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OPIOID-FREE ANESTHESIA: SURGICAL VIEW.

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Abstract:

Opioid-free anesthesia (OFA) is a cutting-edge perioperative treatment strategy designed to maximize patient outcomes while reducing the negative consequences of opioid use. An extensive summary of the most recent research on OFA is given in this abstract, with special attention to the adjuvant function of dexmedetomidine (Dex). Important conclusions from numerous trials conducted in a range of surgical settings are compiled, emphasizing the advantages of OFA in lowering opiate use, and minimizing postoperative pain, nausea, and vomiting. Additionally, OFA exhibits promise in a few patient populations, such as the obese, the respiratoryly ill, and those with chronic pain; however, close observation for side effects including bradycardia and hypotension is necessary. A multimodal strategy for managing anesthesia that includes customized patient care, non-opioid analgesic drugs, regional anesthesia methods, and cutting-edge monitoring technologies is essential to the effectiveness of OFA. Even with the encouraging results, there are still issues like study heterogeneity and unsolved long-term ramifications questions. Large-scale randomized controlled trials and standardized procedures are required to provide solid proof in favor of OFA's broad use. OFA has the potential to completely transform perioperative care, increasing patient safety and improving outcomes in surgical settings with further study and cooperation.

Key words: opioid-free anesthesia, dexmedetomidine, perioperative care, postoperative pain, anesthesia management, adverse effects, multimodal approach, randomized controlled trials.

Introduction:

Globally, anesthesiologists are favoring opioid-free anesthesia (OFA) more and more [1]. It is an emerging technique and a modern research approach based on the hypothesis that avoiding intraoperative opioids could be associated with improved postoperative results. Since the limitations of opioids have been well-documented, it has been recommended—a notion that

has been long-supported in the literature—to minimize their administration across the perioperative continuum [1]. As a result, multimodal postoperative analgesia has been the standard for more than 25 years, allowing for opioid sparing and producing better results than morphine alone for postoperative analgesia [1]. Similar to this, OFA rejects the idea that opioids may be replaced by a single agent. Rather, it emphasizes the cooperative use of pharmaceuticals and/or methods to attain efficient general anesthesia without the need for opioids. These combinations could consist of sodium channel blockers (like local anesthetics), alpha-2 agonists (like clonidine and dexmedetomidine) and NMDA antagonists (like ketamine, lidocaine, and magnesium sulfate) as well as anti-inflammatory drugs (such NSAIDs and dexamethasone and local anesthetics) [1]. It is obviously not advisable to administer all of these agents/techniques to the same patient at the same time due to concerns about toxicity. Moreover, every one of these agents has known adverse consequences. While the idea of OFA is certainly intriguing, there isn't much written about it in the literature yet. The majority of the data now available is in the form of anecdotal observations from individual practitioners or retrospective case reports; few well-designed research provide scientifically supported insights into the benefits of OFA for patients. Therefore, the purpose of this review is to clarify the fundamental ideas and physiological bases of OFA, outline contemporary approaches to its use, and assess critically the data supporting its advantages and related hazards [1].

Opioids in Surgical Operations:

Over the past fifty years, the introductory line of anesthesia textbooks has always emphasized the dual role of opioids in anesthesia: they enable efficient analgesia while also lessening the need for hypnotic drugs [2]. Synthetic morphine, which suppressed the sympathetic nervous system and preserved hypnotic drugs without causing circulatory collapse or histamine release, transformed the field of anesthesia in the 1960s. Attenuating the response to nociceptive stimuli and, in particular, maintaining control over the ensuing cardiovascular reactions have been the fundamental goals of analgesia [2]. When synthetic opioids were first developed, they were widely accepted because they made it possible to lower the dosages of hypnotic agents that were already on the market, they improved hemodynamic stability, reduced cardiac output without sacrificing coronary perfusion, suppressed spontaneous breathing, and made mechanical ventilation easier. Opioids were quite successful at blocking ascending nociceptive stimuli. However, since pain and nociception are two different phenomena, it's important to understand the differences between them. Nociception is the signal that noxious receptors have been activated, whereas pain is the subjective unpleasant experience of a noxious stimulus. The suppression of the effects of noxious receptor stimulation is known as antinociception. It is possible for nociception to be painless, for example, when under general anesthesia. Therefore, "intraoperative management of the consequences of noxious receptor stimulation" or "regulation of the autonomic nervous system response to nociception" would be more appropriate terms to use instead of the more widely used "intraoperative analgesia" [3]. From a physiological standpoint, serotonin, norepinephrine, enkephalin, and peptides are among the neuromediators

involved in nociception pathways. Thus, manipulating other neuromediators—rather than only enkephalins—can result in antinociception [4]. Opioids are therefore not necessary for general anesthesia [3]. But the current problem is that there are no accurate and reliable intraoperative nociception monitoring techniques [4].

Limiting Opioid Use:

Over the past twenty years, there has been a noticeable improvement in the treatment of pain in recent years [5]. A portion of this progress has been ascribed to the deliberate abuse of opioids. But the widespread and heavy use of opioids at high doses has revealed some of its drawbacks, such as decreased effectiveness in controlling pain during movement, dose-dependent adverse effects that can seriously harm patients and postoperatively delay rehabilitation, dose-dependent hyperalgesia that paradoxically exacerbates both acute and chronic pain, immunomodulatory effects that may have a deleterious effect on infectious or malignant conditions, and worries about possible neurotoxicity [7]. Moreover, the continuous "opioid crisis" in North America has been exacerbated by anesthesiologists and perioperative healthcare providers' overprescription of opioids [8,9]. When opioids were first supplied to patients for acute pain, particularly pain following surgery, they have shifted to acquiring these medicines illegally, frequently turning to more accessible, more affordable, and often more hazardous street drugs [10]. This issue has been linked to both opioid medication for chronic pain and perioperative prescriptions; anesthesiologists have also been implicated [9]. The results have apparently been disastrous, with over 60,000 adult US drug overdose deaths in 2017 [12]. The need to avoid using opioids during general anesthesia and the postoperative period is highlighted by these factors.

In fact, modern postoperative analgesia techniques prioritize opioid sparing, which is consistent with the balanced analgesia principle that was explicated by Kehlet [1] more than twenty-five years ago. To maximize pain relief while minimizing the side effects connected with particular analgesic medications, this strategy promotes combining analgesics from multiple classes and/or using regional anesthetic techniques. Similar changes may be seen in intraoperative anesthesia practice, which went from single-agent to opioid-based to multimodal or balanced anesthesia in the end. As of right now, opioid-free anesthesia (OFA) is possible [13], but there is still a dearth of data addressing "opioid-free anesthesia and analgesia (OFAA)" during the course of the perioperative period. The issue of OFAA persists because there is inconsistency in the reduction of postoperative opioid intake following a large decrease in intraoperative opioid use [14]. Susan et al.'s hypothesis [15] contends that the timing of opioid administration is crucial because, when given during surgery (i.e., during tissue injury), opioids worsen acute postoperative pain; but, when given postoperatively (i.e., after tissue injury), opioids have an analgesic effect. This theory is in line with the idea of OFA, which involves refraining from using opioids during surgery.

Anesthesia without Opioid:

Opioid-free anesthesia (OFA) is a multimodal strategy that uses a combination of medications and methods to provide anesthesia with as little or no intraoperative opioid use as possible. When possible, regional anesthesia/analgesia is the method of choice since it efficiently blocks nociceptive afferents and produces benefits that have been scientifically shown [16]. When regional anesthesia is not an option, a number of additional anesthetic drugs have sympatholytic qualities and help lower the amount of opioids used during surgery: When given intravenously, lidocaine blocks sodium channels, inhibits the excitation of peripheral neurons by nociceptive stimuli, binds to NMDA receptors, and has anti-inflammatory effects. Clinical evidence from a variety of surgical specialties, including spine and abdominal surgeries, demonstrates that these effects translate into analgesic benefits, morphine sparing, shortened hospital stays, faster recovery of gastrointestinal transit, decreased incidence of nausea and vomiting, and accelerated postoperative rehabilitation [17]. By opposing NMDA receptors, ketamine reduces postoperative hyperalgesia. Ketamine has been shown in meta-analyses to have positive benefits on the intensity of postoperative pain, the reduction of pre- and postoperative opioid intake, and the prevention of chronic postoperative pain [19]. Ketamine also helps to maintain intraoperative blood pressure stability [20]. By preventing intracellular calcium flux, magnesium sulfate functions as a noncompetitive antagonist of NMDA receptors. Some investigations have suggested that intraoperative magnesium delivery reduces the need for intraoperative opioids, notwithstanding the paucity of data [21]. Moreover, magnesium infusion has been shown to significantly reduce intraoperative heart rate variability, according to recent meta-analyses [20].
NSAIDs and anti-inflammatory medications like dexamethasone are good substitutes for opioids. When compared to morphine alone, NSAIDs, in particular, show a significant reduction (about 50%) in morphine intake, which leads to lower postoperative nausea and vomiting, sedation, duration of postoperative ileus, and improved pain scores [22]. When given as a single dose at the start of surgery, dexamethasone at the recommended doses for preventing nausea and vomiting (i.e., 8 mg) has been linked to morphine savings, decreased postoperative nausea and vomiting and fatigue, and enhanced postoperative rehabilitation [23].

Hemodynamic stability-promoting medications are essential to OFA tactics. Clonidine and dexmedetomidine are examples of alpha-2 agonists that directly affect the sympathetic nervous system, promoting hemodynamic stability. Both substances provide analgesic, antiemetic, and anxiolytic effects by stimulating alpha-2 adrenergic receptors in the central nervous system [24]. Dexmedetomidine exhibits better morphine sparing effects than clonidine because to its shorter half-life and onset, but both medications include a risk of bradycardia and hypotension [25]. Research has demonstrated that, when compared to clonidine, dexmedetomidine results in higher morphine savings without appreciably delaying postoperative recovery [26]. The administration of dexmedetomidine, however, may raise the risk of bradycardia following surgery, albeit its clinical importance is still unknown [27]. Additionally,

studies and meta-analyses have suggested that beta blockers help maintain hemodynamic stability during OFA by reducing postoperative and intraoperative opioid intake as well as nausea and vomiting. Nonetheless, the administration of beta-blockers during surgery is linked to certain adverse consequences, such as an elevated risk of stroke [36].

Benefits of Opioid Free Anesthesia:

Without opioids, none of the aforementioned medications can provide anesthesia on their own. Nonetheless, their amalgamation with contemporary anesthetic and surgical methodologies offers a substitute for the utilization of opioids. Hanci et al. [37] examined the intubation circumstances when either fentanyl or dexmedetomidine was used in conjunction with lidocaine or propofol for anesthesia. They discovered that although the dexmedetomidine group had more bradycardia (with a lower limit of 60 bpm) than the fentanyl group, which showed greater hypotension, the intubation conditions in the dexmedetomidine group were better. There were no significant side effects noted. Comparing fentanyl and dexmedetomidine during inhaled desflurane anesthesia for bariatric surgery was the focus of another investigation [38]. Decxmedetomidine produced superior analgesia and resulted in a reduction in the need for morphine and desflurane at similar levels of anesthesia as were seen by BIS.

It has been shown that opioid-free anesthesia (OFA) dramatically lowers postoperative nausea and vomiting (PONV). Comparing intravenous anesthesia combining propofol-dexmedetomidine-ketamine with inhaled anesthesia containing opioids, Ziemann-Gimmel et al. [39] demonstrated a 17% reduction in the risk of PONV. In a more recent study, Mulier et al. compared opioid-based anesthesia (propofol, rocuronium, sufentanil, and dexmedetomidine) with current OFA (propofol, rocuronium, lidocaine, and ketamine) in 50 patients undergoing bariatric surgery [40]. Better recovery, increased comfort (measured by the QoR-40 score), less surgical pain with less morphine used, decreased PONV, and fewer cases of postoperative oxygen desaturation were all linked to OFA. Mulier et al. conducted a retrospective analysis on 9246 patients receiving bariatric surgery in a different study [41], and they found that OFA was linked to less postoperative problems. The advantages of OFA have also been emphasized by meta-analyses [42, 43, 44]. However, given the significant degree of heterogeneity (e.g., 83% in Frauenknecht et al. [42]) among the included studies, care should be used when interpreting these results. Furthermore, some of the studies included in these meta-analyses used dexmedetomidine in addition to opioids. Additional carefully planned large-scale research is required to fully show the advantages of OFA for patients. There are currently 14 active trials related to this subject listed on clinicaltrial.gov.

Special Indications of Opioid-Free Anesthesia:

Opioid-free anesthesia (OFA) has the potential to be extremely beneficial for patients who are most susceptible to the negative effects of opioids. This includes people who are more vulnerable to the respiratory depressive effects of opioids, such as obese patients and those with respiratory insufficiency. When a patient is obese and has sleep apnea syndrome, the effects of

morphine administration might cause irregular respiratory cycles, which are characterized by alternating respiratory depression and airway blockage [45]. As a result, research showing dexmedetomidine's benefits during surgery is frequently carried out on obese patients [43]. The advantages of dexmedetomidine-assisted morphine-free anesthesia in super-obese patients (BMI > 50 kg/m2) have also been demonstrated by clinical cases and research [22, 23]. To fully assess the advantages of OFA in these patient populations—as well as in individuals with obstructive bronchopneumopathy or respiratory insufficiency, for which there is currently little data—more research is needed.

Patients who have preoperative opioid use and/or persistent pain may also benefit significantly from OFA. These patients are more likely to require larger doses of postoperative opioids due to the possibility of having significant acute pain following surgery [46]. Additionally, data points to an increased risk of chronic post-surgical pain as a result of this increased opioid exposure [46]. OFA may lessen the need for opioids in this patient population by preventing intraoperative opioid use and, as a result, decreasing the activation of NMDA receptors linked to opioid-induced hyperalgesia. This could help to attenuate both acute and persistent postoperative pain. However, because there is insufficient information at this time, this theory is yet unverified.

The involvement of opioids in the growth of tumors during cancer surgery is complicated and poorly understood. Opioids have been linked to impairments in immunological response, inflammation, angiogenesis, and cell proliferation, although it is unclear how specifically they affect the recurrence of cancer [47]. Contradictory clinical data exist on the possible effects of opioids on cancer recurrence, and at this time, not enough evidence exists to support the recommendation that opioids be avoided following cancer surgery. Lastly, it makes sense to hypothesize that lengthier, more painful procedures would benefit more from opioid-sparing techniques. To support this premise, however, well-designed randomized controlled trials (RCTs) are required.

Special Research About Opioid-Free Anesthesia:

A variety of studies have investigated the efficacy and safety of opioid-free anesthesia (OFA) using dexmedetomidine (Dex) in different surgical contexts. Feld et al. (2006) [38] conducted a study involving 20 patients undergoing bariatric surgery, comparing Dex (0.5 mcg/kg bolus + 0.4 mcg/kg/h infusion) with fentanyl. They observed pain reduction in the Dex group, albeit with a higher incidence of bradycardia and hypotension compared to fentanyl. Similarly, Turgut et al. (2008) [49], in a study with 50 spine surgery patients, found that Dex (0.6 mcg/kg bolus + 0.2 mcg/kg/h infusion) led to reduced postoperative nausea and vomiting (PONV) and delayed rescue analgesia, albeit with more hypotension compared to fentanyl. In another study by Tufanogullari et al. (2008) [50], involving 80 bariatric surgery patients, Dex (at various doses) resulted in reduced postoperative morphine consumption, antiemetic use, and post-anesthesia care unit (PACU) length of stay (LOS), although hypotension was more common

with Dex. Hanci et al. (2010) [37] compared Dex (1 mcg/kg bolus) with fentanyl during intubation, finding superior intubation conditions with Dex, albeit with a higher incidence of bradycardia. Jung et al. (2011) [52] observed increased sedation with Dex in a study involving 50 hysterectomy patients. Zieman-Grimmel et al. (2014) [39] reported a reduction in PONV with Dex in 124 bariatric surgery patients, while Ciftci et al. (2015) [53] found Dex to be associated with less desaturation during intubation in 70 patients with mandibular fractures. Hwang et al. (2015) [54] reported reduced postoperative pain, rescue analgesia, and PONV with Dex in 40 spine surgery patients. Bakan et al. (2015) [28] found decreased postoperative pain and morphine consumption with Dex in 80 cholecystectomy patients, although heart rate (HR) and blood pressure (BP) were lower compared to fentanyl. Similarly, Choi et al. (2017) [55] observed reduced PONV and prolonged PACU length of stay with Dex in 80 thyroidectomy patients, again with lower HR and BP compared to remifentanil. Finally, Mullier et al. (2018) [40] reported reductions in postoperative desaturation, PONV, pain, and opioid consumption with Dex in 50 bariatric surgery patients. These studies collectively suggest the potential benefits of OFA with Dex across various surgical scenarios, although careful monitoring for adverse effects, particularly bradycardia and hypotension, is warranted.

Conclusion:

In conclusion, the concept of opioid-free anesthesia (OFA) represents a promising paradigm shift in perioperative care, aiming to mitigate the adverse effects associated with opioid use while optimizing patient outcomes. The multitude of studies examining the efficacy and safety of OFA, particularly when utilizing dexmedetomidine (Dex) as an adjuvant, underscores its potential as a viable alternative to traditional opioid-based anesthesia. The findings from these studies reveal several key insights into the benefits and challenges of OFA implementation across various surgical contexts. Firstly, OFA, when combined with Dex, has consistently demonstrated advantages such as reduced postoperative pain, nausea, and vomiting, as well as decreased opioid consumption, leading to enhanced recovery and improved patient satisfaction. Moreover, OFA has shown potential in specific patient populations, including obese individuals, those with respiratory insufficiency, and chronic pain sufferers, where the deleterious effects of opioids are particularly pronounced. However, careful consideration must be given to the occurrence of adverse events such as bradycardia and hypotension, which are more prevalent with Dex administration. Furthermore, the success of OFA is contingent upon individualized patient care and a multimodal approach to anesthesia management. While Dex serves as a cornerstone in many OFA protocols, its optimal dosing and administration require meticulous attention to patient characteristics and surgical requirements. Additionally, the integration of other non-opioid analgesic agents, regional anesthesia techniques, and advanced monitoring technologies are essential components in achieving the desired outcomes of OFA while ensuring patient safety.

Despite the promising findings, several challenges and unanswered questions remain. The heterogeneity of study designs, patient populations, and outcome measures across the existing

literature highlight the need for standardized protocols and large-scale randomized controlled trials to establish robust evidence supporting the widespread adoption of OFA. Moreover, further investigation is warranted to elucidate the long-term implications of OFA on patient recovery, chronic pain management, and cancer recurrence, as well as its cost-effectiveness and feasibility in different healthcare settings. In summary, while OFA holds great potential in revolutionizing perioperative care, its implementation requires a balanced approach that considers both the benefits and challenges associated with opioid-free anesthesia. Through continued research, innovation, and collaboration among clinicians, researchers, and policymakers, OFA has the opportunity to become a cornerstone of modern anesthesia practice, improving outcomes and enhancing the quality of care for patients undergoing surgical procedures.

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