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EDITORIAL

Should opioid free anesthesia be integrated in enhanced recovery protocols?

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Abstract : These last decades, Enhanced Recovery after Surgery (ERAS) protocols have grown in popularity; they recommend multimodal analgesia in order to decrease opioid requirements during and after surgery, which leads to less opioid side effects. As consequences, postoperative complications and length of hospital stay are reduced. Opioid free anesthesia seeks after the same goal as ERAS protocols. There exist several studies reporting its benefits, and sometimes its superiority to conventional opioid anesthesia, including less postoperative analgesic requirements, and decreased incidence of postoperative nausea and vomiting. Working daily with opioids as anesthesiologists, we are curious to know if ERAS protocols should integrate opioid free anesthesia. The present review summarizes the available data concerning positive impacts of opioid free anesthesia on 5 opioids side effects using Pubmed, Google Scholar and Cochrane Library. The paucity of the literature prevented us from any conclusion, but a liberal opioid use during the perioperative period should be avoided.

Keywords : opioid free anesthesia ; enhanced recovery after surgery ; multimodal analgesia ; opioids side effects; opioid crisis.

Introduction

In order to reduce postoperative complications, improve surgical outcome, and shorten hospital length of stay, Henrik Kehlet introduced, in the 90s, the fast-track surgery concept, also known as Enhanced Recovery After Surgery (ERAS). One of the key elements of ERAS is the intra- and postoperative pain control (1, 2) through multimodal analgesia (3).

It is well established that undertreated acute postoperative pain leads to multiple complications, such as respiratory or cardiovascular complications, thromboembolism events, and chronic pain (4). Opioid medications are a mainstay of acute postoperative pain management (5). Unfortunately, their effectiveness comes with side effects, which can worsen postsurgical patient outcome and increase costs (6). This is the reason why one may wonder if opioids are mandatory to insure good anesthesia? According to conventional textbooks, anesthesia is based on the triad of hypnotics, opioids and neuromuscular blockers. Opioid-sparing drugs and techniques are more and more popular with regard to ERAS protocols (7), but opioid free anesthesia (OFA) opens a new area: it breaks down the myth where opioids are a cornerstone of anesthesia.

We will here focus our review on 5 opioids side effects. Three of them (postoperative ileus, postoperative nausea and vomiting, and post-operative urinary retention) are the most common opioid side effects. The two others, opioid induced hyperalgesia and opioid abuse, are clinical challenges for anesthesiologists. In order to decrease their incidence, ERAS protocols are a good starting point. However, time has come to wonder whether integrating OFA to ERAS protocols could improve patient outcome.

Methods

We searched Pubmed, Google Scholar and Cochrane Library for relevant articles using various keywords: opioid free anesthesia, narcotic free anesthesia, multimodal analgesia, enhanced recovery after surgery, α_2-agonists, opioids side effects, opioid induced hyperalgesia, opioid epi-

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demic. There was no time limitation but a language restriction was applied (French and English). We did not find articles studying OFA associated with or compared to ERAS protocols. However, we did find studies on the incidence of opioid side effects and postoperative analgesic consumption when OFA is provided. We selected the literature according to its relevance to the topic and to the referenced keywords.

Results : Opioid side effects

Every anesthesiologist can list the adverse effects of opioids by heart. In 2002, a review found that gastrointestinal and central nervous system side effects were the most common ones, followed by urinary retention (8).

1. Postoperative ileus

In 2016, an international consensus defined the postoperative ileus (POI) as a "*…temporary inhibition of gastrointestinal motility after surgical intervention due to non-mechanical causes and prevents sufficient oral intake*" (9). It often occurs after major abdominal surgery (10). Due to numerous definitions of POI, its incidence is not easy to estimate (11): it varies from 3% to 40% after abdominal surgery (11, 12). POI slows down recovery time, and hence increases length of stay, postoperative morbidity, and costs (10, 12). Luckily, with minimally invasive surgery, the period of POI seems to be shortened (13).

During the perioperative period, multiple factors decrease gastrointestinal (GI) motility, leading to POI, particularly when abdominal surgery is concerned. Opioids, through the μ-opioid receptors, as well as manipulation of the GI tract and inflammatory responses to surgical trauma are responsible for the inhibition of the GI nervous system and muscles (10, 13, 14, 15). Postoperative pain, through an increase in sympathetic tone, also decreases GI motility (10). Multimodal therapies need to be combined in order to prevent POI (10).

NSAIDs play a main role in the prevention of POI by inhibiting prostaglandin synthesis, and having an opioid-sparing effect (16). A preemptive dose of NSAIDs decreases by nearly 50% the postoperative use of opioids after laparoscopic cholecystectomy (17). Unfortunately, the effects of NSAIDs on POI has been poorly explored. When adding NSAIDs to a morphine patient-controlled analgesia (PCA) system, as compared to morphine PCA alone, Chen *et al.* found that the morphine group is 5 times more at risk of developing POI than the Morphine and NSAIDs group (18).

By decreasing the surgical stress response, and by reducing surgical pain, epidural analgesia seems to be a good alternative to improve postoperative pain relief and shorten POI (19). However, more efficient measures can be undertaken. In 2016, a Cochrane review showed that the duration of POI was shortened by nearly 17 hours when epidural analgesia containing local anesthetic agents only was used, as compared to an epidural containing opioids (20). However, according to some authors, epidural analgesia increases the risk of urinary retention (21). In addition, there can be contraindications to epidural analgesia, as well as technical failures. For these reasons, intravenous lidocaine during the intra- and postoperative periods has been proposed as an alternative (22). After abdominal surgery, an intravenous lidocaine infusion seems to accelerate the return of gastrointestinal motility, decrease the severity of pain, and decrease the length of hospital stay (23). All these benefits are due to a decreased opioid consumption (23, 24).

Table 1.
Suggested strategies to reduce the incidence of POI.

– Laparoscopic surgery
– Thoracic epidural analgesia
– Opioid-sparing drugs: Lidocaine, NSAIDs, Ketamine
– Ovoid intraoperative fluid excess
– Ovoid splanchnic hypoperfusion
– Mobilization
– Gum-chewing
– Early feeding
– Avoidance prophylactic use of nasogastric tube
– Laxative

As previously described, several techniques exist to prevent POI. With ERAS protocols, various strategies can be used in order to reduce the incidence of POI (Table 1) (25, 26).

2. Postoperative nausea and vomiting

Postoperative nausea and vomiting (PONV) occur in approximately 30% of the surgical population (27). However, the incidence of PONV can be higher among high risk patients. Delay for discharge, or hospital readmission, dehydration, and sometimes pulmonary aspirations are among the complications of PONV, which increase the health care cost (28).

The pathophysiology of PONV is complex and includes multiple factors, including patient own risk, perioperative fasting, and anxiety (29). Opioids induce nausea and vomiting by stimulating the opioid receptors located in the chemoreceptor

trigger zone (29). PONV are major adverse effects of opioids. They can lead to patient discomfort and to undertreated postoperative pain (28). For these reasons, PONV must be reduced as much as possible. Preventing measures include the administration of dexamethasone (30), regional anesthesia preferred to general anesthesia, avoidance of inhaled anesthetic agents, and, last but not least, opioid avoidance (31).

As already said, using opioid-sparing medications helps decreasing the incidence of opioid adverse effects (32). In a systematic review, Marret *et al.* demonstrated that NSAIDs significantly reduce the incidence of PONV by decreasing morphine consumption during the postoperative period. This incidence decrease is of a 30% magnitude (33). Those results have been confirmed by others (32, 34, 35). Paracetamol, also known as an opioid-sparing medication, does not have antiemetic properties (32). Alpha$_2$-agonists such as clonidine or dexmedetomidine significantly reduce the risk of PONV. This is explained by their opioid-sparing effects (34). Their effects against PONV seem to be active only during the early postoperative period, that is during the first 8 hours after surgery (36). Unfortunately, it has not been possible to determine whether α_2-agonists have intrinsic antiemetic proprieties, due to a lack of relevant trials (36). In 2014, a randomized study in bariatric surgery reported the incidence of PONV after OFA: patients who received OFA had a 17.3% lower risk of developing PONV than patients who received perioperative opioids, even when PONV prophylaxis was given (37).

Finally, even if dexamethasone decreases the incidence of PONV, it does not have opioid-sparing effects, proving that dexamethasone works as an antiemetic drug and not as an analgesic (34).

3. Postoperative urinary retention

Postoperative urinary retention (POUR) can be defined as a dysfunction of bladder emptying after anesthesia and surgery (38). For Baldini, POUR can be diagnosed by physical examination, bladder catheterization, which is also the treatment, and ultrasonography (21).

The incidence of postoperative urinary retention (POUR) varies according to type of surgery. In general surgery, incidence of POUR is approximately 5% (39). A higher incidence (up to 75%) has been found in orthopedic surgery (40). Risk factors for POUR include age (>50), gender, comorbidities (neurologic diseases), drugs (opioids, drugs with anticholinergic activitie), type and duration of surgery, and use of neuraxial anesthesia (41, 42, 21, 43). Baldini shown that the incidence of POUR was higher in patients who received neuraxial anesthesia (21). This was confirmed by Bjerregaard, who demonstrated that spinal anesthesia favors POUR as compared to general anesthesia for lower limb arthroplasty (38). The question to know whether the opioid dose used in neuraxial anesthesia may influence the incidence of POUR is still a matter of debate (21), but urinary retention is rare after total joint arthroplasty when using opioid-free regional anesthesia (44).

Alpha$_2$-agonists such as clonidine and dexmedetomidine are the cornerstone of opioid free anesthesia. However, they theoretically act on the urinary tract by increasing the urethral resistance (21) and so may increase the incidence of POUR. In 1996, Gentili conducted a randomized double-blind study, comparing the incidence of POUR after spinal anesthesia using clonidine or morphine (45). They found a lower incidence of POUR when clonidine was used, and urinary output was higher in the clonidine group (45). In 2015, a double-blinded randomized controlled trial demonstrated that patients who received epidural clonidine have significantly less urinary retention as compared to patients with epidural bupivacaine (46). Moreover, in the epidural clonidine group, no extra opioids were used for pain control (46). Different mechanisms of the effect of clonidine on urinary tract have been described. Clonidine decreases the sympathetic tone, which facilitates micturition (45) and has a diuretic effect (47).

The treatment of POUR is bladder catheterization (42, 21, 43), which carries a risk of infections and leads to delay to hospital discharge (48, 39). Furthermore, less catheterizations mean better mobility, and, in case of lower limb surgery, faster recovery (39). This is precisely one of the purposes of ERAS protocols.

4. Opioid induced hyperalgesia

Opioids have been widely used for pain management since the 19th century. The discovery of synthetized morphine and the invention of the hypodermic needle allowed pain relief from neuralgia, but unfortunately also led to opioid abuse and addiction (49). Opioid-induced hyperalgesia (OIH) was first described in 1940, but it has been only two decades since its clinical impact has started to be evaluated (50). OIH is characterized "*...as a state of nociceptive sensitization caused by exposure to opioids*" (51), with the paradox that "*…a patient receiving opioids for the treatment of pain could*

actually become more sensitive to certain painful stimuli" (51). Several mechanisms to explain OIH have been described, among them, genetic variations of the opioid receptors and activation of N-methyl-D-aspartate (NMDA) receptors (51, 52) have been advocated.

Twenty-four % of patients among the surgical population complain about undertreated postoperative pain (53), which leads to opioid use and misuse, and, therefore, more frequent opioid side effects and longer hospital stay (54).

Among drugs responsible for OIH, remifentanil was the most studied opioid. At doses used in common clinical practice, remifentanil has been shown to produce postoperative hyperalgesia, with increased postoperative morphine consumption (55). Fletcher, in his review paper, came to the same conclusion. High intraoperative dose of Remifentanil causes a significant increase in postoperative pain intensity at rest, that persists for 24 hours after surgery. This is associated with an increase in morphine needs after surgery (56). In order to prevent OIH, α_2-agonists and Ketamine were studied in the early 2000s. Their adjunction to remifentanil decreases pain scores when remifentanil-induced hyperalgesia is involved (55, 57). In 2012, a meta-analysis including nearly 1800 patients concluded that perioperative α_2-agonists reduce postoperative opioid requirements, as well as intensity of postoperative pain (36). However, all analyzed trials were conducted by comparing α_2-agonists or placebo associated to perioperative opioids (36). In a comparative study, patients who underwent breast reduction without perioperative opioids presented less postoperative pain and less hospital readmissions compared to those who received opioids during the perioperative period (58). Another study showed similar results for patients undergoing laparoscopic cholecystectomy (59). Those who receive OFA have significantly lower postoperative pain scores, and need less postoperative analgesic medications during the first 2 hours after surgery as compared to those who received a perioperative remifentanil-infusion (59).

5. *Opioid crisis*

Since the 2000's, the abuse of opioid prescription is a major health care issue in the USA (60). Deaths by overdose of prescribed opioids have exceeded those caused by illegal drugs overdose (61). This phenomenon has also been observed in the United Kingdom and in Australia (61). In the early 1990s, in the USA, there was an urge to recognize the undertreated pain, leading to the development of pain scale measurement and pain management guidelines (62). Unfortunately, with better undertreated pain recognition, the number of opioid prescriptions has exploded, leading to a growing abuse of opioids (62). Within 10 years, opioids consumption has increased by 700% in the USA (63).

Multiple risk factors for chronic opioid use were identified, including preoperative drug or alcohol abuse, depression, and male gender (64). Surprisingly, even when the most common surgery was performed, such as a cholecystectomy or a mastectomy, chronic opioid use was observed thereafter (64). For Mancini, "*preventing initial exposure to opioids should be considered whenever possible*" (63). To face this opioid abuse crisis, major American health care organizations encourage the use of opioid-sparing analgesic agents and multimodal analgesia during the perioperative period (65). According to the Centers for Disease Control and Prevention (CDC), the probability of chronic opioid abuse increases with the number of days the patient uses opioids. After the third day, for each additional day under opioids, chronic opioids use at 1 year is very likely (66).

Discussion

The literature comparing strict OFA and conventional opioid anesthesia (OA) is very poor. Alpha$_2$-agonists are often combined with opioids, but, often, only postoperative opioid requirement or opioid side effect incidence are studied.

The aim of ERAS is to accelerate recovery (67). There is clinical evidence that OFA decreases postoperative pain scores, as well as postoperative opioid needs (58, 59). The incidence of PONV (59, 37) and POUR (44, 45, 46) is also decreased whenever OFA is performed. The duration of POI (20) is shortened by 17 hours when opioid free epidural is used for postoperative analgesia. The main studies showing the benefit of OFA are summarized in Table 2.

For Mulier, the use of opioids makes sense only when the patient is awake, that is during the postoperative period only (68). During the intraoperative period, avoiding the surgical stress by sympathetic block should be the main concern of the anesthesiologist, as well as using opioid-sparing analgesic agents. For decades, opioids were the best choice for treating surgical pain. Unfortunately their side effects, a slower rehabilitation, and the public health crisis concerning opioid abuse should warn us against their misuse.

Table 2.
Main studies showing the benefit of opioid free anesthesia (OFA).

Study	Number of patients (n)	Interventions	Conclusion in favor of OFA
Guay, 2016 (20)	5846	Postoperative epidural with local anesthetics vs systemic or epidural opioids	- POI shortened by nearly 17 hours
Ziemann-Gimmel, 2014 (37)	119	OFA (Dexmedetomidine + Propofol) vs opioid anesthesia (Fentanyl + inhaled anesthetics)	- Decrease by 17,3% the risk of PONV
Tischler, 2016 (44)	842	Opioid free spinal anesthesia	- POUR is rare
Gentili, 1996 (45)	40	Spinal anesthesia Bupivacaine + Clonidine vs Bupivacaine + Morphine	- Less POUR
Abd-Elsayed, 2015 (46)	40	Epidural Clonidine vs Epidural bupivacaine	- No extra opioids needed during the intraoperative and postoperative period - Significantly less POUR
Parsa, 2017 (58)	83	OFA vs OA	- Less postoperative pain - Less hospital readmissions
Bakan , 2015 (59)	80	OFA (Dexmedetomidine) vs Opioid anesthesia (Remifentanil) + postoperative PCA Fentanyl for both group	- Lower postoperative pain score - Less postoperative analgesics need - Less PONV

Nowadays, there are multiple non-opioid analgesic agents that can be safely used, and that have demonstrated effectiveness, including paracetamol, non-steroidal anti-inflammatory drugs, ketamine, or lidocaine. Regional anesthesia can also be opioid-free, which leads to a lower incidence of POUR. Intraoperatively, α_2-agonists such as clonidine and dexmedetomidine have demonstrated their effectiveness as well as their positive opioid-sparing effects during the postoperative period. Dexmedetomidine, due to its short duration of action, has become very popular during the intra- and postoperative period. All these listed non opioid drugs act together by targeting multiple pain pathways, with the result of decreasing dose of each drug.

In our center, we are deeply convinced by the multiple advantages of OFA, and therefore used to provide it as frequently as possible. For novices, we understand the concerns about this technique. Alpha$_2$-agonists do have side effects, such as hypotension, bradycardia, and sometimes excessive sedation. As a consequence, it can be delicate to provide blindly OFA to all surgical patients. Frail and elderly patients are amongst the most vulnerable people. With opioid anesthesia, intraoperative hemodynamic stability can be easily and safely achieved. This is sometimes more difficult with OFA. Moreover, the increasing ambulatory surgical population forces us to use short-acting drugs, in order to insure a rapid induction and emergence with minimum side effects (69). The α_2-agonists' pharmacodynamics are such that postoperative sedation and recovery time are prolonged (70). This is a major limitation to providing OFA to outpatients, who need to be discharged from the post-anesthesia care unit as soon as possible.

However, using intraoperative opioids does not mean that no multimodal analgesia is insured. We truly think that multimodal anesthesia is the modern anesthesia, in order to reduce opioid consumption and to enhance recovery. Sometimes, this multimodal anesthesia will be opioid-free, and sometimes opioid-sparing. As anesthesiologists, one of our main concerns should be screening the patients in order to insure the safest and best anesthesia. Clinical evidences and patient benefits should always be balanced.

Each patient is unique in his response to surgical pain. This is the reason why we should take account of his/her current pain medications, and investigate his physiologic and psychologic response to injury, in order to provide the best management, and hence earlier recovery.

For those reasons, editing strict protocols can be tricky. A one-size-fits-all protocol is neither our thinking nor our desire.

Conclusion

In the ERAS area, multimodal anesthesia and opioid-sparing analgesic agents are the key words. OFA allows decreasing the postoperative amount of opioids, and hence decreasing the incidence of opioid side effects. This leads to less hospital readmission. Unfortunately, no study comparing OFA and opioid anesthesia in the field of ERAS has been undertaken. Further research, especially randomized controlled trials, are needed to demonstrate whether or not OFA

is a safe and appropriate technique to be integrated to ERAS protocols.

Finally, the opioid abuse crisis in the USA should raise the anesthesiologist's awareness of liberal opioid use during the perioperative period. It is our responsibility, with regard to our patients, to tackle this issue. By extending the use of multimodal anesthesia, whether in the form of OFA or opioid-sparing anesthesia, we could help control this problematic.

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