Chapter

From the Origins of the Opioid Use (and Misuse) to the Challenge of Opioid-Free Pain Management in Surgery

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Abstract

Pain is a physiologic mechanism of the human body. Early cultures believed pain to have demonic and spiritual origins. In the early nineteenth century, morphine was first isolated by the German pharmacist Friedrich Wilhelm Adam Ferdinand Serturner. Since then, synthetic opioids and other derivatives of morphine have been developed for a wide variety of purposes, including pain relief during surgery. Opioids mainly act through the stimulation of μ-receptors, which has inhibitory effects on the propagation of pain signals to the brain. However, opioids also have unwanted side effects like nausea, vomiting, constipation, postoperative sedation, dizziness, and addiction, and are associated with significant morbidity, prolong hospital stays, increase use of medications needed to reverse side effects, and decrease patient satisfaction. Furthermore, use and abuse of opioids have contributed to an opioid epidemic, especially in the United States since the beginning of the twenty-first century. Opioid-free anesthesia is an alternative aimed at providing pain relief without the opioid-related adverse effects and to enhance recovery. Non-opioid alternatives and preoperative patient education strategies have been shown to be superior in the management of postoperative pain and opioid requirements. Clinicals have embraced these concepts enthusiastically and have begun to incorporate an opioid-free pain management approach in surgery.

Keywords: opioids, opioid-free anesthesia, opioid-free pain management, surgery

1. Introduction

The perception of pain is an integral part of human existence. Although uncomfortable to the individual, the perception of pain is necessary to protect the body from harm. A painful sensation causes man to seek an explanation for the reason of this discomfort. A brief history of the origins of pain and the development of pain medications is presented, followed by the current understanding of the physiology of pain and modern concern about opioid use. In the second half of the twentieth century, synthetic opioids were introduced to achieve hemodynamic stability during anesthesia. Furthermore, combined with hypnotics and muscle relaxants, the opioids administration is considered a keystone of anesthesia. For instance, a prevalence of 30% of unwanted effects of opioids such as nausea, vomiting, dizziness and constipation has been reported [1].

An increased occurrence of confusion and postoperative delirium [2], respiratory depression, increased postoperative pain and opioids consumption with abuse, immunodepression, hyperalgesia and chronic postoperative pain have also been described. Of note, opioid tolerance to analgesia can occur after a single dose. Thus, the management of pain in surgery is currently moving in the direction of the reduction of opioid use preoperatively, perioperatively, and postoperatively. The modern multimodal anesthesia and analgesia with intraoperative hemodynamic stability, immobility and anticipation of postoperative analgesia can be achieved without opioids. The concept of opioid-free anesthesia (OFA) is based on the idea that hemodynamic stability can be obtained without opioids during anesthesia. In particular, OFA is a fascinating multimodal approach to anesthesia which provides the combination of hypnotics, N-methyl-D-aspartate (NMDA) antagonists, local anesthetics, anti-inflammatory drugs and alpha-2 agonists such as dexmedetomidine, and no intra-operative systemic, neuraxial, or intracavitary opioid is administered during anesthesia and the perioperative course. This strategy is aimed to prevent postoperative opioid-related adverse effects and to enhance recovery after surgery.

2. Pain and pain management from ancient cultures to the nineteenth century

Early theories of the origin of pain, especially from internal diseases, revolved around demonic and religious beliefs. Shamans and sorcerers treated patients with the use of amulets, magic sculptures, talismans, magic ceremonies and rituals to ward off demons and evil spirits. It was believed that spirits and demons should leave the body from the same way it entered, resulting in cultural scarifications to allow bad fluids, spirits and demons to escape. In Egypt, religious ceremonies and prayers were believed to help relieve pain. Incantations to God Horus and other deities were thought to relieve unilateral headaches [3].

Ancient cultures have used leaves of cocoa plant and opium for religious and medical purposes. The earliest anthropological evidence of the use of cocoa leaves was from the pre-Inca culture in Peru, dated to 1300 B.C. The Peruvians used cocoa leaves as a local anesthetic in trepanation operations. Opium was introduced to Egypt around 1500–1300 B.C., and was used as a cream for external application and for the fumigation of toothaches. In India and China, opium was used for the treatment of toothache and joint pain. In these cultures, opium could not be separated from its "recreational" use [3].

In the seventeenth century, physicians began to consider the human body as a machine with different parts in constant motion. The French philosopher Rene Descartes proposed one of the earliest concepts of modern physiology: a movement or touch initiated at the peripheral nerve endings propagated to the brain. This concept, which formed the basis of nineteenth century pain theories, is illustrated by Descartes famous figure [3] of a boy, whose foot is being stimulated by heat from a fire. Several scientific discoveries followed Descartes physiologic concept of pain, including that of Sir Humphrey Davy's reports of pain relief from inhalation of nitrous oxide in 1800 and James Moore's report of opium use for postoperative analgesia in 1784 [3].

3. The era of opioid analgesics and the discovery of anesthesia

With a better understanding of the physiology and pathways of pain, pharmacologic discoveries, particularly of morphine, were made in the beginning of the nineteenth century. The German pharmacist Friedrich Wilhelm Adam Ferdinand

Serturner was the first to isolate morphine from poppy in 1805. He named the substance after Morpheus, the Greek god of sleep. The invention of the hypodermic hollow needles and syringes by Charles Gabriel Pravaz and Alexander Wood in the 1850s allowed the ease of subcutaneous application. While this helped the widespread use of morphine, it also paved way for the use and abuse of morphine that spread rapidly during the American Civil War (1861–1865) and the French-German War (1870–1871). Opioid addiction became known as the "soldier's disease" and spurred research efforts to find substances with a lower risk of abuse [3].

Stemming from the discovery of morphine, scientists began to experiment and develop different forms of morphine. In 1874 Charles Adler Wright synthesized diacetyl-morphine, which in 1898 was registered under the name of heroin. This drug showed stronger cough suppression but lower analgesic effects when compared to morphine in animal models. Toward the beginning of the twentieth century, addiction to heroin became a growing problem in the USA, and in 1914, the government began implementing stricter regulations, limiting the maximum amount of heroin in preparations. These regulations also prohibited opium, morphine, cocaine, and several other substances from non-prescription preparations [3].

The development of new opioid analgesics continued. Derivatives of morphine and codeine such as hydromorphone, dihydrocodeine, hydrocodone, oxymorphone, meperidine, and oxycodone emerged at the beginning of the twentieth century. Methadone was developed during World War II in Germany and was used primarily as a substitution therapy in drug addicts. Methadone is a μ-receptor agonist and a noncompetitive NMDA antagonist. The NMDA receptor is involved in the pathophysiology of neuropathic pain. Fentanyl was developed by Paul A.J. Janssen in 1953 and was proved to be approximately 40 times more active than morphine. Subsequently, similar compounds with stronger potency developed, including carfentanil, sufentanil, and alfentanil [3].

The techniques for pain relief, such as spinal cord analgesia, knee surgeries, and different routes of administration for medications, began to develop after further research suggested opioid receptors in the human brain and the demonstration of endogenous opioids, the endorphins and enkephalins, constituting an internal system of pain modulation. Opioid receptors were found in high density in the substantia gelatinosa of the spinal cord, as well as the limbic system and periaqueductal gray area of the brainstem. This led to the reintroduction of spinal opioid application in clinical medicine. Peripheral opioid receptors were demonstrated in the late 1980s, and Stein and colleagues showed reduced operative pain following arthroscopy of the knee joint following intraarticular injection of morphine. Sustained release formula and transdermal route of administration provided a profound impact on the management of chronic pain. It made pain management much more comfortable for the patients, resulting in an improved quality of life. Morphine was available in the sustained release formula in 1983, while fentanyl was available in the transdermal system. Various opioids in sustained release formula and transdermal systems followed [3].

Surgical anesthesia experimentations in the nineteenth century allowed for major development in pain-free surgeries. One of particular note was the Dr. William Morton's experimentation with ether as a local anesthetic for a surgical neck operation. The dentist Horace Wells previously used gas during teeth extraction procedures. The first surgical ether anesthetized procedure was by the dentist William Thomas Green Morton at Massachusetts General Hospital, Boston, in 1846. Dr. John C. Warren was the senior surgeon operating on a congenital vascular tumor on the neck of a young man, Gilbert Abbott. To the audience's amazement, Abbott did not cry out in pain during the procedure, and this ushered in the era of pain-free surgery [3]. Painters Warren and Lucia Prosperi were commissioned in 2000

to immortalize this milestone in anesthetic surgery with a painting that became known as the Ether Dome painting.

Further significant steps in anesthesia in surgical environments continued. The use of chloroform in the management of childbirth was introduced into the medical world by Sir James Young Simpson in 1847, the same year physiologist Marie Jean Pierre Flourens had discovered the anesthetic properties of chloroform in animals. Chloroform remained the preferred anesthetic until the end of the nineteenth century even though the use of chloroform resulted in significantly more deaths than with ether [3].

Cocaine in local anesthesia marked another milestone in the advancement of pain management in surgery. During the nineteenth century, Albert Niemann, a scientist from Gottingen, isolated cocaine out of the mixture of alkaloids of the cocoa plant. The extracts became popular for conditions such as toothaches, digestive disorders, hysteria, and melancholia, as well as for being an aphrodisiac. Carl Koller experimented with cocaine as a local anesthetic on frog eyes, other animals, his assistants, and even himself. His paper, which demonstrated cocaine's efficacy, was presented at the Heidelberg Ophthalmological Society in 1884 by his colleague Josef Brettauer. The presentation was widely received and others began experimenting with cocaine's surgical applications [3].

After the Heidelberg presentation, scientists began experimenting with cocaine as a nerve block, in advanced cancer patients, and in spinal cord operations. American surgeon William Steward Halsted [4] began experimenting with cocaine as a nerve block, which opened up new possibilities in surgery anesthetics. Halsted and several of his colleagues eventually became addicted to cocaine during their experimentations with the drug. James Leonard Corning used cocaine as a spinal anesthetic in 1885. Dr. Herbert Snow was the first physician to incorporate cocaine into cancer pain treatment. In 1896, he administered cocaine with opium for pain relief to patients with advanced diseases. He later developed the "Brompton Cocktail," a mixture containing morphine, cocaine, and alcohol. German surgeon August Bier and his colleagues published their clinical results of spinal anesthesia, including intrathecal injections on each other. He introduced intravenous regional anesthesia in 1908. Rudolph Matas administered the first morphine anesthetic to the spinal cord in 1909. Most of the nerve blocking techniques during this time period were developed for surgical anesthesia [3].

Further experimentation with cocaine as an analgesic continued during the nineteenth century, resulting in the development of new local anesthetics including synthetic substitutes. Alfred Einhorn synthesized procaine in 1905. Lofgren and Lundqvist synthesized Lignocaine in 1943. Other local anesthetics followed including cinchocaine and amethocaine in the 1920s, mepivacaine, prilocaine, and bupivacaine in the late 1950s, etidocaine in the 1970s, and ropivacaine in the 1980s [3].

The current understanding of the physiology of pain involves the activation of the nervous system. Noxious stimuli, including intense thermal, mechanical, or chemical stimuli, are recognized by nociceptors in the peripheral nervous system. The threshold for pain activation is relatively high, requiring a large stimulus for signal propagation. The signals either travel through Aδ-fibers, Aβ-fibers, or C-fibers. While the Aδ-fibers and Aβ-fibers are myelinated and transmit "acute, well-localized, fast pain," the C-fibers are unmyelinated and transmit "slow" pain, often described as an ache. The signals travel to the dorsal root ganglion, are transmitted through the spinal cord and synapse on the somatosensory cortex and limbic system. The modification of this pathway by medications aims to reduce or eliminate pain [5].

4. The public health issue of prescription opioid abuse

Although opioids have historically been significant medications in the management of pain, opioids have also been the source of significant public health concern because of the addictive and destructive adverse effects of the medication. During the twentieth century, there were positive attitudes for the use of opioids, as a letter written to the New England Journal of Medicine underscored the safety and low addictive potential of opioid use in chronic pain patients, with subsequent letters and reviews supporting this perspective. With the impression that there was very little risk, particularly of addictive potential, in prescribing opioids for chronic pain, the demand for opioid use increased in clinical settings. However, by 2000, attitudes are beginning to shift and a reduction of opioid use is becoming the trend [5].

The detrimental overuse, abuse and addiction of opioids can precipitate from prolonged treatment of opioids. Opioid tolerance occurs when there is a reduction in the analgesic and sedative effects of these medications. Tolerance to the euphoric effects also develop, further increasing the risk of addiction. Opioid dependence results from the overactivation of the somatomotor cortex and autonomic nervous system due to the increased signaling of the cells while on the inhibitory medications. Cessation of opioid use or the administration of opioid receptor antagonists such as naloxone or naltrexone cause the withdrawal symptoms, including diarrhea, vomiting, agitation, hyperalgesia, hyperthermia, and hypertension [5].

In the United States, the opioid abuse has reached epidemic proportions and have become a public health issue. The treatment of opioid dependence is unclear, but there have been significant public health prevention efforts to combat the trends of increased abuse and overdose deaths [5]. On the topic of opioid epidemic, the United States Surgeon General Dr. Jerome Adams supports overdose education and awareness, and suggests co-prescribing naloxone to patients on high morphine milligram equivalent who are at risk [6]. Nearly all the U.S. states have laws supporting naloxone provision to lay persons. Further, the U.S. Department of Health and Human Services highlighted naloxone rescue kit access and emergency overdose as a priority to address the opioid crisis. The benefits of naloxone programming have been demonstrated in San Francisco, as well as in North Carolina, where a 70% decline in prescription opioid-related overdose death rates was observed from 2009 to 2010 [7].

5. Special issues on perioperative opioids administration

The current trend in surgery is in the direction away from general anesthesia that traditionally requires opioids preoperatively, intraoperatively, and postoperatively, and toward a more multi-modal regimen approach with preoperatively patient education, specifically highlighting the interplay between opioids and the human body's natural pain management system.

Currently, many surgical operations have been traditionally performed under general anesthesia with adjunct opioid use. The main mechanism of action of opioids is the stimulation of μ receptors, which has inhibitory effects on the propagation of pain signals to the brain [8]. However, there are a wide variety of associated adverse effects of opioids including nausea, vomiting, constipation, postoperative sedation, dizziness, and addiction [9]. Opioid use also carries significant morbidity, prolong hospital stays, increase use of medications needed to reverse side effects, and decrease patient satisfaction [10, 11]. Further, opioids may also cause paradoxical hyperalgesia

due to opioid-induced neural plasticity. This appears to affect both the central and peripheral nervous systems, and may lead to sensitization of the pain pathways [12].

In addition to the wide variety of adverse effects, opioids use may also hamper the effects of the human body's own natural pain killers, endorphins. Opioid administration reduces the production of beta-endorphins and impairs the function of mu-opioid receptors [13]. Beta-endorphins have significant natural analgesic effects and have been proposed to yield 18–33 times greater analgesic potency than morphine. Endorphin release is believed to enhance in response to a stressor, such as sharp pain, and can be quickly utilized to control the pain. The stressor causes the hypothalamus to release corticotrophin-releasing hormone (CRH), a peptide hormone and neurotransmitter, from the periventricular nucleus. CRH stimulates the cleavage of protein proopiomelanocortin (POMC) from basophilic cells, resulting in smaller proteins, one of them being beta-endorphin. In the peripheral nervous system, beta-endorphins bind to the μ receptors on both pre-synaptic and post-synaptic nerve terminals. The binding leads to the release of gamma-aminobutyric acid (GABA), which inhibits the release of substance P, a tachykinin protein involved in the transmission of pain. Endorphins not only have greater analgesic potency than morphine, but also enhances individuals' mood and well-being, due to indirect elevation of dopamine [13]. In the central nervous system, beta-endorphins bind the μ receptors on the pre-synaptic nerve terminals and inhibit release of GABA, which normally inhibits the release of dopamine. The overall effect of beta-endorphins, which is decreased in opioid use, is a decrease in pain and an elevation in wellbeing.

6. The concept of opioid-free anesthesia

Opioid-free anesthesia is an anesthetic technique without intraoperative systemic, neuraxial or intracavitary opioids, and that avoids perioperative opioids. There are a number of therapeutic uses and indications for opioid-free anesthesia including narcotic history (acute and chronic opioid addiction), opioid intolerance, morbidly obese patients with obstructive sleep apnea, hyperalgesia, history of chronic pain, immune deficiency, oncologic surgery, inflammatory disease, chronic obstructive pulmonary disease, and asthma [14].

Postoperative complications, such as respiratory depression, central muscle rigidity, pharyngeal muscle weakness, obstructed breathing, negative inotropism, nausea, vomiting, ileus and constipation, urinary retention, tolerance and addiction, dizziness, and excessive somnolence, can be reduced or prevented. Decrease histamine release (allergy/anaphylaxis), increase patient satisfaction, and enhanced recovery after surgery and anesthesia (ERAS) are other beneficial effects of opioid-free anesthesia [14–16].

Opioid-free anesthesia should be avoided in patients with allergy to any adjuvant drugs, and should be used cautiously in patients with disorders of autonomic failure, cerebrovascular disease, critical coronary stenosis, acute coronary ischemia, heart block, extreme bradycardia, non-stabilized hypovolemic shock or polytrauma patients, controlled hypotension for minimal blood loss, and elderly patients on beta-blockers.

Interest and use of adjuvant modalities, including ketamine, gabapentinoids, intravenous lidocaine, magnesium sulfate, alpha-2 adrenoreceptor agonists, and beta-blockers, is increasing because of enhanced recovery, particularly in specific patient populations like chronic pain and opioid dependent patients [15].

7. Opioid alternatives for postoperative pain control

In light of the serious adverse effects associated with opioids, many clinicians are forgoing prescribing opioids excessively and using opioid alternatives for postoperative pain control. These non-opioid alternatives, including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDS)/cyclooxygenase-2 (COX-2) inhibitors, gabapentin, local anesthetic infusion pumps, paravertebral or transverse abdominis plane nerve blocks, long-acting local anesthetics, and botulinum toxins, have been shown to produce analgesic effects and decrease opioid use postoperatively. Combinations of non-opioid alternatives have been shown to be superior in the management of postoperative pain and opioid requirements. In 2008, Parsa demonstrated that gabapentin and celecoxib in combination preoperatively for subpectoral breast augmentation was significantly superior than celecoxib alone in reducing postoperative pain and opioid use [17]. Stephan and Parsa have extensive experience using non-opioid modalities of postoperative pain control, which has resulted in significant reduction in opioid administration postoperatively for patients undergoing various plastic surgery procedures [13].

Several other opioid reduction strategies in a surgical setting have been tested and shown to be effective in managing pain and decreasing opioid use. Preoperative patient education has shown to be effective in reducing the opioid requirement postoperatively. Sugai et al. demonstrated that preoperative oral and written education concerning the body's response to pain reduced preoperative and postoperative opioid prescriptions [18]. When comparing patients that had opioid-free procedures to the patients receiving adjunct opioids, Parsa et al. found statistically significant reduction in time from end of operation to discharge, unplanned postoperative hospital admissions, and opioid use in the post-anesthesia care unit [19].

8. Conclusions

Pain treatment and management has come a long way since ancient cultures. Several innovations during the nineteenth century made significant headway in opioid analgesics, and by the end of the twentieth century, hemodynamic stability during anesthesia was achievable through the application of opioids. However, in an era with significant opioid abuse, limiting opioid requirements in postoperative pain management is of greater importance. Opioids are associated with unwanted side effects, including nausea, vomiting, dizziness, constipation, and hyperalgesia. Not only are there several adverse effects with opioid use, including a high addictive potential, opioids also interfere with beta-endorphins, the human body's potent natural analgesic. Opioid-free anesthesia provides a technique that can achieve intraoperative hemodynamic stability, immobility, and postoperative analgesia without opioids, and therefore, in the absence of the significant associated side effects. Judicious utilization of adjuvants like ketamine, gabapentinoids, intravenous lidocaine, magnesium sulfate, alpha-2 adrenoreceptor agonists, and beta-blockers contribute to enhanced recovery in specific patients with chronic pain and opioid dependence. Opioid-free anesthesia and other opioid-free pain relief strategies are essential in the control of the opioid crisis, are key in effective analgesia without unwanted opioid-related side effects, and are needed for postoperative recovery.

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