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Opioid Free Anesthesia

Onur Koyuncu, Senem Urfali and Selim Turhanoglu*

Department of Anesthesiology and Reanimation, Hatay Mustafa Kemal University, Turkey

Abstract

The first use of opioids in human history dates back to ancient times. It has gained popularity again with the synthesis of synthetic morphine in the last 50 years. Since this date, it has become the primary drug of anesthesia practices. It even led to the emergence of the concept of opioid-based anesthesia; it has become dispensable importance in anesthesia practices.

Purposes of getting involved in the practice of anesthesia at the beginning were; a) reducing the consumption of the hypnotic agents, b) inhibiting the activity of the sympathetic system without any histamine release, c) providing effective perioperative analgesia, d) reducing cardiac output with stable coronary perfusion and hemodynamic, e) blocking the ascending nociceptive stimuli.

Over the years, as opioids have been used, a large number of undesirable effects have emerged. The main ones are nausea-vomiting, itching, constipation, respiratory depression, hyperalgesia, persistent surgical pain, chronic pain, delirium, immune deficiency, increased hospital stays and associated increased costs.

Keywords: Opioids; Respiratory depression; Oxycodone

Introduction

Approximately 320 thousand major surgery records performed in 450 different hospitals between 2008 and 2010 were analyzed retrospectively. Primary surgical procedures were open colectomy, laparoscopic colectomy, laparoscopic cholecystectomy, total abdominal hysterectomy and hip replacement. The ICD-9 codes of the opioid related adverse events of those surgeries like hypoxemia, constipation, and paralytic ileus etc. were determined. A very serious proportion of patients who have undergone surgeries (12%) had opioid related adverse events.

Comparing patients who developed adverse events with those who did not, the cost per patient in patients who had adverse events was an average of 4707$ more. The hospital stay of the patients in this group is 3.3 days longer. In addition, these patients have higher rates of re-admissions to the hospital [1]. In another similar study, the ratio of the opioid-related adverse drug events is 2.7% (n=1586). The main opioid related adverse events were postoperative nausea-vomiting (n=1071, 67%), itching and dermal issues (n=504, 33%), confusion/agitation (n=97), urinary retention (n=20), respiratory depression with an associated high risk of death (n=112). When we examine the drugs that cause these adverse events, we encounter morphine (n=1173, 74%) and meperidine (n=303, 19%), which often used in daily anesthesia practice [2].

A study was conducted examining the association between code blue and opioids. Approximately 43% of the patients have received any form of opioid like PCA (5.2%), boluses (10.4%) or continuous infusion (5.2%) in last 24 h. The main opioids are morphine and fentanyl, while the others are hydromorphone and oxycodone [3].

Respiratory depression leads to brain hypoxia due to high amounts of opioids. The study was conducted to evaluate changes in brain oxygen levels due to administration of 4 different opioids (heroin, fentanyl, oxycodone and morphine) in freely moving rats. We know that some of these drugs have an importance in daily anesthesia practice. In this study researchers used two different localizations to measure oxygen fluctuations. A primarily substrate-specific sensor coupled with amperometry was used to evaluate brain oxygen fluctuations in nucleus accumbens (brain's motivation-reinforcement circuit). The other localization is the subcutaneous space, which is thought to reflect the systemic blood oxygen level. As a result of the intravenous administration of increasing doses of morphine, increased depression in respiration and a serious decrease in oxygen levels in both the nucleus accumbens and the subcutaneous space were observed. When fentanyl was given 4 times more than the first dose, it was observed that there was a very serious decrease

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Correspondence:
Onur Koyuncu, Department of Anesthesiology and Reanimation, Hatay Mustafa Kemal University, Tayfur Ata Sokmen Medicine Faculty, Hatay, Turkey,
E-mail: okoyuncu@mku.edu.tr

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in oxygen levels in both of the localizations. The most striking result of this study is the comparison of fentanyl with heroin and heroin-fentanyl combination. The reason why it was used as a heroin-fentanyl combination in the study is because it is known that fentanyl increases the effect of heroin used as an illegal drug. The result is that fentanyl lowers oxygen levels much faster and more sharply than heroin. This brings to mind how high the respiratory depression potential of fentanyl used in the practice of anesthesia and analgesia is. As a result, researchers argue that fentanyl is 10 times stronger than heroin in terms of respiratory depression. While morphine is the least potent of these drugs and its effects on brain oxygen were much slower and longer than the others [4].

Opioid Free Anesthesia

The undesirable effects of opioids were not limited to the acute period. Unfortunately, researches indicate that there may be a strong association between opioids and cancer. One of the important studies was related to the fact that morphine plays an active role in the development of breast cancer by stimulating angiogenesis [5]. Later studies focused on the relevance of opioids to metastasis [6]. Clues on this subject took the subject to another dimension, the relationship of opioids with recurrence and survival rates [7]. Even meta-analysis has been written about the association between opioids and breast cancer [8]. All these positive signs brought to mind the question of whether there is a relationship between opioids and cancer in other organs of the body [9]. With the contribution of opioids, 'anesthesia and oncology, friend or foe?' started to be questioned in the world of science [10].

Of course, opioids have different effects on the immune system in themselves. While morphine has positive/negative effects on the immune system, fentanyl and codeine are immunosuppressants. While tramadol is immunostimulant, buprenorphine, oxycodone, hydromorphone has neutral effects on the immune system [11]. As a result, opioids impair both cellular and humoral immune functions in humans [12]. The most important point in terms of opioid free anesthesia is that non-opioids protect natural killer cell functions and prevent cancer cell metastasis [13]. In a laboratory study on the role of mu receptors in lung cancer progression, the effect of methylnaltrexone, an opioid antagonist, was researched. In the study, human lung tissue and human non-small cell lung cancer cells have been used. Methylnaltrexone has been shown to reduce primary large cell carcinoma tumor growth and lung metastasis [14]. A retrospective study was conducted to investigate the effect of different anesthesia techniques on cancer recurrence after radical prostatectomy surgery. While epidural analgesia was applied with general anesthesia to one group of patients, and the other group was administered opioid analgesia together with general anesthesia. Prostate specific antigen was used to determine biochemical recurrence during the follow-up period. Recurrence developed much later in the group that received epidural analgesia instead of opioid analgesia. In fact, in the seventh-year follow-up, this rate almost doubled between the two groups (49 *vs.* 84) [15].

The relationship of opioids with pain and analgesia is not limited to these topics. Suzan et al. [16] have a hypothesis regarding pain and opioid use. Researchers state that the time of opioid administration is very important and argue that if it is applied during surgery (tissue damage), it increases postoperative pain. If opioid is applied postoperatively (after tissue damage), it provides reversely analgesia and also reduce opioid consumption. And they base this theory on three possible mechanisms. The first two of these mechanisms are tolerance and hyperalgesia. The last one states that while opioids act on μ receptors in the posterior horn of the spinal cord, they also decrease the activity of pain-inhibiting mechanisms in descending pain pathways [16]. We also know that opioids can increase sensitivity to noxious stimuli.

The ability of opioids to induce hyperalgesia has always been an interesting topic. Because opioids used for analgesia, unlike it has been observed that they increase pain sensitivity. The possible mechanism is that they cause up-regulation in compensatory pronociceptive pathways and the result in favor of pain in the balance of pronociceptive/anti-nociceptive pathways [17]. A meta-analysis of 27 studies including 1,494 patients about opioid-induced hyperalgesia was conducted. The effects of three different opioids (remifentanil, sufentanil, fentanyl) on postoperative analgesia and morphine consumption were evaluated. As a result, it was stated that as intraoperative opioid consumption increased, postoperative 24-h pain and morphine consumption increased. In addition, the researchers state that the agent mostly responsible for this result is remifentanil [18]. Naturally, the result of this study brings another question to mind. Is the concept of opioid-induced hyperalgesia unique to remifentanil? Studies with other opioids prove that this is not actually the case. For example, in this study, patients were divided into two groups and two different doses of fentanyl (1 μg/kg *vs.* 15 μg/kg) infusion were administered 20 min before induction under close supervision of an anesthesiologist. It has been reported that postoperative pain scores and fentanyl consumption were higher in the group receiving high-dose opioid infusion before induction [19].

Studies investigating the relationship between persistent surgical pain/chronic pain and intraoperative high-dose opioid consumption are available in the literature. In this prospective study, the effects of different anesthesia techniques on the incidence of chronic pain after thoracotomy were compared. Patients were randomized into two groups and Target control infusion (propofol + remifentanil) method was applied to both groups. The first group was high-dose remifentanil (average effect-site concentration 5.61 ± 0.84 ng/ml) with epidural analgesia started at the end of surgery, the other group was low-dose remifentanil (average effect-site concentration 1.99 ± 0.02 ng/ml) with epidural analgesia with 0.5% ropivacaine started at the beginning of the anesthesia. The surface area of allodynia measured with von Frey hairs was almost three times greater in the high-dose remifentanil group. Sixth month and end-of-study (6 to 13 months, average 9 months) DN4 scores were higher (≥ 4) in the high-dose opioid group. Numbers of the patients with pain were evaluated in the both groups. Although there was not much difference in the number of patients with persistent pain in the first month of the study, the numbers of patients were 3 times more in the third and sixth months, and even reach 4 times at the end of the study. In conclusion, it has been reported that the incidence of chronic pain is higher in patients receiving high-dose opioids [20].

The most serious problem with opioids is their potential for addiction and related deaths. We see that the rates of drug involved overdose deaths in the United States of America increased very seriously between 1999 and 2020 (approximately 19000 to 91000 deaths). We observe a similar increase in mortality, including opioids and even prescribed opioids. Despite all the precautions taken, many article titles include the concepts of 'opioid crisis, opioid epidemics, and washout opioids'. Although the United States is the country at the center of the opioid crisis, Europe and Turkey are also negatively

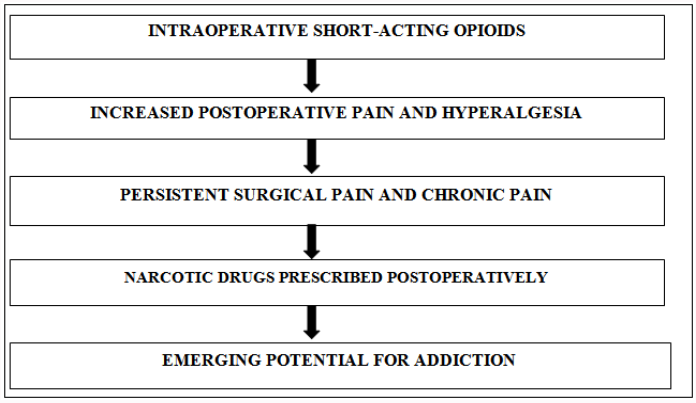

Figure 1: The role of intraoperative drugs in addiction development.

affected by this situation. Deaths due to overdose including opioids have been increasing in Turkey over the years.

There are studies in the literature that painkiller addiction can lead to drug addiction later on. According to the study, while the rate of heroin users with painkiller addiction was 21% between 2004 to 2007, it was 45% (2-fold) between 2011 to 2013. The same study reports that those who abused prescription pain relievers had a 19-fold higher incidence of heroin use than those who were never prescribed. All these determinations bring to mind the concept of 'gateway drug'. So people with potential for drug addiction have likely used a painkiller before their addiction started.

In this case, the questions that come to mind is the following: Do the anesthesiologists have any responsibility for the development of addiction potential? Are only the drugs prescribed by surgeons or algologists responsible for addictions originating from medical sources? Could it be that anesthetists indirectly compel surgeons to prescribe opioids? The answer to all these confusing questions can be explained with the help of the Figure 1.

Three terminologies are important in understanding opioid-free anesthesia, pain, nociception and anti-nociception.

1. **Pain:** An undesirable conscious state that occurs due to the perception of a noxious stimulus.

2. **Nociception:** The release of serotonin, norepinephrine, enkephalin and peptides due to the stimulation of noxius receptors.

3. **Anti-nociception:** Inhibition of the consequences that occur due to the released mediators.

As it can be understood from these definitions, we can never say that nociception equals pain. If nociception is a beginning, perception of pain is an outcome. If we liken the caterpillar to nociception, the butterfly can be likened to pain. Exactly what opioid free anesthesia seeks to achieve is to touch this life cycle before a butterfly is formed.

The primary goal of opioid free anesthesia is to provide high quality anesthesia. As in opioid-based anesthesia, a single drug is never used in the intraoperative process. It should be used as a drug combination in practice like magnesium, dexmedetomidine, lidocaine, ketamine, anti-inflammatory drugs (dexamethasone and non-steroidal anti-inflammatories), and beta-blockers. The blockage of nociceptive afferences is ensured by regional techniques (anesthesia/analgesia) and due to its benefits, it has taken its place in anesthesia practice for a very long time. It also has a very important place in the application of opioid free anesthesia. Because with a small amount of sedation followed by regional anesthesia, it is possible to complete the operation of the patient without consuming any opioids.

A meta-analysis including 21 trials of perioperative systemic lidocaine application on postoperative analgesia and gastrointestinal recovery has been published. In the results section, the researchers stated that patients who received perioperative lidocaine consumed less postoperative opioids. Similarly, gastrointestinal recovery values (time to first flatus time, time to first bowel movement) were much better in the patients of the same group. Moreover, shorter hospital stays have been reported in the meta-analysis [21].

A bariatric surgery study was performed comparing the results of intraoperative fentanyl (0.5 μg/kg/h) and dexmedetomidine (0.4 μg/kg/h) infusions. For all the patients end-tidal desflurane was adjusted to maintain the bispectral index at 45 to 50. Desflurane consumption was less and end of surgery to extubation was shorter in the dexmedetomidine group. Pain scores and morphine consumption were lower in the first two hours in post-anesthesia care unit in the same patient's group [22].

Conclusion

- Any amount of opioid we apply has serious short or long-term undesirable effects and anesthesiologists are responsible for them.
- We need to create our opioid-free anesthesia plans.
- We should provide continuing opioid education to physicians and patients.
- Opioid restriction protocols should be adopted by all health centers.

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