Review Article

The progress in the clinical application of opioid-free anesthesia: a narrative review

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Background and Objective: Opioid-free anesthesia (OFA) is a new concept of anesthesia, but its evaluation is still controversial in the domestic and international anesthesiology community. This review summarizes the latest research progress, the advantages, the disadvantages of OFA, clinical applications as well as current challenges and perspectives. Studies have shown that opioid abuse and misuse produce a series of serious problems, and weighing their advantages and disadvantages, the rational use of opioid analgesics in anesthesia and pain management has attracted the attention of scholars at home and abroad. Although opioid use in our surgical patients is currently low, there is a clear upward trend, so anesthesiologists should actively confront the issue of opioid side effects and its abuse and addiction. Over the past 30 years, postoperative pain management efforts have been driven by the idea of reducing/eliminating postoperative opioids. However, in line with modern concepts of anesthesia, we should actively explore ways to eliminate opioids in the perioperative period in order to achieve a balanced, opioid-free approach to anesthesia (i.e., OFA).

Methods: PubMed, Cochrane, and Scopus databases were searched with related keywords. All publication types in English that were related to adult humans between December 1993 and December 2021 were included.

Key Content and Findings: Cancer surgery and head, neck, and maxillofacial surgery may be potential indications for OFA.

Conclusions: OFA, as part of a multimodal approach to anesthesia, has been shown to be effective in specific types of surgery. We should be fully researched and developed.

Keywords: Opioid-free; opioid-free anesthesia (OFA); multimodal anesthesia

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Introduction

The use of opioids for pain relief dates back to the 17th century, and with the development of medical treatment and the research and development of opioids, opioids have been widely used in clinical treatment, among them, especially, strong opioids have become the main drugs for the treatment of acute pain and chronic pain due to their powerful analgesic effects (1). However, opioids are a double-edged sword, bringing effective analgesia along with other inevitable side effects, such as respiratory depression, nausea and vomiting, pain allergy, immunosuppression, skin pruritus, myoclonus, and other serious side effects. In response to the adverse effects associated with the perioperative use of opioid analgesics, retrospective studies have indicated that patients who experienced these adverse

effects had poor regression, long hospital stays, and high readmission rates, leading to increased medical costs and thus reduced patient satisfaction (2). Recent studies on opioids have shown that perioperative opioid use may be associated with increased postoperative adverse event morbidity and mortality and is strongly associated with postoperative recurrence or metastasis in tumor patients (3).

With the introduction of the concept of "comfort medicine", the medical community has paid more attention to pain management, hoping to avoid or reduce the occurrence of adverse effects with effective analgesia. Opioid-free anesthesia (OFA) is a multimodal anesthetic strategy that combines multiple non-opioid drugs and/or techniques to obtain high-quality anesthesia without the use of opioids (4). The mechanism of action of opioid analgesics is to act on opioid receptors thereby producing blockade of nociceptive nerve conduction and transmission. Studies have shown that this anti-injurious sensory transmission can be obtained by interfering with various neural mediators, not exclusively through opioids (5). Several OFA regimens have been published, all of which include the use of a large number of non-opioid medications, resulting in a significant reduction in the need for postoperative opioids. For example, intravenous lidocaine blocks sodium channels and peripheral neuronal firing induced by injurious stimuli, inhibits N-methyl-D-aspartic acid (NMDA) receptor, exerts analgesic and hypnotic effects and suppresses the autonomic nerves system (ANS) response to surgical stress; ketamine produces analgesic and hypnotic effects and prevents postoperative nociceptive hypersensitivity; colistin and Dexmedetomidine stimulate α-2 adrenergic receptors located in the central nervous system, producing sedative, hypnotic, anxiolytic, sympatholytic and analgesic effects, and is a good adjuvant for OFA; non-steroidal anti-inflammatory drugs (NSAIDs) can reduce the use of morphine by 50%, and both NSAIDs and dexamethasone can produce analgesic effects. In addition, techniques such as nerve blocks, needling, and local infiltration of local anesthetics can provide analgesia (6). And OFA fits perfectly into the concept of enhanced recovery after surgery (ERAS) with multimodal anesthesia and pain management, which can significantly improve patient prognosis, reduce the incidence of postoperative adverse effects, and promote patient recovery (7). This review summarizes the latest research progress, the advantages, the disadvantages of OFA, clinical applications as well as current challenges and perspectives. We present the following article in accordance with the Narrative Review reporting checklist (available at https://joma.amegroups.com/article/view/10.21037/joma-22-7/rc).

Methods

Literature search (information sources; search)

A literature search for literature between December 1993 and December 2021 was performed using the PubMed, Cochrane, and Scopus databases. The following keywords were used in the search: "opioid-free"; "analgesia"; "opioid-free" AND "anesthesia" OR "analgesia"; "Enhanced Recovery After Surgery" OR "ERAS"; "opioid". The literature search was conducted between January 1 and 3, 2022.

Eligibility criteria and study selection

Studies were included if they: (I) involved the use of OFA; (II) were relevant to humans; (III) were clinical studies or meta-analyses; (IV) published between December 1993 and December 2021; (V) and the full text of the study results were published in English. The titles and abstracts of all pieces of literature were screened for relevance. All records identified through searched databases and other sources were firstly screened for duplicates. The remaining records were screened for relevance by title and abstract. Then the full texts of the remaining articles were retrieved and screened for inclusion in the qualitative synthesis. Additional studies were identified from the references of screened articles. All full-text articles were identified by QW, checked and approved by MX to ensure that they met the inclusion criteria and could be included for review (*Table 1*).

Benefits of OFA

Reducing the incidence of perioperative adverse effects

Perioperative opioid use is associated with respiratory depression, impaired gastrointestinal function, postoperative nausea and vomiting (PONV), pruritus, urinary retention, postoperative delirium, and opioid addiction. A meta-analysis including 33 RCT studies showed that OFA had a strong and long-lasting antiemetic effect compared to opioid anesthesia. This effect was clinically important, with a 54% reduction in nausea and a 66% reduction in vomiting in the Post Anesthesia Care Unit (PACU). These results conclude that OFA is a very effective technique for the prevention of PONV (8). In a randomized controlled

Table 1 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	January 1 and 3, 2022
Databases and other sources searched	PubMed, Cochrane, and Scopus databases
Search terms used (including MeSH and free text search terms and filters)	Search terms: "opioid-free", "analgesia", "opioid-free". "anesthesia", "analgesia", "Enhanced Recovery After Surgery", "ERAS", "opioid"
	Search strategy of PubMed database: (((((((opioid-free) OR (analgesia)) OR (anesthesia)) OR (opioid-free anesthesia)) OR (opioid-free analgesia)) OR (Enhanced Recovery After Surgery)) OR (ERAS)) OR (opioid)
Timeframe	Between December 1993 and December 2021
Inclusion and exclusion criteria (study type, language restrictions, etc.)	Inclusion criteria:
	(I) Involved the use of OFA
	(II) Were relevant to humans
	(III) Were clinical studies or meta-analyses
	(IV) Published between December 1993 and December 2021
	(V) English-language article
	Exclusion criteria:
	(I) Study was written in non-English language
	(II) Narrative overview
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	The titles and abstracts of all pieces of literature were screened for relevance. Additional studies were identified from the references of screened articles. All full-text articles were identified by QW, checked and approved by MX to ensure that they met the inclusion criteria and could be included for review
Any additional considerations, if applicable	None

study of 80 gynecologic lumpectomies, patients were randomized into two groups: the opioid-based anesthesia (OA) group with opioids and the OA group without opioids. The primary prognostic index was the QOR-40 at 24 hours postoperatively, and the secondary prognostic index was the postoperative numeric rating scale (NRS), time to first rescue analgesia, number of rescue analgesia, and incidence of PONV. The results showed that the OFA group was significantly better than the OA group in terms of adverse events, such as improved quality of life the next day, prolonged postoperative analgesia, and reduced incidence of PONV. In addition, it reduces the need for isoproterenol and maintains intraoperative hemodynamic stability and reduces opioid consumption in the PACU (9). Not only does OFA significantly reduce opioid-related adverse effects in all types of surgery in adults, but the significant benefits of OFA protocols have also been highlighted in studies of pediatric patients. In a study of pediatric patients undergoing hand surgery and tonsillectomy, the incidence of PONV, use of postoperative analgesics, and time to discharge criteria were reduced in the OFA group compared to the OA group (10-12); in addition to being evaluated in prospective studies, a de-opioidized approach to surgical pain management has also been shown to be beneficial in patients presenting with complications or who are unable to use opioid patients on the regimen are beneficial. For example, morbidly obese patients prone to respiratory depression, patients at high risk of opioid-induced PONV, postpartum patients, or patients with opioid-induced delirium have been shown to benefit from this technology (13). An analysis of the MarketScan database (including patients who used opioids during emergency or hospitalization) showed that patients with opioids in their prescriptions incurred higher overall

health care resource utilization costs than patients without opioids in their prescriptions ($49,766:$19,875) (14). Recent studies have shown that OFA can reduce the incidence of adverse reactions such as respiratory depression, nausea and vomiting, reduce the use of postoperative opioid analgesics, reduce the risk of opioid abuse and addiction, and also improve patient prognosis, promote patient recovery and functional recovery, and shorten the length of hospital stay, thereby reducing medical costs, alleviating the financial burden on patients, improving medical satisfaction, improving medical resource utilization, and reducing healthcare costs.

Reduce tumor recurrence and metastasis

Opioid analgesics may promote tumor metastasis and recurrence. The main goal of treatment for patients with advanced cancer pain is to provide analgesia, reduce the patient's adverse experience, improve quality of life, and prolong survival. Morphine, the classic and "golden standard" drug, has been the main treatment for cancer pain and chronic pain, but it also has side effects such as immunosuppression, constipation, and addiction. This means that cancer pain patients who have been using opioids such as morphine for a long time may be able to escape from cancer pain with dignity, but are not immune to the risk of tumor spread and metastasis. Studies have shown that opioids may promote tumor cell growth by suppressing cellular immunity and stimulating angiogenesis. Therefore, perioperative opioid use may affect the long-term regression of patients undergoing cancer surgery. Research data suggest that perioperative opioid use can produce cellular and humoral immunosuppression by suppressing immune cells such as macrophages and B cells (15). In addition, Neeman *et al.* (16) showed that morphine promoted angiogenesis and cancer cell growth in ER-negative breast cancer tissues in both *in vivo* and *in vitro* experiments. In contrast, tramadol has no immunosuppressive effect, although it also acts on mu receptors. The results of a retrospective analysis of breast cancer patients from 2005 to 2010 showed that postoperative pain control with tramadol in breast cancer patients significantly reduced postoperative recurrence and mortality, and *in vitro* experiments showed that tramadol exerts antitumor effects through adrenergic receptor pathways that inhibit proliferation, induce apoptosis, and act on 5-HT receptors and TRPV 1 (17).

Opioid-free analgesics or techniques may have a negative modulating effect on tumor metastasis and recurrence. OFA achieves a negative modulating effect on tumor metastasis by using drugs or techniques such as ketamine, dexmedetomidine, local anesthetics, and nerve blocks instead of opioids by nodal opioid effects. A retrospective analysis of surgical patients with aggressive prostate cancer (18) showed that recurrence of prostate cancer was reduced by 57% through epidural analgesia combined with general anesthesia than in patients with opioids combined with general anesthesia. Studies have analyzed that most amide local anesthetics not only reduce the use of opioid analgesics, but also produce antitumor effects by inhibiting the proliferation and metastasis of tumor cells and inducing their apoptosis through various pathways such as inhibiting the production of various cytokines or blocking nerve conduction (19). propofol-paravertebral anesthesia (PPA) is a unique combination of paravertebral nerve blocks (PVBs) and isoproterenol that modulates the cellular microenvironment during surgery (20). A small sample randomized controlled study showed that PPA has attenuated perioperative immunosuppression (21). Another study that included 120 patients undergoing surgery for esophageal cancer compared general anesthesia, PVB combined with general anesthesia, and epidural anesthesia combined with general anesthesia, and found that PVB or epidural anesthesia combined with general anesthesia improved perioperative immune function and long-term outcomes in patients undergoing surgery for esophageal cancer (22). However, recent studies have also shown that regional anesthetic analgesia (paravertebral block and propofol) did not reduce breast cancer recurrence after radical surgery compared with volatile anesthetics (sevoflurane) and opioids, and the proportion and severity of persistent breast incision pain were similar. Clinicians can choose either regional or general anesthetic analgesia and do not affect breast cancer recurrence and persistent incisional pain (23). Therefore, the role of opioids potentially promoting tumor metastasis recurrence still needs further in-depth study.

Disadvantages of OFA

Hemodynamic instability

In addition to producing effective analgesia during anesthesia, opioids also stabilize hemodynamics by depressing the sympathetic nervous system. A controlled clinical trial of thoracic surgery showed a significantly higher incidence of hypertensive events in the OFA group

than in the opioid anesthesia group (24). The results in a retrospective study of the effects of de-opioid anesthesia in the postoperative period of cardiac surgery, on the other hand, suggest that OFA may be associated with certain adverse effects, such as a higher incidence of adverse hemodynamic events or adverse effects caused by toxic plasma levels. The trend towards increased use of norepinephrine and antihypertensives may be related to factors such as the increased dosage of isoproterenol, the half-life of urapidil/nicardipine, and the vasoactive effects of lidocaine (7).

Side effects of OFA

The OFA view is that avoiding intraoperative opioids will lead to better prognostic outcomes. Reducing opioids and combining multiple analgesics during general anesthesia may lead to unanticipated idiosyncratic adverse events, drug interactions, and synergistic drug-specific adverse events in patients (25). Different analgesics differ in mechanism of action, potency, efficacy, adverse effects, and drug-drug interactions. For example, regional nerve block technique may have side effects such as local anesthetic overdose intoxication and bleeding; non-opioid drugs such as NSAIDs drugs have analgesic capping doses and may be associated with abnormal platelet function, reduced gastrointestinal function and bleeding as well as abnormal renal function; acetaminophen does not inhibit platelet aggregation, gastrointestinal motility, cardiovascular activity and trigger bleeding and some other side effects associated with NSAIDs, but the analgesic effect is mild and there is no anti-inflammatory effect (4).

Lack of precise monitoring indicators

There is a lack of accurate biological monitoring metrics to monitor intraoperative injury perception. Sympathetic/parasympathetic balance is used to address adverse events associated with intraoperative injury stimulation. The shift from opioid to OFA anesthesia raises the issue of injury perception monitoring, i.e., monitoring the pathophysiological response to anesthesia and surgical stress (26). "Injury perception" is still often misunderstood as "pain", but there is a substantial difference between the two, as pain is an unpleasant subjective sensation with or without substantial tissue damage. The input of injury sensations to the central nervous system causes central sensitization, which in turn leads to acute and persistent postoperative pain, and anesthesiologists need to assess intraoperative injury sensations directly. Therefore, the development of accurate intraoperative injury sensation monitoring instruments is a major challenge for OFA (27).

Clinical application of OFA

Somatic surgeries

Somatic surgeries include thoracic surgery, cardiac macrovascular surgery, and abdominal surgery. Pain from surgery is mainly caused by injurious irritation of the skin, subcutaneous tissue and part of the peritoneal or pleural wall caused by surgery, pain caused by intra-abdominal tissue and organ damage, and medical stimuli such as indwelling drains, which can activate somatic or visceral pain; injurious stimulus signals can lead to local and central pain sensitization through the somatic nerves. Different nerve injuries and myofascial damage can easily develop into a chronic pain syndrome, resulting in a postoperative pain duration of several months.

OFA in thoracoabdominal surgery should be used with multiple anesthetic methods, combined with multiple analgesic drugs, to avoid the use of opioids and their associated side effects such as nausea and vomiting and intestinal paralysis, to avoid increasing tension in the thoracoabdominal wall, and to promote intestinal venting, early diet, bed activity, and rapid recovery. Frequently seen hernia repair surgery can be done under anesthesia such as local anesthetic infiltration of the incision, epidural anesthesia or ultrasound-guided nerve block (28). General anesthesia combined with a continuous epidural in the thoracic segment is effective in thoracic surgery and can significantly reduce the application of intraoperative opioids and reduce side effects such as nausea and vomiting. Most obstetrical surgeries are performed with intradural anesthesia, and postoperative combined with epidural or intravenous analgesic pump can help to reduce incisional pain and contraction pain. For prolonged surgery such as laparoscopic surgery, hepatobiliary, pancreatic, gastric and intestinal procedures, binary, ternary or quadruple mixtures of drugs such as lidocaine, magnesium sulfate, ketamine, dexmedetomidine, or colistin, combined or not combined with nerve block or intralesional anesthesia (if combined with nerve block or intralesional anesthesia, intravenous lidocaine should be used with caution) (29-33).

General anesthesia combined with nerve block has gained wide attention in recent years (34-36). Ultrasound-guided

nerve blocks have a well-established analgesic effect and can significantly reduce the application of opioids. For example, thoracic PVBs and erector spinae plane nerve blocks have analgesic effects similar to those of thoracic segment epidurals (37-44). The application of regional nerve blocks such as anterior serratus block, intercostal nerve block, transversus abdominis plane block and quadratus lumborum block can reduce the application of general anesthetic drugs, especially opioids, and enable early postoperative activity and functional recovery of patients, which is also a better analgesic choice (45-51).

Extremity surgeries

The sensory innervation nerves of the extremities are mainly from the somatic nerves, so preventive analgesia can be performed with a combination of analgesics with multiple mechanisms of action on the basis of epidural and peripheral nerve blocks. For short and minor surgeries, nerve blocks and intralesional anesthesia should be used as much as possible to facilitate patients' postoperative recovery and early functional exercise and to reduce the incidence of postoperative mortality and other serious complications (52). Most upper extremity surgeries can be completed with a brachial plexus block. In surgical patients undergoing arthroscopic shoulder surgery, supraclavicular combined with axillary brachial plexus block significantly reduces early postoperative pain. In patients undergoing simultaneous surgery on both upper extremities, a combination of local anesthesia with de-opioidized general anesthesia can be used (53). Intralesional anesthesia is most often used for lower extremity surgery, and continuous nerve blocks can be chosen for patients with poor cardiopulmonary function or where intralesional anesthesia is contraindicated. Nerve blocks for lower extremity surgery include lumbar from, sacral plexus block, lumbar major, lumbar interosseous groove block, femoral nerve block, sciatic nerve block, etc., with smooth intraoperative vital signs and analgesic effect lasting until the early postoperative period, facilitating early functional exercise (54).

Head and neck surgeries

Head and neck surgeries include neurosurgery, eye, ear, nose and throat, oral cavity, and some neck surgeries. Surgical trauma can affect patients' sensory and speech functions to varying degrees, which can aggravate patients' pain sensation. Severe pain that is not controlled in a timely manner can significantly increase the patient's stress response, affecting the outcome of treatment and delaying the patient's recovery. When searching for OFA in major databases, most of the studies are on thoracic and abdominal surgeries, and head and neck surgeries have been rarely studied due to their site specificity and their requirements for anesthetic management. In a study of 62 patients undergoing head and neck tumor surgery, all 62 patients completed the surgery successfully under multimodal analgesia using dexmedetomidine, lidocaine, nefopam, and sevoflurane (55). There are many types of ENT surgeries, and the distribution of nerves in various parts of the maxillofacial, oral cavity, and pharynx is very rich, and the problem of shared airway makes high demands on anesthesia management. Oral and maxillofacial surgical sites accumulate in the nasopharyngeal cavity, tongue base, floor of the mouth and anterior neck area, and postoperative tissue edema, poor lymphatic flow and swelling of the surgical site, compression of the airway and other adverse effects occur more frequently. The use of intraoperative opioids has significantly increased the incidence of postoperative nausea, vomiting, respiratory depression, and upper airway obstruction compared to other types of surgery. With the rapid development of ultrasound technology, more and more head and neck regional block techniques are being used with clinical applications, and it is believed that these studies will greatly improve the anesthetic management of patients undergoing head and neck surgery (56).

Conclusions

OFA is based on multimodal anesthesia and analgesia to avoid the use of opioid analgesics, which not only avoids opioid-related adverse effects, but also provides additional benefits. Physiologically, although the intraoperative use of opioids can significantly suppress the patient's pain, the injury stimulus has already been formed. Using OFA can block the injury stimulus transmission in the injury stimulus transmission pathway, which not only can exert analgesic effects, but also can avoid a series of adverse reactions brought about by the injury stimulus. In principle, therefore, OFA is more beneficial than harmful and practicable, however, evidence-based practice is lacked to confirm the benefits of OFA.

The feasibility of OFA has been confirmed based on existing studies showing that it significantly reduces the incidence of postoperative adverse effects in patients

undergoing surgery with diseases such as obesity, obstructive sleep apnea syndrome or opioid dependence (4). Although studies have shown that OFA can reduce tumor recurrence and mortality in anesthesia and postoperative pain treatment in patients with tumors such as gastroesophageal cancer, breast cancer, and prostate cancer, further studies are needed to show whether OFA can reduce postoperative recurrence and metastasis and mortality in tumor patients, and the mechanism of its negative regulation of tumor cells has yet to be refined (57). With the attention of a wide range of scholars on the relationship between opioids and tumors in recent years, OFA may have potentially great advantages in clinical anesthesia and analgesia for surgery in patients with tumor, and even the use of weak opioidization strategies in clinical pathways where opioids cannot be completely removed may partially play the advantageous role of opioid-free techniques. PONV and intestinal paralysis adverse effects due to opioids are a particularly serious problem after ophthalmic surgery, upper gastrointestinal surgery, and head and neck and neurosurgical procedures that may result in bleeding or cerebrospinal fluid leakage. Therefore, these procedures may be another potential indication for de-opioidizing anesthetic techniques. The main goals of perioperative medicine are to promote recovery, reduce complications, and improve outcomes, not just through the use or absence of opioids in the perioperative period, and OFA should be fully investigated and developed as a part of the multimodal approach to anesthesia. Whether OFA can be safely applied in head, neck, and maxillofacial surgery and improve the prognosis of this group of patients requires more in-depth studies by a wide range of scholars.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://joma.amegroups.com/article/view/10.21037/joma-22-7/rc

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://joma.amegroups.com/article/view/10.21037/joma-22-7/coif). MX serves as the unpaid Executive Editor-in-Chief of *Journal of Oral and Maxillofacial Anesthesia* from June 2021 to May 2026. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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