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EXPERTS' OPINION

Opioid free anesthesia: evidence for short and long-term outcome

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ABSTRACT

The introduction of synthetic opioids in clinical practice played a major role in the history of anesthesiology. For years, anesthesiologists have been thinking that opioids are needed for intraoperative anesthesia. However, we now know that opioids (especially synthetic short-acting molecules) are definitely not ideal analgesics and may even be counterproductive, increasing postoperative pain. As well, opioids have revealed important drawbacks associated to poor perioperative outcomes. As a matter of fact, efforts in postoperative pain management in the last 30 years were driven by the idea of reducing/eliminating opioids from the postoperative period. However, a modern concept of anesthesia should eliminate opioids already intra-operatively towards a balanced, opioid-free approach (opioid-free anesthesia - OFA). In OFA drugs and techniques historically proven for their efficacy are combined in rational and defined protocols. They include ketamine, alpha-2 agonists, lidocaine, magnesium, anti-inflammatory drugs and regional anesthesia. Promising results have been obtained on perioperative outcome. For sure, analgesia is not reduced with OFA, but it is effective and with less opioid-related side effects. These benefits may be of particular importance in some high-risk patients, like OSAS, obese and chronic opioid-users/abusers. OFA may also increase patient-reported outcomes; despite it is difficult to specifically rule out the effect of intraoperative opioids. Finally, few data are available on long-term outcomes (persistent pain and opioid abuse, cancer outcome). New studies and data are required to elaborate the optimal approach for each patient/surgery, but interest and publication are increasing and may open the road to the wider adoption of OFA.

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KEY WORDS: Analgesics, opioid; Adjuvants, pharmaceutic; Anesthesia.

The introduction of synthetic opioids in clinical practice has been a turning point in modern anesthesia. However, "a saint is a sinner, too:" opioids have shown several drawbacks, and the concept of "modern anesthesia" has changed. Opioid-based anesthesia (OBA) has been questioned and perioperative medicine has evolved to the concept of balanced anesthesia. Unfortunately, balanced anesthesia too often still relies on opioids.[1] Anesthesiology has been notoriously slow to adopt new analgesic techniques,[2] but it is now time for a paradigm shift.[3] We will review the concepts behind opioid-free anesthesia (OFA) and what is actually known regarding OFA's influence on short- and long-term outcomes after surgery.

The concept of opioid-free anesthesia

The "Saint:" why are we using opioids for anesthesia?

The main question for anyone approaching OFA should be "Why are we using opioids during anesthesia?" Opioids are used to reduce hypnotic agents and to produce hemodynamic stability.

Their use is only partially justified by analgesia because they are not ideal analgesics. Indeed, "pain" (*i.e.* an unpleasant sensory and emotional experience,[4] which implies a cognitive perception) is far to happen during general anesthesia. What we call "analgesia" is actually "anti-nociception"[5] (and the resulting inhibition of surgical stress response), a complex phenomenon that should not be obtained by interfering with opioid signaling alone.[6]

The "Sinner:" why should we avoid opioids for anesthesia?

"Opioids are not ideal, but they work well and they are safe," anyone should reply. While opioids have contributed to improve pain management, the use of high doses of exogenous opioids has demonstrated the risks associated to the "hijacking of the endogenous opioid system to treat pain."[7] More, crucial administration timing separates between beneficial and counterproductive effects on pain and recovery.[8, 9]

A recent review article pointed out that the use of opioids during anesthesia does not reduce postoperative pain, but increases side effects, especially nausea and vomiting, undermining rehabilitation efforts. Further, opioids (especially synthetic, short-acting opioids, both when administered by systemic or spinal route) cause dose-dependent hyperalgesia and tolerance,[9, 10] resulting in higher postoperative pain and eventually promoting the development of persistent pain. Although conclusive evidence is still lacking on their effects on cancer survival,[11] as well as on infectious complications, reduced immune function by opioids is well documented.[12] Finally, perioperative over-prescription is part of the "opioid crisis" in North America. Perioperative prescriptions have been incriminated on the same extent of those for chronic pain.[13]

To summarize: opioids do not always work well and are definitely not always safe.

Opioid-free anesthesia in practice

The concept of OFA may be summarized as "multimodal anesthesia" to supply for OBA. A rational strategy implies: 1) combining anti-nociceptive agents to target different circuits involved in nociceptive transmission; 2) monitoring nociception; 3) explicitly using sedative effects of anti-nociceptive agents to reduce the doses of hypnotic agents; and 4) providing prolonged pain control.[1]

However, OFA implementation remains difficult because of the lack in consensus. Whether everyone agrees that OFA may be safe,[2, 14, 15] major questions remain: how to choose and to combine anti-nociceptive agents? Should the choice of agents be "patient-related" or "procedure-related?"

Despite the open questions, some drugs seem to be cornerstones for OFA approach whatever the type of surgery. Table I[16-26] summarizes the drugs currently used for OFA.

Ketamine possesses both analgesic and anti-hyperalgesic properties. Ketamine reduces postoperative pain and analgesic needs, regardless the type of surgery and pain intensity.[27] Benefits are also observed when regional anesthesia is concomitantly used. Further, ketamine reduces intraoperative blood pressure variability.[21]

As a major feature of opioids is to maintain intraoperative hemodynamic stability, OFA strategy should minimize sympathetic response. α2-adrenergic agonists (clonidine and dexmedetomidine) may provide analgesia, anti-hyperalgesia, sedation/hypnosis, anxiolysis, anti-emesis and sympatholysis.[22] Alpha-2 adrenergic agonists should be considered as hemodynamics stabilizers.

Beta-blockers (*i.e.* esmolol, propanolol) have also been proposed for OFA because of their analgesic and opioid-sparing effects. These effects are still poorly explained and their use during OFA remains uncommon.[28]

Intravenous lidocaine carries various beneficial effects related to both anti-nociceptive and anti-hyperalgesic properties. Lidocaine also acts as an anti-inflammatory drug. Combined mechanisms of action translate into clinical benefits: analgesia with morphine sparing effect, secondary reduction of PONV, earlier resumption of transit, faster rehabilitation and reduced length of stay.[24]

Magnesium sulfate is a non-competitive antagonist of NMDA receptors. The combination of ketamine and magnesium may act in a super-additive manner. Magnesium also reduces intraoperative heart rate variability.[21]

TABLE I.—*Drugs used during OFA.*

Drugs	Mechanism(s) of action	Clinical profile	Side effects (SE)
Ketamine[16]	• NMDA receptor antagonist • Homeostatic for the immune-inflammatory system[17] by reducing the production of pro-inflammatory cytokines following injury: interaction with the nuclear transcription precursor (NF-kB - nuclear factor kB) and/or reinforcement of the anti-inflammatory cholinergic reflex. This property is original and not directly related to its antagonism at the NMDA receptor and may explain why better results are obtained with ketamine than with other NMDA antagonists, such as magnesium • Ketamine has a unique profile combining analgesia and sedation by dissociative effect	Sedation Analgesia Anti-hyperalgesia Homeostatic for hemodynamics (reduced blood pressure variability)	The classic teaching is that SE are ubiquitous with ketamine use, rather than being dose dependent.15 This misconception needs to be rectified. OFA includes the use of sub-anesthetic doses of ketamine (0.3-0.5 mg/kg+0.1-0.25 mg/kg/h); recent data confirm that ketamine confers analgesia and is generally well tolerated with minor and easily manageable SE, dispelling the pervasive myth that intolerable or significant SE always occur with the use of this analgesic.[18] Stopping infusion and traditional benzodiazepines reverse psycho-mimetic SEs. Some data show that ketamine protects from emergence delirium; however alpha-2 agonists are the highly protective and are a major component of OFA.[19, 20] Hemodynamic effects are difficult to happen at low dosages, which in turn showed to lead to better stability.[21]
A2-agonists	• Block sympathetic response by binding pre-synaptic α2-receptors and blocking norepinephrine release in the CNS • Centrally, they also activate descending inhibitory pathways. • Adjuvant to local anesthetics for neuraxial anesthesia: at spinal level, analgesic and anti-hyperalgesic effects are combined with the blunting effect on the surgical stress response (mediated by pre-ganglionic block in the sympathetic chain) • Clonidine use may be limited by the longer onset of action (20 minutes) and prolonged half-life (15 hours). Dexmedethomidine is more selective for the α2 subunit of presynaptic receptors, with rapid onset (6 minutes) and shorter half-life (2 h) that are more suitable also for continuous infusion.	Sedation Analgesia Anti-hyperalgesia Sympatolysis Adjuvants for RA	SE relevance in the clinical scenario is questionable: studies has documented hypotension and bradycardia, but with optimal hemodynamic stability. Noteworthy, patient treated with remifentanyl in some studies displayed more bradycardia than those treated with dexmedethomidine. Potential contraindications and side effects are related to sympatolysis; monitoring is essential and traditional strategies should be adopted against alterations in BP or HR. Drowsiness may help to counterbalance some case of hypersalivation given by ketamine. Dosages can vary, but clonidine 4mcg/kg in 20 minutes iv before surgery resulted in substantial benefits.[22] Dosages of dexmedetomidine include a bolus of 0.5-1 mcg/kg in 10 minutes iv followed by infusion of 0.2 to 0.8 mcg/kg/min.[23]
Lidocaine	• Na-channel block • Reduces the excessive inputs from the injured peripheral nerves, suppressing development of flare formation and secondary hyperalgesia through peripheral and central mechanisms • Anti-inflammatory properties	Analgesia Anti-hyperalgesia Anti-inflammatory	There have been no reports of increased risk of life-threatening events, despite clinical studies have not always addressed adverse events. When addressed, only minor symptoms are reported. Lidocaine infusion is contraindicated for patients with anaphylaxis to lidocaine, and strict monitoring is recommended especially in the setting of known cardiac arrhythmias. Reported dosages are not uniform but bolus 1-1.5 mg/kg and infusion1-1.5 mg/kg/h iv are mostly used.[24]
Paracetamol	• Central analgesic effect that is mediated through activation of descending serotonergic pathways. Mechanism is incompletely understood, but may be due to: • Central COX inhibition or • Modulation of the endogenous cannabinoid system	Analgesic	Dose reduction recommended in liver dysfunction
NSAIDs (non-steroidal anti-inflammatory drugs)	• Peripheral inhibition of COX isoforms 1 and 2; according to the type of NSAID the inhibition can be purely COX1/2 or balanced. • Inhibition of induced inflammation within the CNS with a balanced COX1/COX2 inhibition and by acting on nuclear mechanisms in the glial cells	Anti-inflammatory Analgesics Anti-hyperalgesic	Gastric toxicity is mainly related to COX-1 inhibitors. COX-2 inhibition has been associated with increased cardiovascular (CV) morbidity; however, this association is documented for high-dose and long-term administration in chronic pain patients. There is no data supporting the higher CV morbidity associated to COX-2 inhibition for short-term exposure in the perioperative setting. Kidney failure is a concern for all NSAIDs.
Steroids	Inhibition of inflammation by nuclear mechanisms	Analgesia Anti-emetic Anti-inflammatory Adjuvants for peripheral nerve blocks	No reports of side effects even at high dose. 0.1 mg/kg iv of dexamethasone is the recommended dose for both pain and PONV prophylaxis.[25]
Magnesium	Non-competitive antagonist of NMDA receptors	Analgesia Hemodynamics homeostatic (reduced heart rate variability)	No reported cases of clinical toxicity. 20-30 mg/kg iv in 20 minutes is the recommended dose. Continuous infusion can also be used.[26]

NMDA: N-methyl D-Aspartate; CNS: central nervous system; COX: cyclooxygenase

Inflammation is the major mechanism underlying postoperative pain. Thus, drugs with anti-inflammatory properties are mandatory when OFA techniques are pursued. Beside ketamine and lidocaine, which modulate the inflammatory reaction, non-steroidal anti-inflammatory drugs (NSAIDs) blunt not only the peripheral inflammatory reaction, but also affect central inflammation in response to tissue trauma and mediate an anti-hyperalgesic effect.[29] NSAIDs demonstrate significant opioid sparing effects and are among the most effective analgesics for postoperative pain control.[30] Moreover, perioperative steroids have ubiquitous effect on inflammatory response. They showed benefit on several aspects of perioperative rehabilitation and should be (pending any contraindications) part of OFA approach: steroids affect stress response to surgery, reducing pain, nausea and fatigue.[25, 31]

Paracetamol (acetaminophen) remains a very popular analgesic/antipyretic, displaying a central effect.

Finally, regional anesthesia (RA) has a prominent role in OFA (both neuraxial and peripheral techniques. Blocking afferent inputs blunts the stress response to surgery and sympathetic activation. RA leads to effective opioid-sparing analgesia and enhanced rehabilitation. Benefits or RA can extend to the whole perioperative period by continuous technique, and might also improve long-term outcomes.[32] Further, RA and OFA should not be considered as "alternatives" and do not exclude each other, improving pain relief once combined.[33] RA should be therefore implemented in any OFA protocol, whenever possible and not contraindicated.

OFA and patient related outcomes: evidences for improvement of short and longer-term outcome?

With the development of perioperative medicine, patient reported outcomes (PROs)[34-36] have received more and more attention. Healthcare should be safe, timely, efficient and patient-centered.[37] The ultimate goal for clinicians taking care of surgical patients should be to ensure optimal free-disability survival. Consequently, anesthesia evolution should reflect these goals. PROs are summarized in Table II.[34-36]

Postoperative delirium and cognitive dysfunction as well as orthostatic hypotension are also part of problematic outcomes.[38] The postoperative problems have multifactorial causes (all including the use of opioids) what makes the real benefit of OFA difficult to demonstrate. Although one cannot deny their importance, the persistence of pain after surgery, the long-lasting use of postoperative opioid analgesics and the recurrence of cancer remain currently understated in the literature concerning PROs. The inclusion of chronic post-surgical pain (CPSP) and post-traumatic

TABLE II.—*Patient Reported Outcomes (PROs) after surgery and anesthesia in the literature.*

Patient's concept of anesthesia success Early outcomes[36]	Patient's comfort endpoints in perioperative medicine* Short term outcomes[34]	Clinical indicators of perioperative medicine success* Long term outcomes[35]
Vomiting	Pain intensity at rest and during movement at 24 h	Length of stay (LOS) in hospital
Gagging on tracheal tube	Nausea and vomiting up to 24 h (use of rescue antiemetic)	Infection of surgical site (at 30 days)
Pain	Quality of recovery scales**	Admission to Intensive Care Unit (<14 days)
Nausea	Time to gastrointestinal recovery (time to tolerate oral diet)	Readmission to hospital (<30 days)
Recall, awareness	Time to mobilization	Stroke (<30 days)
Residual weakness	Sleep quality	Death (<30 days)
Shivering	Delirium, cognitive dysfunctions†	Chronic post-surgical pain†
Sore throat	Orthostatic intolerance†	Cancer recurrence†
Somnolence		

*both publications are the result of Delphi process run among experts in the field. The outcomes analyzed resulted from search in highest impact factor ranked specialty journals in anesthesia and surgery; **quality of recovery (QoR) scales: are derived from initial QoR-40 scale (either QoR-9 or QoR-15 scale). These scales will measure the different aspects of global patient's recovery in five dimensions: pain, physical comfort, physical independence (*i.e.* physical well-being) and psychological support, emotional state (*i.e.* mental well-being); †other outcomes which might be affected by perioperative management.

pain in the new international classification of diseases (ICD-11) might better highlight the importance of CPSP as a major PRO after surgery.[39]

When examining the list of PROs stated in Table II,[34-36] it is clear that perioperative opioids administration negatively affects most of them. We will here focus on the impact of intraoperative OFA *versus* intraoperative OBA to affect PROs after surgery.

The available literature agrees on the fact that using OFA reduces the postoperative occurrence of nausea and vomiting by at least 20%.[40] In bariatric surgery, the effect of using OFA would even be more efficacious that using a triple antiemetic prophylaxis.[41] More, no study has demonstrated that OFA might cause higher acute postoperative pain than traditional OBA approach.[40] In contrast, intraoperative use of opioids either fentanyl or the ultra-short acting remifentanyl has been associated with higher postoperative pain and analgesics needs.[42, 43] The recent publication of Niedermayer even critically questions the intraoperative administration of remifentanyl in surgical procedures where severe postoperative pain is expected. At this purpose, the benefits of OFA might be greater in highly painful surgeries because analgesic and anti-hyperalgesic adjuvants used for OFA play a major role in the control of postoperative pain.[2] Ketamine and magnesium have been associated to reduced pain during mobilization after orthopedic procedures where patients often suffer severe preoperative pain. The quality of recovery also seems better in patients who received OFA in comparison with OBA[44] not only regarding postoperative pain but also considering emotional state (less anxiety and less depressed mood). Ketamine antidepressant effects are now recognized which show early onset and duration of a few days.[45] Also, α2-adrenergic agonists like clonidine possess anxiolytic properties that are greater than benzodiazepine or melatonin effects.[46, 47]

The intraoperative opioid dose is an independent predictor of 30-day readmission, particularly in ambulatory surgery, in relation with either pain or local surgery site infection.[48] In the available studies, OFA is associated to better outcome in term of early discharge and fewer hospital readmissions after colorectal surgery[49] and breast reduction.[50] Consequently, OFA use might be a method to improve patient and financial outcomes in surgery,[49] but economic impact is still far from being conclusively established.

As OFA promotes the more liberal use of not only loco-regional analgesia but also drugs that possess opioid-sparing properties, OFA usually allows decreasing postoperative opioids needs. This opioid-sparing effect facilitates early hospital discharge for various reasons related to the well-known side effects of postoperative opioids (*e.g.* nausea-vomiting, orthostatic hypotension, dizziness, urinary retention).[38, 51]

Sparing perioperative opioids may be of greater benefit in specific subgroup of high-risk patients. Morphine is correlated with abnormal respiratory patterns (accentuated in patients with OSAS/obesity);[52] benefits of OFA in these patients have been documented, even in the super-obese population (BMI>50)[53]or patients with chronic obstructive pulmonary disease (COPD).[54] As well, chronic opioids users/abusers suffer higher postoperative pain. Arguably, a comprehensive action on nociceptive circuits, including reduced NMDA activation, may mitigate hypersensitivity and tolerance. Ketamine specifically reduces pain scores (up to 6 weeks after surgery), opioid consumption and sedation in opioid-tolerant patients.[55, 56]

The next question concerns the benefit of OFA on postoperative opioid use after hospital discharge. Here, it is mandatory to point out the need of both health care givers' and patients' education. There is now doubt that postoperative persistent opioids' intake is associate to poorer outcome (including persistent pain, poor function, dependence and misuse). Unfortunately, OFA does not seem to affect postoperative opioids prescriptions.[57] An original study has highlighted the lack of correlation between 24-hour pre-discharge opioids use and the number of opioids prescribed at hospital discharge, what underlines that opioids are not regularly prescribed in a patient-specific manner to postoperative patients.[58] According to the aforementioned observations, OFA has little impact on persistent opioids use, except the power to invite health care providers to be more rational when prescribing postoperative analgesics.

The impact of OFA on long-term outcomes like chronic postsurgical pain or cancer recurrence may be really difficult to assess. Many confounding factors have to be taken into account in the perioperative period and very large populations of patients are required to allow consistent statistical analysis. Until now, the majority of OFA studies have only concerned a small number of patients. Ongoing studies exist on cancer anesthesia, but only retrospective data are available so far; conclusive evidence is lacking that OFA can improve cancer outcomes, despite the impact of OBA on immunity is documented.[12]

Finally: ketamine, lidocaine and alpha2-agonists can impact on hyperalgesia and pain,[59-61] even at months from surgery (especially in selected populations). As well, the use of continuous regional anesthesia may have impact for longer term pain and functional outcomes.[62] However, due to the abovementioned issues, it is still difficult to assume that OFA is able to reduce PPSP and in which specific surgical setting. This evidence, once demonstrated, may hit the road to a new concept of ERAS.[63]

Conclusions

OFA is a different approach to anesthesia, which relies on the concept of "multimodal" anesthesia. Promising results have been observed and the "to-do list" includes: 1) understanding the actual "state of the art" on OFA. While the number of publications is increasing (Figure 1), it remains difficult to quantify how frequently OFA is used in clinical practice. Many anesthesiologists are still tightly bound to opioid-based (OBA) techniques; 2) producing high quality RCTs documenting the OFA superiority. Optimal dosing and combinations of non-opioid alternative drugs should be defined. Currently, at least 30 ongoing trials can be retrieved on ClinicalTrials.gov, which will arguably produce new consensus in the future; and 3) fixing the major issue of nociceptive monitoring. Despite the initial enthusiasm, current data show that none of the proposed technologies can be reliably used in clinical practice. Promising results on measuring the parasympathetic/sympathetic balance cannot be translated on OFA, because OFA implies the modulation of sympathetic tone. In conclusion, OFA seems to be safe and positive results have already been observed on early outcomes. Much more work is needed, but this new approach of anesthesia is expected to grow in the future to overcome the limitations of opioids and to improve patient's surgical outcomes. OFA might become a "state of the art" for intraoperative anesthesia.

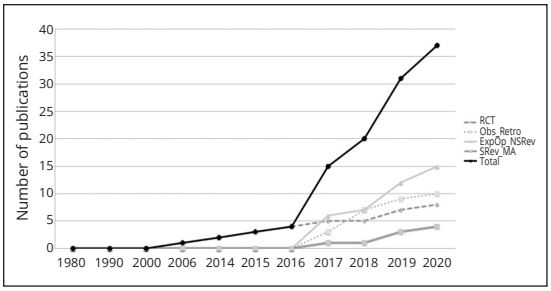

Figure 1.—Number of PubMed Indexed publications on OFA per year, according to the type of paper.
RCT: randomized clinical trial; Obs_Retro: observational and retrospective studies; ExpOp_NSRev: expert's opinions and non-systematic reviews; SRev_MA: systematic reviews and meta-analyses.

Key messages

• Traditional opioid-based anesthesia leads to short and long-term side effects. Opiods had a major role in the history of anesthesia, but they are not "ideal" analgesics. Modern approaches should switch towards an opiod-free paradigm.

• Opioid free anesthesia is possible and at least not inferior to traditional opioid-based techniques. OFA includes the use of multiple drugs and regional techniques that act together on the different mechanisms involved in pain perception.

• Opioid free anesthesia provides benefits in terms of pain relief and analgesic consumption in the postoperative period, hereby reducing traditional side effects associated with opioids (namely PONV). Other potential benefits have been advocated in the perioperative period, as well as in long-term outcome.

• Focused studies are needed in specific surgeries and patient populations. Initial evidence is promising, but specific protocols need to be defined to increase the practice of OFA.

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