Opioid-free anesthesia

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Abstract

Opioid Free Anesthesia (OFA) is emerging as a new stimulating research perspective. The rationale to propose OFA is based on the aim to avoid the negative impact of intraoperative opioid on patient's postoperative outcomes and also on the physiology of pathways involved in intraoperative nociception. It is based on the concept of multimodal anesthesia. OFA has been shown to be feasible but the literature is still scarce on the clinically meaningful benefits for patients as well as on the side effects and / or complications that might be associated with it. This review focused first on the physiology of nociception, the reasons for using or not opioids during anesthesia, and then on the literature reporting evidence-based proofs of benefits / risks associated with OFA.

Keywords: opioid-free anesthesia, opioid, ketamine, lidocaine, alpha 2 agonists

Practice points:

- OFA is a multimodal anesthesia associating drugs and/or techniques that allows a good quality general anesthesia with no need for opioids

- Anti-nociception during general anesthesia can be obtained by interfering with various neuromediators not only by interfering with enkephalins with opioids
- Studies have shown that OFA allows a postoperative morphine sparing, PONV reduction and a trend towards a reduction of opioid-related adverse events

Introduction

Opioid-free anesthesia (OFA) has become more and more popular amongst anesthesiologists around the world. It is an emerging technique and a recent research perspective based on the idea that avoiding intraoperative opioids would be associated with better postoperative outcomes. Indeed, opioids have shown their limits, and reducing opioids administration ~~ered~~, at any time during the perioperative period, has been proposed for many years in the literature. Thus, multimodal postoperative analgesia has been the gold standard for more than 25 years [1]. It allows opioid-sparing and better outcomes than morphine administered as a sole analgesic agent after surgery. OFA is based on the same concept, as one drug will not replace opioids. It is the association of drugs and/or techniques that allows a good quality general anesthesia with no need for opioids. The association can combine NMDA antagonists (ketamine, lidocaine, magnesium sulfate), sodium channel blockers (local anesthetics (LA)), anti-inflammatory drugs (NSAID, dexamethasone, LA) and alpha-2 agonists (dexmetedomidine, clonidine). Of course, for toxicity reasons all these drugs / techniques will not be administered simultaneously to the same patient. Moreover, all these drugs have documented side effects. The idea of OFA is very exciting! However, the literature remains scare on the subject. Many retrospective, case reports or single-physician experience, are available today but only few well-designed studies bringing evidence-based proofs of the benefits of OFA for the patients, have been published so far. This is why this review will first focus on the principles and physiology on which OFA is based on, then it will

detail what is known so far on how to perform OFA and finally report the evidence-based proofs of benefits / risks associated with it.

Why do we use intraoperative opioids?

Anesthesia textbooks published in the last 50 years have an identical first paragraph ~~on the~~ concerning the use of opioids during anesthesia with a double objective: ~~the objective is twofold:~~ 1) to reduce the need for hypnotic agents and 2) to ensure effective analgesia. The introduction of synthetic morphine in the 1960s ~~revolutionized~~ changed anesthesia's practice by ~~allowing~~ savings ~~in~~ hypnotic agents consumption and inhibiting ~~on of~~ the sympathetic system without cardiovascular collapse or histamine release. With regard to analgesia, the aim is to limit the reaction to nociceptive stimuli and in particular to ensure the control of the resulting cardiovascular reactions [2]. Synthetic opioids were therefore widely adopted as soon as they appeared to limit the effects of hypnotic agents available at the time, by reducing their doses, facilitating~~e~~ hemodynamic stability, reducing~~e~~ cardiac output without reducing coronary perfusion, blocking spontaneous breathing and facilitating~~e~~ mechanical ventilation. By blocking the ascending nociceptive stimuli, opioids are indeed very effective. However, pain and nociception are two different things! Pain is indeed a conscious unpleasant perception of a noxious stimulus and nociception is the stimulation of noxious receptors. Anti-nociception is ~~then~~ the suppression of the consequences of the stimulation of the noxious receptors. Nociception without pain is possible, i.e. under general anesthesia. What we routinely call "intraoperative analgesia" should indeed be called "intraoperative control of the consequences of the stimulation of noxious receptors" or "control of the autonomous nervous system response to nociception" [3]. Looking at the physiology, various mediators are involved in nociception pathways: serotonin, norepinephrine, enkephalin, peptides…etc. Anti-nociception can then be obtained by interfering with various neuromediators not only by interfering with enkephalins with opioids [4]. Then, opioids are

not ~~indispensable~~ essential for general anesthesia [3]. However, we are currently lacking accurate and validated monitoring ~~to measure~~ of intra-operative nociception [4].

Why reducing or avoiding opioids perioperatively?

After decades of under-treatment of pain, the most recent audits have shown a clear progress over the last 20 years [5]. The systematic use of opioids contributed to this advance. However, this broad and high-dose use of opioids has revealed its limits: less efficacy on pain during movement, dose-dependent side effects, which can be very disabling for the patient and delay postoperative rehabilitation, dose-dependent hyperalgesia paradoxical source of acute and chronic pain, immunomodulation that may have a negative impact on infectious or cancerous pathologies [6] and finally, doubt about possible neurotoxicity [7]. Moreover, anesthesiologists and perioperative opioids over prescriptions are part of the current so called 'opioid crisis' currently happening in North America [8,9]. Patients who were initially prescribed opioids to treat acute pain including pain after surgery transitioned to acquire their substance of abuse on the black market and often move on to use more affordable and available (but also more deadly) related street drugs [10]. Perioperative prescriptions have been incriminated [11] as well as opioid treatment for chronic pain. Anesthesiologists are also part of the problem [9]. The consequences are devastating with more than 60 000 US adult alleged to be dead from drug overdose in 2017 [12]. All these reasons explain the motivation to move away from opioids administration in the postoperative period but also during general anesthesia. Indeed, modern postoperative analgesia is based on opioid sparing. The principle of balanced analgesia described by Kehlet [1] has been prevailing for more than 25 years. The ~~prescriptions of~~ combinations of analgesics of different classes and / or techniques of regional anesthesia are recommended to optimize ~~analgesia~~ pain control while limiting the adverse ~~undesirable~~ effects ~~attributable to the different~~ of each analgesic agent~~s~~. The evolution of intraoperative anesthesia is comparable

~~similar~~. Indeed, it evolved from single agent anesthesia to opioid-based anesthesia and then multimodal or balanced anesthesia. Nowadays, balanced anesthesia without opioids (opioid-free anesthesia (OFA)) is feasible [13]. While there are evidences ~~evidence-based proofs are showing~~ that OFA is associated with benefits for the patients (cf. below), proofs are lacking concerning "opioid-free anesthesia and analgesia (OFAA)" which includes the total perioperative period. OFAA is still a challenge today. Indeed, a dramatic reduction of intraoperative opioids is not always associated with a reduction of postoperative opioids [14]. However, according to Susan et al' [15] hypothesis, the timing of administration of opioids is crucial: when administered during surgery (= tissue injury), opioids aggravate acute postoperative (= post-injury) pain, in contrast to their analgesic effect when given after surgery (= after tissue injury). The concept of OFA; i.e. no opioids during surgery, fits well with this theory.

How to perform anesthesia without opioids?

Opioid-free anesthesia is a multimodal anesthesia combining different drugs and / or techniques. Regional anesthesia/ analgesia is, of course, the best technique to reduce or avoid intraoperative opioids. Indeed, the blockage of nociceptive afferences is perfectly ensured by regional anesthesia/ analgesia and benefits have been long proven in the literature [16].

When regional anesthesia is not applicable, many other anesthetic drugs inhibit the sympathetic system and reduce the consumption of opioids perioperatively:

- Intravenous **lidocaine** administered intravenously blocks sodium channels and discharges of peripheral neurons excited by nociceptive stimuli, inhibits NMDA receptors and has anti-inflammatory properties. All these effects are clinically translated into an analgesic benefit, morphine sparing, a decrease in length of stay, an earlier resumption of transit, a reduction in the incidence of nausea and vomiting and a faster postoperative rehabilitation [17]. This has been shown in different types of surgery (abdominal but also spine surgery) [18].

- By antagonizing NMDA receptors, **ketamine** prevents postoperative hyperalgesia. Several meta-analyzes have reported a beneficial effect of ketamine on the intensity of postoperative pain, the reduction of opioid consumption per and postoperatively and the reduction of chronic pain after surgery [19]. Ketamine is also helpful in reducing intraoperative blood pressure variability [20].

- **Magnesium sulfate** is a noncompetitive antagonist of NMDA receptors by inhibition of intracellular calcium flow. Evidences are lacking, but some studies have shown morphine sparing when magnesium is administered intraoperatively [21]. Moreover, a recent meta-analysis reported that magnesium significantly reduces intraoperative heart rate variability [20].

- **Anti-inflammatory drugs** (dexamethasone and NSAIDs) are also helpful when avoiding opioids. NSAIDs ~~allow a savings of~~ spare about 50% in morphine, ~~which results~~ resulting in a reduction in PONV, sedation and duration of postoperative ileus, as well as an improvement in pain scores compared with morphine alone. ~~This morphine savings is the most interesting when compared to other non-morphine analgesics used in current practice (nefopam, paracetamol)~~ Morphine sparing effect of NSAIDs is more important than the one of paracetamol and nefopam [22]. With regard to dexamethasone, there are now numerous studies showing morphine savings associated with a reduction in PONV and fatigue and better postoperative rehabilitation with the doses recommended for the prevention of nausea and vomiting; i.e. 8 mg. The single dose administered at the beginning of the procedure (0.1 mg / kg) thus allows both a prevention of PONV and an analgesic benefit [23].

- **Drugs ensuring hemodynamic stability**:

Opioids have been used because they provide a good hemodynamic stability. It has been shown several times that intraoperative hemodynamic instability is associated with increased postoperative morbidity. Therefore, as P Forget stated [20], any strategy oriented to reduce the use of opioids should also minimize the sympathetic response triggered by surgery.

Alpha-2 agonists (clonidine, dexmedetomidine (Dex)) have been proposed to ensure this stability. They allow a direct sympathetic blockade. Thanks to their pharmacological characteristics (sedation, hypnosis, anxiolysis, sympatholysis and analgesia), they are interesting adjuvants to multimodal analgesia / anesthesia. Their antinociceptive effects are attributed to the stimulation of alpha-2 adrenergic receptors located in the central nervous system. The analgesic, anti-emetic and anxiolytic properties of clonidine are well known [24]. Its use could be limited because of a long delay of action (20 minutes) and a prolonged half-life (15 hours). Dexmedetomidine is ~~a~~ more selective agonist of alpha-2 receptors. Its delay of action ~~is shorter~~ (6 minutes) and its half-life ~~shorter~~ (2 hours) are shorter than those of clonidine. In terms of side effects, both drugs are associated with risks of hypotension and bradycardia [25]. Meta-analysis have shown that clonidine and dexmedetomidine ~~Dex provide~~ induce morphine sparing, analgesia ~~with~~ and PONV reduction [26,27]. The morphine savings of dexmedetomidine ~~Dex~~ were 3 times greater than that of clonidine [26]. This was not associated with sedative effects delaying postoperative rehabilitation. However, the use of dexmedetomidine ~~Dex~~ was associated with a higher risk of postoperative bradycardia. The clinical relevance and consequences of this side effect are hardly appreciable because none of the studies included in the meta-analysis reported major adverse events. In addition, the definition of bradycardia is unclear in all studies. When comparing intravenous anesthesia with propofol – dexmedetomidine - lidocaine with propofol – remifentanil, in laparoscopic cholecystectomies, patients receiving remifentanil ~~were experiencing~~ experienced more bradycardia than those in the dexmedetomidine ~~Dex~~ group [28]. However, some studies have chosen to study OFA with dexmedetomidine ~~Dex~~ with the objective of hemodynamic stability and controlled hypotension [29,30]. While some studies were negative [31], most studies reported a good hemodynamic stability with often bradycardia and hypotension with dexmedetomidine ~~Dex~~ (which were the objectives in these studies) [32,33]. This limitation to the systematic use of dexmedetomidine ~~Dex~~ requires further studies whose main objective will be the evaluation of side effects and their clinical consequences.

Beta blockers (BB) have also been proposed to ensure hemodynamic stability during OFA [34,35]. Studies and meta-analysis have reported benefits in reducing intraoperative and postoperative opioids and PONV. However, the literature is scarce on the subject (BB used during an OFA) and perioperative administration of beta blockers is associated with specific side effects including a doubt in increasing the risk of stroke [36].

What are the benefits of OFA?

~~The isolated administration of the previously presented drugs does not allow to perform anesthesia without opioids~~. None of the drugs introduced before allows by one-self performing anesthesia without opioids. However, their association with modern techniques of anesthesia and surgery is an alternative to the use of opioids. Hanci et al [37] compared intubation conditions during lidocaine and propofol-associated anesthesia with dexmedetomidine ~~Dex~~ or fentanyl. The intubation conditions were better in the dexmedetomidine ~~Dex~~ group. They reported more bradycardia (lower low limit: 60 bpm) in the dexmedetomidine ~~Dex~~ group and more hypotension in the fentanyl group, with no major adverse effects ~~events~~ reported. Another ~~older~~ study compared dexmedetomidine ~~Dex~~ and fentanyl during an inhaled desflurane anesthesia for bariatric surgery [38]. For a comparable depth of anesthesia monitored by BIS, dexmedetomidine ~~The Dex~~ allowed desflurane savings ~~for an identical depth of anesthesia measured by BIS~~, ~~a~~ morphine saving and better analgesia. OFA has been shown ~~Morphic sparing with OFA was shown~~ to result in a significant reduction in PONV: Ziemann-Gimmel et al [39] demonstrated a 17% reduction in the risk of PONV by comparing ~~an~~ intravenous anesthesia combining propofol-dexmedetomidine ~~Dex~~ -ketamine with an inhaled anesthesia with opioids. More recently, Mulier et al reported, in a small randomized controlled trial ~~RCT~~ (n = 50) the benefits of modern OFA (propofol, rocuronium, dexmedetomidine ~~Dex~~, lidocaine, ketamine) when compared with OBA (propofol, rocuronium, sufentanil) during bariatric surgery [40]. OFA was

associated with a better recovery, better comfort (QoR-40 score), reduced postoperative pain while consuming less postoperative morphine, reduced PONV and less postoperative oxygen desaturation. In a second ~~publication~~ study [41], performed in ~~they retrospectively reported in~~ 9246 patients who underwent bariatric surgery, they retrospectively reported that OFA was associated with less postoperative complications. Meta-analysis have also reported benefits with OFA [42, 43,44]. However, results have to be analyzed with caution as the heterogeneity of the studies included was high (i.e. 83 % in Frauenknecht et al [42]). In addition, ~~and~~ all these meta-analysis included some studies in which dexmedetomidine ~~Dex~~ was administered as the same time as opioids. More well-designed large-scale studies are definitely ~~needed~~ required to further document ~~show~~ the benefits of OAF for the patients. There are currently 14 on going trials registered on clinical trial.gov on this topic.

Are there specific indications for OFA?

Patients who can benefit from ~~this type of anesthesia~~ OFA are those who are most sensitive to deleterious side effects of opioids. Obese patients and patients suffering from respiratory insufficiency are, of course, crossing mind firstly ~~the first to come to mind~~. Morphine administration is associated with an abnormal respiratory cycle (alternating respiratory depression with airway obstruction) [45]. This is accentuated and aggravated in obese patients with sleep apnea syndrome [45]. Thus, part of the studies showing the interest of dexmedetomidine ~~Dex~~ perioperatively, were ~~made~~ performed in obese patients [43]. Several clinical cases and studies have described the benefit of morphine-free anesthesia with dexmedetomidine ~~Dex~~ in super-obese patients (BMI> 50 kg / m2) (22,23). Other studies are obviously needed to evaluate the real benefit of opioid-free anesthesia in these patients. It can also be assumed that OFA would be beneficial in patients with respiratory insufficiency or obstructive bronchopneumopathy. Data are missing to date to validate these indications.

Another subgroup of patients suffering from chronic pain and / or consuming opioids before surgery, would be another subpopulation that could benefit the most from OFA. These patients are at higher risk of ~~more intense~~ severe postoperative acute pain while consuming more postoperative opioids [46]. It has been shown that all this increases the risk of post-surgical pain chronicization [46]. One could hypothesize that reducing the activation of NMDA receptors and therefore opioid-induced hyperalgesia by avoiding intraoperative opioids could reduce postoperative acute and chronic pain and opioid needs in these patients. However, no data are currently available to confirm this hypothesis.

The question also arises for ~~oncological~~ cancer surgery (see chapter on postoperative pain after cancer). ~~The~~ Opioids impair cell proliferation, inflammation, angiogenesis and the immune response. This could participate in the evolution of the tumor. However, the interactions and cellular mechanisms involved in the role played by opioids in cancer recurrence are complex and far from fully understood, as the pain itself is immunosuppressive [47]. Clinical data on the potential implication of opioids on cancer recurrence are contradictory. No evidence-based proofs are available today to formally suggest that opioids should be avoided during surgery for cancer.

Finally, intuitively, one could suggest that the more painful and the longer the surgery, the ~~bigger~~ greater the impact of opioid-sparing strategies would be. However, well-designed RCTs are needed to confirm this suggestion.

Unanswered questions and future research agenda

OFA is a multimodal anesthesia and therefore consist of a combination of multiple drugs. Many institutions have their own ‘cocktail’, some of them are even published [48]. However, as presented above, the proofs of the benefits of such combinations of multiple drugs are still

scarce in the literature [12]. 'Cocktails' published without any evidence-based proof of a positive balance of benefits over risks should not be recommended. Moreover, the doses of each of the drugs included in the 'cocktail' are also not clearly defined especially for dexmedetomidine ~~Dex~~. As ~~presented~~ shown in table 1, doses vary from one study to another, and no formal recommendation can be formulated. The optimal dose of dexmedetomidine ~~Dex~~ allowing benefits with acceptable risks of bradycardia and hypotension has not been determined yet.

As stated by P Lavand'homme in a recent editorial [13], there is an urgent need to develop accurate monitoring of intraoperative nociception.

Finally, most publications on OFA involved patients undergoing bariatric surgery. There is a lack of studies showing benefits in other types of surgery. Procedure-specific studies and protocols are needed.

Conclusion

Some authors present opioid-free anesthesia as a new paradigm that will revolutionize and change our practices in the years to come. While it is true that multimodal anesthesia like multimodal analgesia has shown benefits, studies and data are lacking. In terms of benefits, OFA has never been studied with modern monitoring of intraoperative analgesia. Evidence-based proofs of short and long-term benefits of OFA as well as well documented intraoperative protocols are still yet to come.

Conflict of interest: Helene Beloeil has received honoraria from Orion, BBraun and Abbvie.

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Legends of the tables:

Table 1:

Randomized controlled trials comparing opioid-free anesthesia using dexmetedomidine vs opioid-based anesthesia. LOS: length of stay; HR: heart rate; MBP: mean blood pressure Dex: dexmetedomidine; NS: non-statistically significant; NA: non-applicable.

References	n	Doses of Dex	Surgery	Results in Dex group	Bradycardia (lowest HR) Hypotension (lowest MBP)
Feld, 2006 (38)	20	0.5 mcg/kg + 0.4 mcg/kg/h vs fentanyl	Bariatric	Pain reduction	HR (60), MBP (60). HR and MBP lower with Dex
Turgut, 2008 (49)	50	0.6 mcg/kg + 0.2 mcg/kg/h vs fentanyl	spine	PONV reduction Delayed rescue analgesia	HR (70): NS More hypotension with dex
Tufanogullari, 2008 (50)	80	0.2 vs 0.4 vs 0.8 mcg/kg/h vs saline	Bariatric	Reduction in postop morphine consumption, anti-emetics and PACU LOS	HR (60), MBP (60). More hypotension with Dex
Hanci, 2010 (37)	60	Bolus 1 mcg/kg vs fentanyl	intubation	OFA better	HR (60), MBP (60). HR lower with dex
Olutoye, 2010 (51)	109	0.75 or 1 mcg/kg vs morphine	Tonsillectomy (children)	NS	No bradycardia
Jung, 2011 (52)	50	1 mcg/kg + 0.2-0.7 mcg/kg/h vs remifentanil in PACU	hysterectomy	More sedation with Dex	FC: NS
Zieman-Grimmel, 2014(39)	124	0.5 mcg/kg + 0.1-0.3 mcg/kg/h vs fentanyl	Bariatric	PONV reduction	Bradycardia: NS
Cifti, 2015 (53)	70	Bolus 1 mcg/kg vs remifentanil (bolus)	intubation during mandibular fracture	Pain: NS. Dex=less desaturation	NS
Hwang, 2015 (54)	40	0.01-0.02 mcg/kg/min vs remifentanil	spine	Reduction in postoperative: pain, rescue analgesia, PONV	NA
Bakan, 2015(28)	80	0.6 mcg/kg + 0.3 mcg/kg/h vs fentanyl	cholecystectomy	Reduction in postoperative: pain, morphine consumption	HR and FC lower with remifentanil
Choi EK, 2017 (55)	80	1 mcg/kg + 0.3-0.5 mcg/kg/h vs remifentanil	thyroidectomy	Reduction in PONV. delayed extubation, prolonged PACU LOS	HR (60), MBP (60). HR and MBP lower with Dex
Mullier, 2018 (40)	50	0.5 mcg/kg + 0.25-1 mcg/kg/h vs sufentanil	Bariatric	Reduction in postoperative: desaturation, PONV, pain and	NS