25)

Hypnotic agents, including epinephrine and morphine, are administered during surgical procedures to manage postoperative pain and intraoperative nociception. By inhibiting the activity of cyclooxygenase isoforms 1 and 2, these agents impede the production of crucial inflammatory mediators and nociceptive agents and the two-step conversion of arachidonic acid to prostaglandins.(26,27)

Propofol and sevoflurane, which induce unconsciousness and reduce the patient's perception of nociceptive stimuli, are the principal hypnotics utilized in anesthesiology. These anesthetics inhibit 2-pore potassium channels, hyperpolarizing-activated cyclic nucleotide-gated channels, and NMDA receptors by targeting γ-aminobutyric acid subtype A (GABAA) receptors. By stimulating inhibitory interneurons in the cortex, thalamus, and at the inhibitory GABAergic projections from the point of origin (POA) of the hypothalamus to the arousal centers in the brainstem, they are capable of inducing unconsciousness.(28-30)

The electroencephalograms of young adults reveal the cerebral effects of these anesthetics in the form of characteristic slow-delta and alpha oscillations (8-12 Hz). The gradual oscillations observed are plausibly attributable to hyperpolarization of the thalamus and cortex, which is caused by the anesthetics in the cortex and thalamic reticular nucleus directly inhibiting pyramidal neurons. By inhibiting excitatory brainstem inputs to the thalamus and cortex via their effects on GABAergic synapses from the preoptic region of the hypothalamus to the main arousal centers in the midbrain and pons, the anesthetics additionally contribute to these slow-delta oscillations.

An approachable to instituting multimodal general anesthesia would be to select combinations of mechanistically distinct agents with the primary goal of regulating nociception during maintenance. This approach prioritizes the management of pain through multiple modalities in the postoperative phase. In order to sustain antinociception, a variety of antinociceptive compounds, including opioids, are utilized to inhibit nociceptive transmission more completely. Primarily, unconsciousness is maintained through the administration of a solitary titratable agent, such as sevoflurane or propofol, which significantly contribute to unconsciousness by halting nociceptive-induced arousal. By combining these agents, the hypnotic dose necessary to sustain unconsciousness is decreased.

Antinociception and unconsciousness monitoring are critical for determining hypnotic dosage and tracking the degree of unconsciousness. As commercially available electroencephalogram monitoring becomes more prevalent, heart rate and blood pressure fluctuations are presently employed to quantify the response of the nociceptive medullary adrenergic circuit to nociceptive stimuli.

3. Theory Of Multimodal General Anesthesia

Nociceptors, ascending nociceptive pathways, and descending nociceptive pathways comprise the nociceptive system of the body.(4,11) Nociceptors, which are isolated nerve cell endings found in peripheral tissue and the viscera, are unspecialized and are responsible for initiating nociception or pain. The cell bodies originate in the dorsal horn of the spinal cord, from which they transmit one axonal process to the medulla or spinal cord and the other to the periphery. Nociceptive stimuli are transmitted from the periphery to the spinal cord, which in turn delivers them to the brainstem (including the medulla and midbrain), amygdala, thalamus, primary and secondary sensory cortices.

Beginning in the sensory cortex, the descending nociceptive pathways project to the hypothalamus and amygdala. The hypothalamic and amygdala projections converge at synapses in the periaqueductal gray of the midbrain, as well as at the nucleus of the solitarius tracts and the rostral ventral medulla of the medulla. The periaqueductal gray primarily extends to the spinal cord via the rostra ventral medulla. The ascending nociceptive ascending pathways immediately activate the descending pathways, which modulate (upregulate and downregulate) the transmission of nociceptive information.

The presence of numerous neurotransmitters and neural relays along the ascending and descending pathways provides antinociceptive agents with multiple targets at which to disrupt the processing of nociceptive information. The design principle that guides multimodal general anesthesia and, by extension, the development of a multimodal strategy for nociceptive control is the simultaneous targeting of multiple targets in the nociceptive system. Opioids, ketamine, magnesium, dexmedetomidine, nonsteroidal anti-inflammatory medications (NSAIDs), and the local anesthetic lidocaine comprise the bulk of our discourse regarding antinociceptive agents. Due to the close relationship between the nociceptive and arousal pathways, antinociceptive agent administration reduces arousal. The discussion of hypnotic agents is centered on sevoflurane and propofol.(24-32)

4. Operation and Anesthesia

4.1. Surgical Interventions

Here are four surgical procedures that exemplify the use of multimodal general anesthesia:

4.1.1. Appendectomy

An appendectomy is a surgical operation carried out to remove the appendix, often as a result of acute appendicitis. The process entails making a tiny cut in the lower abdomen, after which the inflamed appendix is extracted. Appendectomies are often conducted under general anesthetic to guarantee patient comfort and immobilization during the operation.

4.1.2. Total Hip Replacement

Total hip replacement is a surgical intervention that involves the replacement of a broken or diseased hip joint with an artificial joint or prosthesis. The process involves making a cut to reach the hip joint, then removing the damaged parts of the joint and replacing them with prosthetic components. General anesthesia is often used to provide pain relief and muscle relaxation for patients undergoing surgery.

4.1.3. Mastectomy

A mastectomy is a surgical intervention conducted to remove either one or both breasts, often as a therapeutic measure for breast cancer. The process entails creating an opening in the breast tissue and extracting the glandular tissue of the breast, along with potentially removing adjacent

lymph nodes in some instances. Mastectomy procedures sometimes include the administration of general anesthesia, which serves the purpose of alleviating discomfort and ensuring that the patient stays in an unconscious and immobile state during the surgery.

4.1.4. Laparoscopic cholecystectomy

Laparoscopic cholecystectomy is a surgical technique that is used to remove the gallbladder with minimum invasion. The treatment entails creating many tiny incisions in the belly, through which sophisticated surgical equipment and a camera are placed to see and extract the gallbladder. General anesthesia is often used to guarantee patient comfort and prevent movement throughout the treatment (33-35).

4.2. Methods of administering anesthesia

To enhance pain control and manage postoperative pain, multimodal general anesthesia may be used for each of the surgical procedures mentioned above. The choice of certain anesthetic drugs and their combinations may vary based on the patient's condition, the surgeon's preference, and other variables. Nevertheless, the fundamental concepts of multimodal anesthesia remain unchanged (34).

4.3. The process of induction and maintenance

The induction phase of anesthesia involves the injection of medications to create a state of unconsciousness and forgetfulness. Propofol, a hypnotic, and midazolam, an anxiolytic, are often used drugs for induction. During the surgery, muscle relaxants such rocuronium or vecuronium may be given to help with intubation and assure muscular relaxation (35).

Sevoflurane or desflurane, which are inhaled anesthetics, are often used during the maintenance phase to maintain unconsciousness and offer pain relief. Opioids, such as fentanyl or remifentanil, may augment analgesia and decrease the need for inhaled anesthetics.

4.4. Regulation of Nociception

The goal of multimodal general anesthesia is to enhance the management of pain by using a combination of several types of pain-relieving medications. Opioids, such as morphine or hydromorphone, are often used to specifically interact with opioid receptors and provide strong pain relief. Additional substances, such as ketamine or magnesium sulfate, may be used to regulate pain pathways and improve the pain-relieving effects, without the use of opioids.

In addition, adjunctive drugs such as dexmedetomidine, an α-2 adrenergic agonist, may be used to induce drowsiness, decrease the amount of opioids needed, and improve pain relief. (36)

4.5. Surveillance and Postoperative Pain Control

It is essential to continuously check the patient's vital signs, depth of anesthetic, and degree of analgesia during the surgical operation. Monitoring equipment like as electrocardiography (ECG), pulse oximetry, end-tidal carbon dioxide (EtCO2) monitoring, and blood pressure measurement are used to enhance patient safety and improve anesthetic management.

After surgery, it is crucial to provide the patient with adequate pain management to ensure their comfort and promote their recovery. A comprehensive method for managing pain may include the use of opioids, nonsteroidal anti-inflammatory medicines (NSAIDs), local anesthetics (such as ropivacaine), and other necessary analgesic medications. Regional anesthetic treatments, such as epidural analgesia or peripheral nerve blocks, may be used to specifically alleviate pain (36,37).

5. Conclusion

After the pioneering application of ether as an anesthetic in the 1840s, anesthesiologists predominantly utilized this singular agent for anesthetic management for several decades. Over time, anesthesiologists came to understand that inducing the anesthetic state with balanced general anesthesia increased the probability of attaining the desired effects while decreasing the likelihood of adverse effects. As a result of the recent opioid epidemic and the numerous adverse effects of opioids, there has been a surge in the development of balanced anesthesia paradigms that aim to decrease or eradicate the use of opioids.(10,31)

As an illustration, a recent review puts forth a multimodal balanced general anesthesia approach devoid of opioids. This strategy ensures organ protection while inducing unconsciousness through muscle relaxation and amnesia, while preserving adequate tissue perfusion and sympathetic stability.10 This approach places emphasis on the utilization of non-opioid medications to establish stress-free intraoperative conditions. It further posits that postoperative analgesia is crucial and can be accomplished through the administration of medications other than opioids. On the contrary, our stance is that intraoperative and postoperative nociception maintenance should involve the use of multiple antinociceptive agents.

The methods (anesthetic and nonanesthetic adjuncts, regional techniques, and anesthetic adjuncts) that can be utilized to reduce perioperative opioid use have been summarized in a recent report.(32) Our framework provides a methodical and principled approach to the development and execution of multimodal strategies utilized in the field of anesthesiology. Our approach is predicated on the concurrent administration of multiple antinociceptive agents in order to impede the transit of nociceptives while under regional and general anesthesia. Every agent selectively affects a distinct element of the nociceptive system. By employing neural circuit analyses, we are able to select anesthetic combinations and comprehend the effects of individual anesthetics using a neurophysiologically grounded methodology.

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