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ORIGINAL RESEARCH ARTICLE

Lessons from the Analysis of a Retrospective Cohort of Patients Who Underwent Large Open Abdominal Surgery Under Total Intravenous Opioid-Free Anesthesia

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Abstract

Background Opioid-free anesthesia (OFA) is a new method of anesthesia based on a paradigm shift. Under general anesthesia, the physiology and/or the pathophysiological variations clinically observed are more a reflection of a systemic reaction to the stress (surgical and anesthesia stresses) than a true reflection of pain.

Objective To report the results of a large monocenter, retrospective, non-interventional observational study of all consecutive patients who received a total intravenous (IV)-OFA protocol for the surgical management of major open abdominal and urological surgery.

Patients and Methods We retrospectively extracted the anesthesia files of 311 consecutive patients (regional anesthesia excluded). No opioids were administered to any of these patients during the surgery. IV morphine administered in the recovery room was the primary endpoint of the study. The secondary endpoints included the amount of opioid required during the first two postoperative days, as well as the maximum pain intensity.

Results Only very small doses of IV morphine were administered. The mean total morphine titration was 2 mg (1.9 ± 2.9 mg), corresponding to control of the maximal level of pain to 2.1 ± 2.6 as evaluated with a numerical scale in the postoperative care unit. Similarly, we observed a very low level of morphine consumption during the first two postoperative days.

Conclusions These results highlight the safety and the feasibility of our total IV-OFA protocol, thus confirming this new paradigm. Under general anesthesia, the cardiovascular and inflammatory response to the stress could be reliably managed through a multimodal approach without a need for opioids. In the postoperative period, very low doses of opioids were required.

Key Points

Anesthesia without opioids during large open abdominal surgery does not increase the pain and/or the postoperative opioid requirement.

The benefits of opioid-free anesthesia include faster rehabilitation.

Pain is probably best prevented by a multimodal approach rather than focusing on an opioid prescription.

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1 Introduction

There has been great interest in the recent literature regarding the epidemic of opioid misuse [1, 2]. The practice of anesthesiology is widely responsible for liberal perioperative use of opioids [3]. Despite cultural variations [4], anesthesia has largely contributed to reinforcement of the notion that morphine is the most potent drug for pain relief. This has led to acceptance of its side effects. During the perioperative period, the typical adverse effects of opioids (e.g., nausea, vomiting, pruritus, constipation, ventilation depression, etc.) can usually be prevented and/or treated [5]. More recently described other adverse effects (e.g., hyperalgesia, persistent postoperative pain, cognitive dysfunction, immunosuppression, and increased risk of tumor recurrence and infection) are, however, increasingly reported [6–9]. This led us to assess and consider a change of practice [9, 10]. It is worth noting that the definition of pain of the International Association for the Study of Pain (IASP) mandates a state of consciousness as a prerequisite ("an unpleasant sensory and emotional experience…"). Therefore, under general anesthesia (GA), the only evaluation of "pain", or, more precisely, the stress-induced response, is the ensuing changes in cardiovascular parameters (e.g., tachycardia and hypertension). A multimodal opioid-free anesthesia (OFA) protocol has recently been promoted. The results obtained so far are, however, limited. For example, aside from the observational and retrospective nature of the studies to date, the sample sizes have been small in most of the randomized controlled trials (RCTs) and the confounding factors have not been corrected [11–18].

In the abdominal and urologic surgery units of our institution, we have, in the first instance, moved away from opioid-based anesthesia (OBA; a combination of opioids and sedation drugs) to opioid-reduced anesthesia (ORA), whereby opioid-sparing procedures (such as epidurals, multimodal analgesia with intravenous (IV) lidocaine, ketamine, dexamethasone, etc.) are widely implemented. We then extended this approach by implemention of our proposed OFA protocol. In light of our consistently encouraging results with postoperative pain control and cognitive recovery, we gradually phased out IV morphine patient-controlled analgesia (PCA) in favor of opioid sublingual patient-controlled analgesia. This is fully in line with the Enhanced Recovery After Surgery (ERAS) program [12, 19].

A number of preoperative factors have been described as being predictive factors of postoperative pain after opioid based anesthesia (OBA or ORA) [20]. Even with the OFA protocol, some patients require small doses of morphine during the postoperative period (called low opioid analgesia, or LOA). Identification of the preoperative factors predictive of morphine requirement in the Post-Operative Care Unit (PACU) was, therefore, clearly of interest.

We here report a large monocenter, retrospective, non-interventional observational study of all consecutive patients who received a total IV-OFA protocol for the surgical management of major open abdominal and urological surgery over a period of 4 years (from 06/01/15 to 05/31/19). Patients who underwent the OFA protocol but with epidural analgesia were excluded so as to evaluate the feasibility, safety, and effectiveness of the total IV-OFA protocol during long elective open abdominal procedures.

All of the perioperative therapeutic procedures and modalities of care conformed to our usual clinical practice protocols. We applied the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [21] (see File 1 in Electronic Supplementary Material).

2 Methods

2.1 Study Design, Setting, and Population

This retrospective analysis was approved by our National Ethics committee (Comité d'Ethique en Anesthésie Réanimation, CERAR, Prof. Jean Etienne Bazin; IRB number 00010254). The demographic and surgery characteristics of the patients who received total IV-OFA were analyzed. Data on OFA efficacy, safety, tolerability, and the quality of recovery were extracted from electronic patient data files and then examined and anonymized. The study population inclusion criteria were consecutive, major, or complex open abdominal or urologic surgery (i.e., lasting more than 90 min) under GA. In our unit, the choice of using the OFA (described in Sect. 3, Results) or the ORA protocol was not performed as a function of the patients' medical conditions but according to the views of each practitioner practicing their procedures under the OFA or the ORA protocol.

The study population exclusion criteria were any of the following:

- The use of opioids during the surgery (ORA or OBA protocols according to the choice of the practitioner but not according to the surgical procedures).
- Regional anesthesia such as neuraxial analgesia.

Our primary evaluation was based on the amount of IV morphine required in the PACU. The morphine titration was in 2-mg aliquots every 5 min when the numerical pain score (NumeRical Scale, NRS) was ≥ 3 until the pain was considered to be under control (NRS < 3). The 11-points NRS ranges from 0 points (no pain) up to 10 points (the worst imaginable pain) and the values reported were always

recorded according to the patient's response to the assessment of his pain. We also studied the patient demographics, the type of surgery, the perioperative medication used, and the pain protocol.

The secondary endpoints included the amount of opioid required during the first two postoperative days, D1 and D2, as well as the maximum pain intensities (max. NRS) recorded by the nurses in the electronic files.

2.2 Statistics

We retrospectively extracted data from the electronic medical records system. The primary outcome variable was the total opioid consumption in the PACU. Patients requiring an IV morphine titration in the PACU were regrouped into a subgroup called M+, while those who did not receive morphine were assigned into the M− subgroup.

The secondary outcomes were the total opioid consumption during the first and second postoperative days (D1 and D2) and the worst pain score that was recorded at any time during the PACU stay on D1 and on D2. As this was a study with a rather pragmatic nature, we did not predetermine a patient population size. Based on a preliminary evaluation of 125 patients [22], an analysis of every 50 new patients did reveal any variations in the consumption of postoperative morphine in the PACU [expressed as the mean ± the standard deviation (SD)]. Furthermore, since no variations were observed with a significant increase in the number of patients, we capped the study at 300 patients.

The results are presented as a means ± SD for the normally distributed data, and medians and percentiles (interquartile range, IQR) for the skewed data (median, IQR, and minimal and maximal values). The categorical variables are presented as the number of patients (percentage). For the subgroup analysis, Student's *t* tests were utilized to compare discreet data (NRS and opioid consumption). Univariate analysis was first used to analyze the underlying relationship between the baseline and the intra-operative variables and the morphine consumption in the PACU. Variables with a P value less than 0.1 were entered into a multivariable analysis to identify independent risk factors of postoperative opioid requirement. $P \leq 0.05$ was considered significant. The statistical analyses were carried out using the statistical software package SPSS version 25.0.

3 Results

We retrospectively evaluated the anesthesia files of 362 consecutive patients who underwent the OFA protocol between June 2015 and May 2019. Forty-eight patients were excluded because they had received an epidural (OFA-epidural). 314 remaining patients received a total IV-OFA protocol (11 in the last 6 months of 2015, 41 in 2016, 69 in 2017, 139 in 2018, and 54 in the first 5 months of 2019). However, three patients were excluded due to missing PACU data (see Fig. 1, flow chart). Irrespective of the surgery, no patient scheduled to undergo the OFA protocol received intraoperative opioids (i.e., 0% OFA protocol failure).

3.1 Patients Characteristics

The mean age of the 311 included patients was 64.1 ± 12.6 years, and the mean body mass index was 26.1 ± 5.5 kg/m^2 (for details see Table 1). The ratio of females to males was 116 (37.3%)/195. A small number of patients were opioid-tolerant (i.e., they had used opioids before the surgery), $n = 15$ (5.2%). Numerous co-morbidities were reported: hypertension, $n = 133$ (42.8%); use of beta-blockers, $n = 85$ (27.3%); pulmonary diseases, $n = 51$ (16.4%).

3.2 Surgery

The patients were scheduled to undergo a large and long open abdominal elective procedure. The surgical duration (measured as the time between the GA induction and the surgical closure) was approximately 4 h (mean 255 ± 100 min; 230 min; 190–305 min; 85–810 min) for various surgical cancer procedures: liver (139), pancreas (52), colon (47), kidney (29), bladder (15), and others (adrenal, stomach, small intestine, etc.).

3.3 Anesthesia

The patients did not receive any premedication and they walked to the operating room as part of the regular

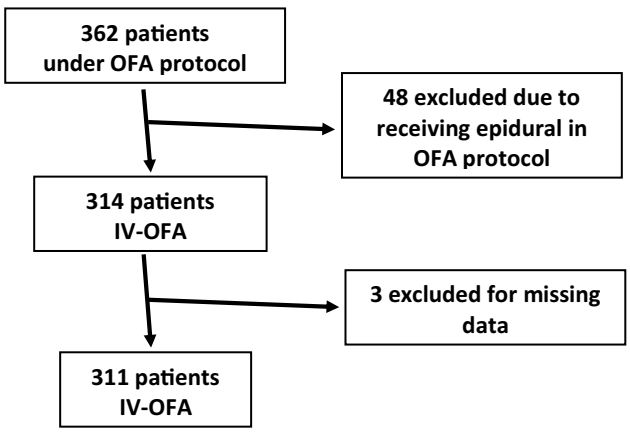

Fig. 1 Flow chart of the patients who underwent the opioid-free anesthesia (OFA) protocol during the evaluation period (January 2015 to December 2018). Only patients receiving total intravenous OFA (IV-OFA) were included (i.e., patients receiving an epidural during the OFA protocol were excluded)

Table 1 Patient demographic data

	Mean	± SD	Median	IQR (25–75%)	Max.	Min.
Age (y)	64.1	12.6	66	58–72	94	19
Height (cm)	168.3	9.3	168	162–175	197	135
Weight (kg)	74.5	15.8	75	62–83	140	39
F/M (*n*, %)	116 (37.3%) /195 (62.5%)					

Results are expressed as mean with standard deviation (± SD); median with interquartile range (IQR) and minimal (min.) and maximal (max.) values; ratio of females to males (F/M)

procedure. The anesthesia protocol had been standardized. The induction of anesthesia was performed with continuous infusion of dexmedetomidine 1.0–1.4 µg/kg/h, with a bolus of lidocaine 1–1.5 mg/kg, ketamine 0.1–0.15 mg/kg, dexamethasone 0.1 mg/kg, and propofol as a function of the bispectral index (BIS) monitoring (according to the guidelines from the manufacturer: < 60). Tracheal intubation was performed under muscle relaxation (cisatracurium 0.1–0.2 mg/kg) with monitoring of the muscle relaxation (train-of-four, TOF). Maintenance of anesthesia was controlled with continuous infusion of lidocaine 1 mg/kg/h and ketamine 0.1 mg/kg/h. When significant bradycardia was observed, the rate of continuous infusion of dexmedetomidine was decreased to approximately 0.8–1.0 µg/kg/h. Halogenated anesthetic (mostly desflurane) was used at a very low concentration (minimal alveolar concentration, MAC: mean = 0.8 ± 0.35; 0.8: 0.7–0.9; 0.4–0.9) with monitoring of the depth of anesthesia based on the BIS (43.4 ± 7.75; 45; 40–45; 10–80). Maintenance of muscle relaxation was achieved using cisatracurium with monitoring of muscle relaxation (total cumulative dose of cisatracurium 31.8 ± 12.9 mg; 30 mg: 22.5–38.5 mg; 8–100 mg). Thirty to 50 min before the surgical closure, the dexmedetomidine and ketamine infusions were stopped. The lidocaine infusion was continued until the end of the PACU stay. As IV lidocaine was used, surgical field infiltration was not allowed. As per usual clinical practice, the IV administration of fluids was on a rather restrictive basis and always under invasive or non-invasive hemodynamic control.

Cardiovascular stability was adequate with the mean arterial pressure (MAP) at 78.2 ± 8.3 mm Hg (80: 70–85; 70–160). The mean cardiac frequency (CF) was adequately controlled: 63.7 ± 9.3 beats/min (65: 55–70; 40–90). The cardiovascular requirements for drugs ($n = 222$; 71%) were mostly with ephedrine (40.5%; 12.3 ± 11.9 mg; 9.0 mg: 0–18 mg; 0–60 mg) and/or atropine (3%), and adrenaline was usually used by continuous infusion during liver exclusion as needed (15%). Only 41 patients (13%) required a transfusion.

The intra-operative multimodal analgesia was completed with paracetamol (1 g) and nefopam administration ($n = 150$; 48.2% usually at the surgical closure) combined with non-steroidal anti-inflammatory drugs (NSAIDs; ketoprofen 100 mg preferably before the surgical incision than at closure) ($n = 141$; 45.3%). A small number of patients received only paracetamol administration ($n = 20$; 6.4%). Monitoring of "nociception" (or the cardiovascular response to the stress) was performed mostly by means of the analgesia nociception index (ANI; 88.7%, mean value = 69.5 ± 11.5; 70; 60–80; 5–99; according to the guidelines from the manufacturer: optimal range of comfort = 50/70 or above 70) and/or by the nociception level index (NOL; 34%; mean value = 10.2 ± 5.4; 9: 6–10; 0–45; according to the guidelines from the manufacturer: optimal range of comfort < 25).

3.4 Postoperative Period

During the evaluation period, no mortalities or major morbidities were recorded.

3.4.1 In the Post-Operative Care Unit (PACU)

The time spent in the PACU was 216.5 ± 112.9 min (190 min; 150–250 min; 60–990 min). The body temperature of the patients on arrival was 36.2 ± 0.8 °C (36.2 °C: 35.8–36.8 °C; 32.8–38 °C). The time of tracheal extubation was 48.2 ± 35.9 min (40 min; 25–65 min; 0–280 min). Recovery from muscle relaxation was obtained by neuromuscular reversal in 62.5% of cases.

The maximal pain (max. NRS) recorded in the PACU was 2.1 ± 2.7 (0: 0–4; 0–9). Only 38.3% of the patients required morphine IV titration (Fig. 2). The mean total morphine consumption in the PACU was 1.9 ± 2.9 mg (0 mg: 0–3 mg; 0–15 mg). No patient required IV-PCA morphine to be started in the PACU.

For the group of patients with morphine titration in the PACU (M+; $n = 119$; 38.3%), the mean morphine IV titration was 4.8 ± 2.7 mg (4 mg: 3–6 mg; 2–15 mg) (Fig. 3) with a maximum NRS of 4.8 ± 1.9 (5: 4–6; 0–9), which was significantly different from the group without morphine titration in PACU (M−; $n = 192$: 61.7%); maximum NRS of 0.3 ± 1.2 (0: 0–0; 0–8); $P < 0.001$. The mean age in the M+ group was 61.9 ± 13.8 years (65 years: 55; 25–71; 24–88), which was significantly lower ($P = 0.0017$) than in

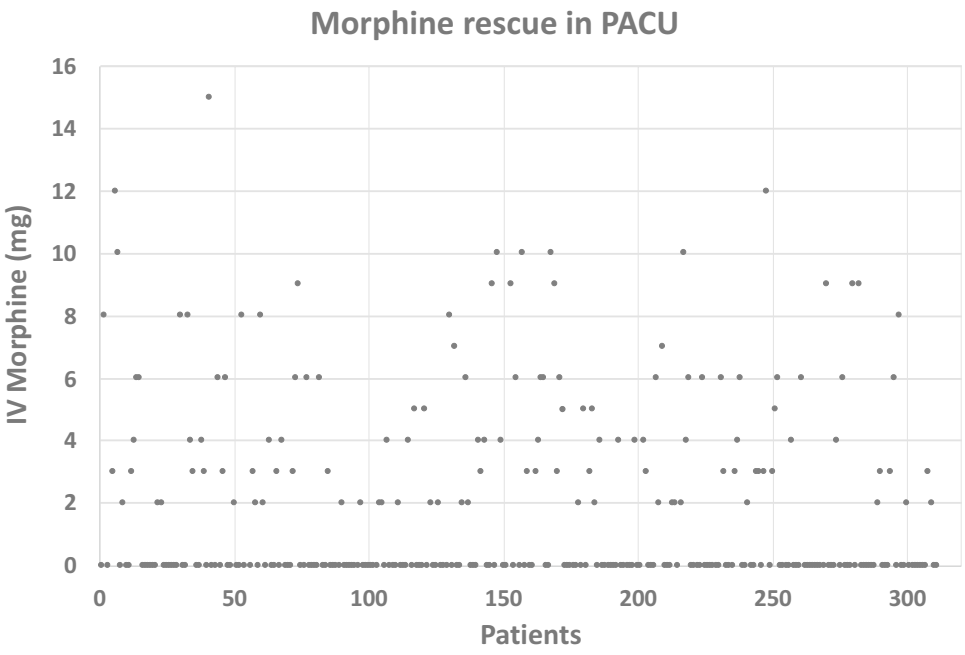

Fig. 2 Scatter plot of the consumption of total intravenous (IV) morphine (mg) in the postoperative care unit (PACU) for each patient ($n = 311$). Only 38.27% of the patients required morphine IV titration

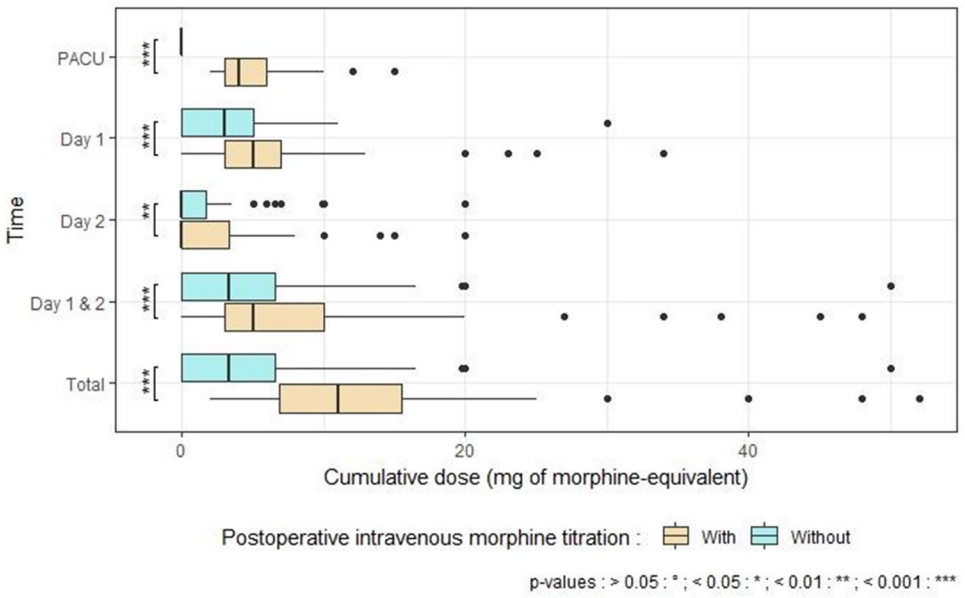

Fig. 3 Comparison of two subgroups, with or without morphine requirement in the postoperative care unit, using a box-plot [box with the median and 50% or interquartile range (IQR)]; bar with 24.65% or ± 1.5*IQR, and dots for the extreme values = 0.35%)

the M− group, 65.5 ± 11.6 years (66 years: 60–73; 19–94), while there was no difference in the sex ratio (M+ group: F/M (41 = 34.5%/78) vs. M− group: F/M (74 = 39.3%/114). There was no clear difference with regard to the number of patients using opioids preoperatively (opioid-tolerant; 12 in M− group (6.3%) vs. four in the M+ group (3.4%)).

However, using univariate analysis and multivariable logistic regression, we found a number of preoperative factors that were predictive of the use of morphine as analgesics rescue in the PACU. Age (65.4 ± 11.67 years for the M− group and 61.98 ± 13.77 years for the M+ group; $P = 0.01$) and BMI (26.87 ± 5.58 for the M− group and 24.71 ± 4.59 for the M+ group, $P = 0.001$) were significantly predictive. Despite a trend of effect, being opioid tolerant ($P = 0.1049$) or under beta-blocker treatment ($P = 0.1940$) were not significant.

Only a few cases ($n = 2$ (0.6%)) required treatment for postoperative nausea and vomiting (PONV), both of which were in the group M+ group.

3.4.2 After the PACU

The mean length of stay (LOS) was 8.2 ± 4.9 days (7 days: 5–10 days; 2–30 days).

During the first postoperative day (D1): Multimodal systemic analgesia was performed with a combination of paracetamol (IV or oral route) and IV nefopam. The maximum NRS recorded during D1 was 5.1 ± 2.1 (5: 2–4; 0–10) (i.e., at rest as well as with movement). The dose of morphine required for rescue by the oral route (expressed in IV morphine equivalents, IV-MEs) was 4.0 ± 4.2 mg (3.3 mg: 1.7–5 mg; 0–34 mg). In 21.2% of cases, no opioids were administered.

Not surprisingly, the subgroup analysis indicated that the patients requiring morphine titration in the PACU (M+ group) required significantly more opioid during the first postoperative day (M+ group: morphine 5.3 ± 5.1 mg (5 mg: 3–7 mg; 0–34 mg) vs. the M− group: morphine 3.1 ± 3.3mg (3.0 mg: 0–5 mg; 0–30 mg); $P < 0.001$) (Fig. 3).

There was a significant difference in terms of the maximal pain for the M+ group (max. NRS = 5.5 ± 2 (5: 4–7; 0–10)) vs. the M− group (max. NRS = 4.8 ± 2.2 (5.0: 4–6; 0–9), $P = 0.005$).

During the second postoperative day (D2): The maximum level of pain observed was = 3.2 ± 2 (max. NRS = 3: 2–4; 0–8), with a mean morphine consumption = 1.6 ± 3.1 mg (IV-ME = 0 mg: 0–2.3 mg; 0–20 mg). For 58.7% of the patients, no opioids were administered.

Again, the M+ group had a significant increase in the amount of morphine required (mean IV-ME = 2.2 ± 3.4 mg (0 mg: 0–3.3 mg; 0–20 mg)) compared to the M− group (1.3 ± 2.8 mg (0 mg: 0–1.7 mg; 0–20 mg; $P < 0.01$). There was also a significant difference in the level of the maximal pain (max. NRS = 3.6 ± 1.9 (3: 2–5; 0–8) for the M+ group vs. max. NRS = 2.9 ± 2 (3: 2–4; 0–8) for the M− group; $P = 0.003$) (Fig. 3).

The mean total amount of morphine (PACU + D1 + D2) required for the treatment of postoperative pain after large open abdominal surgery was 7.4 ± 7.8 mg (6 mg; 2–10.1 mg; 0–52 mg). The mean of the cumulative total morphine consumption was significantly lower in the M− group (total morphine = 4.4 ± 5.3 mg (3.3 mg: 0–6.6 mg; 0–50 mg) compared to the M+ group (total morphine = 12.3 ± 8.6 mg (11 mg: 6.8–15.5 mg; 2–52 mg) ($P < 0.001$).

Despite the large open abdominal surgery, treatment for PONV in the postoperative period (D1 + D2) remained very low: $n = 23$ (7%) (14/119 = 11.8% in M+ group vs. 9/192 = 4.7% in the M− group). No postoperative cognitive dysfunction (POCD) nor awareness and recall during the procedure was reported.

4 Discussion

4.1 General

This is the first real-life application of the IV-OFA protocol in a large cohort of patients undergoing large open elective abdominal surgery (more than 4 h of surgery) without neuraxial analgesia. The choice of the anesthesia protocol was not based on the surgery or patient comorbidities but on the expertise of each practitioner. In other words, the practitioners performed 100% of their anesthesia according to an OFA or ORA protocol.

These results confirm the feasibility and the efficacy of the total IV-OFA protocol. Overall, these data confirmed the new paradigm. Under GA, a blunting or damping of the cardiovascular response and the inflammatory cascade due to the stress could readily be obtained with a multimodal approach without being masked by an epidural. We deliberately took into account the worst pain scores (i.e., we only considered the worst level of pain and not the average pain level).

The increasing number of patients included in such an IV-OFA protocol during the study period was due to the learning curve of each anesthesiologist after the introduction of the protocol by one of the team's practitioners. Over time, and in light of these interesting results, IV-OFA was gradually adopted by the other anesthesiologists. First, according to the epi-OFA protocol. Then, due to the limitations of the epidural in the ERAS-program and due to the efficacy of the total IV-OFA procedure, the practitioners progressed to IV-OFA.

The time spent in the PACU was increased, but corresponds to our current protocol with a transfer of curarized patients. Tracheal extubation is carried out after heating and neuromuscular reversal. The evaluation with a propensity score for the same surgery did not reveal a difference in duration between OFA and ORA [23, 24].

In terms of postoperative opioid consumption, these results can be compared with the large amount of literature with similar surgeries. Although some of the patients received opioid-free analgesia, for this type of invasive surgery it appears to be difficult to get by without a small amount of postoperative morphine. We have, however, found a number of predictive preoperative factors of postoperative pain, as also reported in the literature. Perhaps due to too low a number, some other preoperative factors only stood out as a trend. With such invasive surgery, the IV-OFA protocol does not mean opioid-free postoperative analgesia, although it clearly reduces its use. Therefore, the reduction of the adverse effects of morphine is directly keeping with the objectives of an ERAS program. However, physician behavior, rather than the condition of

the patient, could be the primary determinant of opioid-prescribing practices [10]. Opioid consumption has been reported to be dependent on the reported level of pain. This rate of opioid consumption would be even lower than expected with the level of worst pain reported by the patient. We interpret these results as a reflection of better tolerance in relation to a good cognition recovery, as reported in the literature [10, 25–27]. After an IV-OFA protocol, when a patient reports an NRS of 5, they typically decline a morphine proposal, as they consider that they can tolerate such a level of pain. It cannot be ruled out that switching from opioid-controlled oral analgesia reduces the consumption conventionally observed during IV-controlled analgesia. The reduction of PONV could be due to the small amount of opioid required after surgery and to the use of a multimodal approach (lidocaine and dexamethasone).

4.2 Mechanisms of Action

The control of the hemodynamics during the surgery was good despite some bleeding problems (13% of cases involved transfusion during the surgery). The monitoring of the depth of anesthesia (BIS) and "nociception" (ANI and/or NOL) were in the ranges specified in the guidelines. However, it is important to note that all these tools were validated during the use of opioids and to guide the opioid administration. Further evaluation under OFA is required or when drugs such as ketamine, beta-blockers, and/or dexmedetomidine are used.

The mechanism of action during the IV-OFA protocol is more complex than those based on a single action on opioid receptors in an OBA protocol. There is a specific action on different targets. Ketamine acts on the *N*-methyl-D-aspartate (NMDA) receptors, dexmedetomidine acts on alpha-2 agonist (α-2) receptors, and lidocaine blocks voltage-gated sodium channels [28]. However, the "analgesic" effects are not only due to these specific targets, as described for ketamine [29, 30]. Like NSAIDs and glucocorticoids (dexamethasone), these drugs also have direct anti-inflammatory effects, which can reduce the systemic inflammatory response syndrome (SIRS) [8, 31]. This SIRS can lead to a central sensitization syndrome (CSS) [32]. CSS can be attributed to either direct macro- and microglial activation or indirectly, as a consequence of the blood–brain–barrier alteration [19, 33]. CSS can, in turn, be responsible for neurocognitive disorders. An indirect effect on inflammation by blocking cardiovascular reactivity is observed with bradycardia due to the α-2 agonists action [31]. This effect has also been reported with beta-blockers [34, 35]. However, unlike with beta-blocking, the bradycardia observed with α-2 agonists can readily be treated with atropine or vasoconstrictor drugs (phenylephrine and epinephrine). Thus, a reduction in mortality and morbidity has been reported with dexmedetomidine, even after cardiac surgery [36, 37].

A number of other factors could also be involved, such as physiological sleep observed with dexmedetomidine (in comparison with the other sedative drugs usually used in anesthesia, i.e., propofol and/or halogenated analogs), which could also reduce the POCD [27, 38–40]. As previously discussed, in our experience, patients with a better postoperative cognitive function are more able to tolerate a higher level of pain compared to patients with POCD. The possible effect of ketamine should also be considered. The huge reduction in PONV could be due to the decrease in the amount of opioid required and to the prevention with dexamethasone [41].

Naturally, similar or better results could be obtained with an epidural analgesia. However, epidural analgesia is more difficult to manage in an ERAS program (urine retention, early feeding, prolonged bed rest, anticoagulant management, etc.)

4.3 Limitations

Despite the fact that the study involved a large retrospective cohort, it nonetheless has several limitations. First, it was not an RCT and there was therefore no control group.

There could thus have been an intention-to-treat bias due to patient selection. However, more than a specific selection of patients for the IV-OFA protocol, the practice of the unit was oriented towards 100% use of IV-OFA by most of the anesthesiologists. While some practitioners still used ORA and epi-ORA protocol, they requested that their most vulnerable patients were treated by an experienced IV-OFA practitioner.

We are currently carrying out propensity-score studies with the same surgical procedure [i.e., robotic-assisted partial nephrectomy [23] and open hepatectomy [24] and others are planned (cystectomy, pancreaticoduodenectomy)]. But the aim of this study was, for the first time, to report in a large cohort of patients how the feasibility, safety, and efficacy of the total IV-OFA protocol compare with the literature. Unfortunately, the different dimensions of pain could not be explored [42, 43].

Various aspects of the OFA program still need to be clarified: such as a cognitive function evaluation, markers of inflammatory reaction, and the risk of infection and/or recurrence and metastasis. Despite the lack of trials with adequate power, it would be interesting to perform an assessment of the impact of OFA (in terms of LOS and risk of chronic postsurgical pain). These data need to be confirmed with a large cohort of patients in other types of surgery such as orthopedic, vascular, and gynecologic surgery.

The choice of anesthesia protocol could be seen as a bias of the evaluation. In our institution, the learning curve for

the OFA was established in previous years (2013–2014). During this period, we noted the relevance of moving progressively from the IV-PCA morphine or epidural analgesia to the oral morphine PCA. The evaluation period (2015–2018) corresponds to our current practice; the OFA protocol is used particularly when the patient's conditions and/or the surgery are complex. Furthermore, there is probably no recruitment effect in favor of less invasive surgery or less patient co-morbidity.

5 Conclusion

These findings dispel previous misconceptions regarding body responses to the stress under general anesthesia. This large historical-prospective cohort of open surgery with total intravenous opioid-free anesthesia is a confirmation of the proof of the concept of such an approach. The feasibility of not using regional anesthesia during an invasive open surgical procedure highlights that this is a viable alternative to opioids to control postoperative pain. Our results are based on a large enough cohort to allow comparison with the literature. Even when small doses of morphine are still required, this novel approach to anesthesia still allows for a reduction in adverse effects. The merits and the potential of the ERAS program are readily apparent.

Although there is a need for evidence-based proof, there are more and more clinical series, randomized-controlled trials, and clinical reviews that confirm this paradigm shift. Some aspects remain to be evaluated, particularly in terms of reduction of the risk of persistent postoperative pain (or chronicization) and reduction of the risk of recurrence and metastasis.

Nevertheless, our results indicate that morphine should no longer be considered to be a mandatory centerpiece in pain-management strategies.

Declarations

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Conflict of interest None for any of the authors.

Ethics approval This retrospective analysis was approved by the National Ethics committee (Comité d'Ethique en Anesthésie Réanimation (CERAR), Prof. Jean Etienne Bazin; IRB number 00010254).

Consent to participate Not applicable.

Consent for publication Not applicable.

Data availability Available from the corresponding author.

Code availability Not applicable.

Author contributions All the authors read and approved the manuscript. JPE: designed the study, recruited the patients, collected and analyzed the data, drafted the manuscript, and edited the final manuscript. MM, EA, AD, CB, and KB: recruited the patients and edited the final manuscript. CR analyzed the data and edited the final manuscript.

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