Opioid-free anesthesia: a different regard to anesthesia practice

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Purpose of review
In the past two decades, opioids have been prescribed increasingly for the treatment of various chronic pain conditions and during the perioperative period. Perioperative opioid administration is associated with well known adverse effects and recently to long-term use and poor surgical outcomes. In this context, the anesthesiologists have to face their responsibilities. The review discusses the neurophysiological basis of opioid-free anesthesia (OFA), the rational supporting its use in perioperative medicine as well as barriers and future challenges in the field.

Recent findings
OFA has gained in popularity as a way to enhance early recovery and to spare opioids for the postoperative period. Whether it is possible to deliver safe and stable anesthesia without intraoperative opioids to many patients undergoing various surgical procedures, OFA still raises questions. Accurate monitoring to measure intraoperative nociception and guide the use of adjuvants are not available. There is a need for the development of procedure-specific strategies as well as indications and contraindications to the technique. Finally, objective assessment of OFA use on patient outcomes should be recorded in large multicenter studies.

Summary
OFA stands as a new paradigm, which questions anesthesiology practice and might help to rationalize perioperative opioids use.

Keywords
intraoperative monitoring, intraoperative nociception, opioid-free anesthesia, postoperative recovery

INTRODUCTION

Perioperative opioids: from life-saving to health-threatening role

Opioids have been used for pain relief for several thousands of years and have contributed to improve the quality of life of countless number of patients including patients enduring severe postoperative pain and cancer patients. In the past two decades, opioids have been used increasingly not only for the treatment of various chronic pain conditions but also during the perioperative period. Such unconsidered utilization has led to the actual 'opioid crisis,' particularly obvious in the United States of America [1▪,2]. Recently, the anesthesiologists have been confronted to their responsibilities as perioperative opioid prescribers [1▪,3]. Among patients receiving chronic opioid therapy, treatment was started after surgery in 27% [95% confidence interval (CI)18.5–35.5%] of them [4]. There is a worrisome 5.9–6.5% new persistent opioid use after not only major but also minor surgical procedures [5▪▪]. Long-lasting postoperative use of opioids is a real concern. First, opioids do not really help to control pain in many patients as found after hip and knee arthroplasty where persistent opioid use was not associated with change in joint pain and one may question the incidence of inappropriate use [1▪]. A recent preclinical study in rats even suggests that repeated postoperative morphine doses prolong postoperative pain, perhaps leading to the persistence of postsurgical pain [6]. Finally, from overprescribed

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KEY POINTS

- OFA is possible in daily clinical practice, allowing safe and stable general anesthesia for many patients and procedures; OFA helps to prevent well known early side effects associated to opioid administration and spares opioids as analgesics for the postoperative period.
- OFA-related benefits might extend to late recovery but such benefits need to be objectively documented in large trials, for example, reduction of chronic postsurgical pain development and prevention of cancer recurrence.
- Future challenges for the development of OFA techniques include the development of accurate monitoring to assess intraoperative nociception, the implementation of surgery-specific and patient-specific protocols (rational use of the different adjuvants).
- in the actual context of 'opioids crisis,' OFA as a new paradigm and certainly as a different regard on current anesthesia practice might help to solve the problem.

postoperative opioids, the use of leftover prescriptions remain largely unknown [1▪]. After cesarean delivery, the amount of opioids prescribed exceeds largely the amount consumed without any correlation with patient satisfaction or pain control. In this context, the concept of opioid-free anesthesia (OFA) has gained in popularity but remains controversed and clearly needs scientific evidence (Fig. 1). We here will discuss the neurophysiological basis of OFA, the rational supporting its use in perioperative medicine as well as barriers and future challenges in the field.

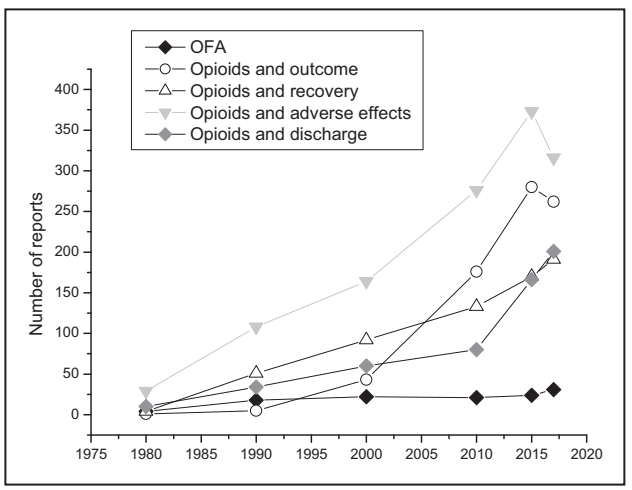

FIGURE 1. Evolution of scientific reports regarding opioid-free anesthesia and opioid-related outcomes from 1980 until 2017 (PubMed indexed publications).

Why do we (think that we) need intra-operative opioids?

The development of synthetic opioids like 'phentanyl' has revolutionized anesthesia [7▪]. In addition to potent analgesic effect, opioids promote hemodynamic stability by suppressing the sympathetic system. The early 'opioid-based anesthesia' has allowed to manage fragile cardiovascular patients. Later, better understanding of opioid-related side effects and their negative impact on patient's recovery has prompted the development of 'balanced anesthesia' where a combination of opioid and non-opioid analgesics is used to improve surgical outcome [7▪,8▪]. Simultaneously, the interest for perioperative use of so-called 'adjuvants' like ketamine, clonidine, lidocaine, magnesium sulfate, dexamethasone, among others, has increased with reports of their beneficial analgesic and antihyperalgesic properties [9]. Taking one step beyond, do we still need intraoperative opioids?

Intraoperative opioids achieve hemodynamic stability. They block the sympathetic reaction to surgical injury while maintaining blood pressure and heart rate. Currently we dispose of very specific drugs to blunt the stress response and the sympathetic reaction to the surgical incision [10,11▪▪]. Intraoperative opioids are mandatory to control intraoperative pain. By definition, pain is an 'unpleasant sensory and emotional experience …' [12]. Under anesthesia, as under other conditions where a patient is unconscious (e.g. the nociception coma scale – [13]) the term 'pain' should not be used and replaced by 'nociception,' which relates to the neural processes of encoding and processing noxious stimuli [11▪▪,12].

Then, are opioids the best way to control intraoperative nociception? Here we are facing two problems, which are the core of OFA. First, there is currently a lack of accurate monitoring to measure intraoperative nociception. Sympathetic/parasympathetic balance is generally used to address the adequacy of intraoperative antinociception [11▪▪]. As 'nociception' is still too often misunderstood as 'pain' and also because it is well established that nociceptive inputs reaching the central nervous system cause central sensitization, which in turn participates to acute and persistent postoperative pain [14,15], anesthesiologists need a direct assessment of intraoperative nociception. Second, there is now sufficient evidence to question the fact that intraoperative opioids contribute to improve postoperative outcomes in terms of analgesia and recovery. Side effects related to intraoperative opioid administration are well known [16]. Among them, neuroadaptation, that is, acute tolerance and activation of pronociceptive processes named 'opioid-induced

hyperalgesia' (OIH) interferes with opioids' ability to provide long-term analgesia [17,18].

Do we have adequate tools to monitor and ensure safe opioid-free anesthesia?

Pain is an extremely complex interaction of biological, cognitive, behavioral, cultural, and environmental factors. Under deep general anesthesia, some of these factors have a reduced impact [11▪▪]. While noxious stimuli induce autonomic neural and hormonal activation, cardiovascular and respiratory changes also have their own effects. The shift from the opioid-based anesthesia to OFA raises the problem of nociceptive monitoring, that is, the monitoring of the pathophysiological response to the anesthesia and surgical stress.

All these monitoring of 'nociception' (probably better defined as sympathetic/parasympathetic balance monitors in response to stress) were validated by a decrease of the signal with increased doses of opioids in response of electric stimulation under general anesthesia. The second step of validation has been crossed by reporting the reduction of intraoperative opioids use when patients have these monitors as a guide to administering a regular protocol of opioid-based anesthesia [19]. However, based on OFA protocols that aims to obtain sympathetic/parasympathetic balance control without opioids, these monitors do not provide conflicting information that may lead to the addition of an opioid. The underlying question remains, therefore posed: which perioperative tool could be used to treat or prevent the pain that may occur postoperatively.

Electroencephalographic recording

The power spectral analysis is an important method for feature detection in electroencephalogram (EEG) signal. Several spectral parameters derived from EEG have been proposed for measuring the depth of anesthesia (bispectral index or BIS, state entropy). The raw EEG is contaminated by various artifacts: natural variations with the age, obesity, by the anesthetic drugs [20], by the use of muscle relaxants or by the interferences because of electrocautery. Due to this cortical effect, one hypothesized that BIS monitoring could reflect the sensory processing of noxious stimuli [21]. However, the brain network called 'pain matrix' is not only associated with a cortical activity but also with a sub-cortical activity (limbic system, as well as midbrain and medullary sites) [22] with in a highly complex network. Propofol, even with burst cortical suppression, does not alter the intense noxious stimuli effects neither at the spinal level nor at the diencephalic transmission [23]. So, it does not make sense to use cortical EEG as monitoring of nociceptive surgical stimuli, particularly when the drug used had different brain targets like dexmedetomide [24] or ketamine [25]. The cerebral tissue oxygen saturation (evaluated by the Near Infrared spectroscopy: NIRS) increases with cortical-neuronal activity. As 'pain' assessment, it was not selective enough as found in human volunteers.

Autonomic nervous system evaluation

The heart rate variability (HRV) obtained from ECG signal (R-R intervals calculation) is in relation to the parasympathetic tone (vagal tone). The analgesia nociception index (ANI) is based on HRV. Despite the large number of publications of ANI-guidance intraoperative opioid administration, correlation between the level of postoperative pain and the average ANI values remains weak. Indeed, HRV may be a marker of two processes: acute stress and cardiovascular status [26]. More, large HRV variability is observed in patients with chronic pain compared with healthy individuals. Surprisingly, ANI provides very little information during the OFA anesthesia. The bradycardia induced by the use of alpha-2 agonists may partially explain this lack of information that, however, contradicts the fact that ANI might reflect opioid administration.

The cardiac baroreflex inhibition with the Cardiovascular DEpth of Analgesia (Cardean index uses ECG and noninvasive continuous blood pressure) was evaluated in few studies. As the previous tools, it cannot be used in patients with arrhythmias or pace makers, and all inotropic, chronotropic, and vasoactive drugs affect the measurements.

Signal acquisition using Pulse Plethysmographic (PPG or pulse rate variability, PRV) is a simplified tool for HRV evaluation [27]. The Surgical Pleth Index (SPI or SSI) derived from photo-plethysmographic waveform was shown to reflect the intraoperative analgesic component by changes in the microcirculation bed positioned on the finger. The new SPI analysis called autonomic nervous system state (ANSS) and ANSS index (ANSSI) based on the pulse-to-pulse interval (PPI) and the pulse plethysmographic amplitude (PPGA) could reflect the operative stress [28]. However, the sensitivity or specificity of SPI to predict postoperative pain is very low, partly in relation to intraoperative abrupt changes in vascular characteristics (bleeding, reperfusion syndrome, etc.) [29].

Alterations in electrogalvanic skin properties measured by changes in skin conductance (SCL) and number of skin conductance fluctuations (NSCF) was proposed for stress evaluation. Pain or stress is associated with increased palmar and plantar sweating, which causes increased SCL. The later may be interpreted as a surrogate marker of stress

[30] but is altered by psychological factors, sudomotor dysfunction or surgical electrocautery.

Pupillometry measures the pupil diameter [either pupil sizes or reflexes: pupillary reflex dilatation (PRD)]. It could be more sensitive to noxious stimulations but does not allow continuous monitoring. Pupillary unrest under ambient light (PUAL) was recently proposed as a tool for evaluation to the analgesic response in awake patients [31]. However, PRD is influenced by depth of hypnosis [19].

Multiparameter approaches are also currently tested like the NoL index based on nonlinear combination of HR, HRV, PRV, SCL, and NSCF [32]. Another multivariate approach (BIS, EMG, HR, BP, and PRV) was used in the construction of the combined index called Steady-state index during general Anesthesia (STAN). The interest of these new multiparameter methods of analysis is being validated under standard anesthesia protocols and under OFA.

Electromyography

Nociceptive flexion reflex measured by electromyography [RIII reflex or nociceptive flexion reflex: (NFR)] evaluates EMG response to a nociceptive stimulus. The major limitation of this technique relies on the degree of neuromuscular blockade. However, NFR evaluations have shown little value to predict postoperative pain in current clinical practice [33].

How does opioid-free anesthesia contribute to improve patient's outcome?

Even short-lasting, intraoperative management of the anesthetized patients may affect their recovery. Perioperative opioid administration induces well known adverse events like nausea–vomiting, pruritus, constipation, urinary retention, sedation and life-threatening respiratory depression. Opioids also disorganize sleep architecture and may provoke postoperative delirium [16]. Consequently, perioperative opioid-sparing strategies hasten recovery [34]. OFA helps to reduce the occurrence of early opioid-induced adverse effects [35] and spares opioids as analgesics for the postoperative period [2,7▪]. In addition, judicious utilization of 'adjuvants' contributes to enhance recovery, particularly in specific patient populations like chronic pain and opioid dependent patients [9,10,36].

Opioid-free anesthesia improves early postoperative analgesia

On the one hand, intraoperative administration of opioids in a dose-related manner induces postoperative acute tolerance and a phenomenon called OIH, which worsens pain and increases postoperative opioid analgesics consumption [37]. High doses of either intraoperative remifentanil [38] or sufentanil [39] worsen postoperative pain. Conversely, any intraoperative opioid sparing strategy, for example, locoregional analgesia, ketamine, clonidine, among others, is associated with improved postoperative analgesia including the use of ß-adrenergic agonists, which do not possess intrinsic analgesic properties [40]. More, OFA technique for laparoscopic cholecystectomy reduced postoperative pain, and specifically movement-evoked pain [41], which intensity may be predictive of chronic postsurgical pain intensity [42].

Opioid-free anesthesia may improve patient's later outcome

Opioids have the capacity to increase the area of secondary hyperalgesia surrounding the surgical wound, even without enhancing postoperative pain scores [43]. They also increase hyperalgesia in parts of the body that have not been operated [37]. The clinical relevance of enhanced hyperalgesia, in the acute postoperative period is still debated, but several studies have shown an association between its extent and the development of chronic pain after various procedures [37]. As chronic postsurgical pain is currently considered as a major concern and its prevention is an indicator of the quality of healthcares, the preventive role of OFA deserves some attention. Finally, the role of opioids in cancer recurrences after oncologic surgery is still debated but may favor OFA, which helps to spare opioids for postoperative pain control [44].

The future challenges of opioid-free anesthesia as 'state-of-the-art anesthesia technique'

As already pointed out, larger recognition of OFA as 'state-of-the art anesthesia technique' by comparison with current standard of care such as 'opioid-based anesthesia' or 'balanced anesthesia' requires an objective assessment of OFA benefits and the development of large multicenter databases. In addition, several questions remain on suspend. First, there is currently little evidence on procedure-specific strategies to conduct OFA what questions the best utilization of the different analgesic and antihyperalgesic adjuvants in the different types of surgical procedures [35,41, 45,46▪]. Moreover, is the technique useful and safe for any patient? hence, who will get the most benefit from OFA? Patients suffering from chronic preoperative pain, those under preoperative opioid treatment and patients with obstructive sleep apnea syndrome are certainly good candidates [8▪].

CONCLUSION

Despite growing evidence, opioids remain the most comfortable choice of a majority of health-care providers in perioperative medicine [9]. In their editorial, Kharasch and Brunt [1▪] mentioned three challenges in the quest to provide optimum perioperative care. At the light of previous discussion, OFA might help to fulfill these challenges. First challenge: to provide adequate perioperative analgesia. Acute postoperative pain is still poorly relieved in up to 30–55% of the patients leading to increased 30-day complications [47] and enhanced risk of persistent pain [48], thereby to decrease postsurgical outcomes. Second challenge: to minimize or prevent opioid-related side effects. Third challenge: to soar volume of opioid prescribing. Unfortunately, to date OFA does not seem to reduce the amount of opioids prescribed at discharge what clearly points to an educational problem among healthcare providers [49▪▪]. Nevertheless, as it stands as a perioperative 'philosophy,' which questions anesthesiology practice, OFA might help to rationalize perioperative opioids use. Beyond the dream of some 'opioid- phobic' individuals, OFA really brings a different regard on current anesthesia practice and probably will stand as a new paradigm.

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Conflicts of interest

There are no conflicts of interest.

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- ▪▪ of outstanding interest

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