ANESTHESIOLOGY

Balanced Opioid-free Anesthesia with Dexmedetomidine *versus* Balanced Anesthesia with Remifentanil for Major or Intermediate Noncardiac Surgery

The Postoperative and Opioid-free Anesthesia (POFA) Randomized Clinical Trial

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The common practice of administering opioids during anesthesia is challenged by some small clinical studies[1–4] suggesting that opioid-free anesthesia may be effective at providing adequate pain control while reducing postoperative opioid consumption. This technique is becoming increasingly popular among anesthesiologists despite a lack of understanding around it.[5] Indeed, the literature is confusing because the definition of opioid-free anesthesia varies in the literature and between centers. The extent of the benefits, limitations, and applicability have been questioned, and some studies did not report any benefit.[5,6]

ABSTRACT

Background: It is speculated that opioid-free anesthesia may provide adequate pain control while reducing postoperative opioid consumption. However, there is currently no evidence to support the speculation. The authors hypothesized that opioid-free balanced anesthetic with dexmedetomidine reduces postoperative opioid-related adverse events compared with balanced anesthetic with remifentanil.

Methods: Patients were randomized to receive a standard balanced anesthetic with either intraoperative remifentanil plus morphine (remifentanil group) or dexmedetomidine (opioid-free group). All patients received intraoperative propofol, desflurane, dexamethasone, lidocaine infusion, ketamine infusion, neuromuscular blockade, and postoperative lidocaine infusion, paracetamol, nefopam, and patient-controlled morphine. The primary outcome was a composite of postoperative opioid-related adverse events (hypoxemia, ileus, or cognitive dysfunction) within the first 48 h after extubation. The main secondary outcomes were episodes of postoperative pain, opioid consumption, and postoperative nausea and vomiting.

Results: The study was stopped prematurely because of five cases of severe bradycardia in the dexmedetomidine group. The primary composite outcome occurred in 122 of 156 (78%) dexmedetomidine group patients compared with 105 of 156 (67%) in the remifentanil group (relative risk, 1.16; 95% CI, 1.01 to 1.33; $P = 0.031$). Hypoxemia occurred 110 of 152 (72%) of dexmedetomidine group and 94 of 155 (61%) of remifentanil group patients (relative risk, 1.19; 95% CI, 1.02 to 1.40; $P = 0.030$). There were no differences in ileus or cognitive dysfunction. Cumulative 0 to 48 h postoperative morphine consumption (11 mg [5 to 21] *versus* 6 mg [0 to 17]) and postoperative nausea and vomiting (58 of 157 [37%] *versus* 37 of 157 [24%]; relative risk, 0.64; 95% CI, 0.45 to 0.90) were both less in the dexmedetomidine group, whereas measures of analgesia were similar in both groups. Dexmedetomidine patients had more delayed extubation and prolonged postanesthesia care unit stay.

Conclusions: This trial refuted the hypothesis that balanced opioid-free anesthesia with dexmedetomidine, compared with remifentanil, would result in fewer postoperative opioid-related adverse events. Conversely, it did result in a greater incidence of serious adverse events, especially hypoxemia and bradycardia.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- It is hoped but not proven that opioid-free anesthesia provides adequate postoperative analgesia and reduced opioid-related side effects
- Dexmedetomidine is sometimes used to replace opioids in balanced opioid-free anesthetics

What This Article Tells Us That Is New

- In a randomized, blinded, multicenter trial, study patients undergoing noncardiac surgery received a standard anesthetic featuring lidocaine and ketamine, plus either remifentanil or an alternative anesthetic where dexmedetomidine was substituted for remifentanil
- The primary outcome, composed of postoperative hypoxemia, ileus, and cognitive dysfunction, was more common among patients receiving opioid-free anesthesia
- Importantly, opioid-free anesthesia with dexmedetomidine was associated with severe bradycardia, and the study was terminated early for that reason

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Previous studies suggested that the intraoperative hemodynamic stability and the antinociception traditionally obtained by opioids could be reached with a multimodal administration of nonopioid agents such as *N*-methyl-D-aspartate antagonists, local anesthetics, and α2 agonists.[7] Some studies, although not powered to answer the question, suggested that opioid-free anesthesia could also reduce opioid-related adverse effects.[8] However, the lack of high-level evidence leaves clinicians uncertain about whether opioid-free anesthesia is beneficial or harmful. Indeed, α2-receptor agonists that are used for this purpose, such as dexmedetomidine, may promote unwanted side effects, including increased risks of hypotension and bradycardia during surgery and prolonged sedation after surgery.

To address this uncertainty, we conducted the Postoperative and Opioid-free Anesthesia (POFA) trial to evaluate the hypothesis that an opioid-free balanced anesthetic with dexmedetomidine (dexmedetomidine group) would improve postoperative outcomes by decreasing postoperative opioid-related adverse events in patients undergoing major or intermediate noncardiac surgery as compared with a balanced anesthetic with remifentanil and morphine (remifentanil group). The choice of opioid-related side effects as the primary outcome was guided by the need for clinically meaningful outcomes to further study the potential benefits of opioid-free anesthesia.

This article is featured in "This Month in Anesthesiology," page 1A. This article is accompanied by an editorial on p. 509 and an article on p. 645. This article has a related Infographic on p. 17A. These results were presented during the annual meeting of the French Society of Anesthesia and Intensive Care in Paris, France, September 21, 2019. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has a video abstract. This article has an audio podcast. This article has a visual abstract available in the online version.

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Materials and Methods

Study Design

This was an investigator-initiated, prospective, multicenter, parallel-group, single-blind randomized, and controlled trial conducted in 10 centers in France (ClinicalTrials.gov NCT03316339; October 20, 2017; principal investigator: H. Beloeil). The rationale and design of the study have been reported previously and is available in Supplemental Digital Content 1 (http://links.lww.com/ALN/C541).[9] The study was approved for all centers by a central ethics committee (Comité de Protection des Personnes d'Ile de France, Paris, France, September 13, 2017). Written informed consent was obtained from all participating patients before inclusion in the study. An independent data and safety monitoring board oversaw the study conduct and reviewed blinded safety data.

Patients

We studied patients older than 18 yr who planned for major or intermediate scheduled surgery,[10] were affiliated to a social security system, and had given written informed consent. Participants were screened, approached, and recruited by study staff, who evaluated patient eligibility, obtained informed consent, and enrolled the participants. Exclusion criteria were known allergies to any of the drugs used for anesthesia or to any of their excipients; pregnancy or breastfeeding; urgent surgery; intracranial surgery; transplant surgery or transplanted patients; surgery with planned regional anesthesia; outpatient surgery; atrioventricular, intraventricular, or sinoatrial block; Adam–Stokes syndrome; patients chronically treated with beta blockers and heart rate of fewer than 50 beats/min; cardiac insufficiency with a left ventricular ejection fraction of less than 40%; epilepsy or seizures; acute cerebral pathology; obstructive sleep apnea syndrome; patients with a preoperative oxygen saturation measured by pulse oximetry (Spo_2) less than 95%; severe hepatic insufficiency (defined as prothrombin ratio less than 15%); adults legally protected (under judicial protection, guardianship, or supervision); persons deprived of their liberty; or patients in whom the Confusion Assessment Method[11,12] could not be performed.

Randomization and Interventions

Patients were randomized in a 1:1 ratio to either the remifentanil group or the dexmedetomidine group. Randomization was centralized and computer-generated, and each patient was given a unique randomization number (patient code). It was a block randomization stratified by center and by the type of surgery: abdominal (digestive, urologic, gynecologic) or nonabdominal. Treatment assignments were concealed from patients, nonmedical research staff, the statistician, and the data and safety monitoring committee. The anesthesiologist in charge of the patient performed the computerized allocation on the day of the surgery. He/she and the anesthesiologist nurse prepared the treatments, administered them to the patient during anesthesia

and collected the data during surgery. They did not participate in the assessment of the patient at any time. Although the staff members who collected data during surgery were aware of the group assignments, outcome assessors (nurses in postanesthesia care unit [PACU] and in the ward) were unaware of these assignments throughout the study. Indeed, PACU and ward nurses did not have access to the patient's anesthesia report.

Intraoperative and Postoperative Care

The previously published trial protocol[9] involved the standardization of anesthesia induction and maintenance. Based on ideal body weight, all patients received propofol (1.5 to 2 mg/kg) and then desflurane, IV lidocaine (1.5 mg/kg bolus plus 1.5 mg · kg^{-1} · h^{-1}), IV ketamine (0.5 mg/kg bolus plus 0.25 mg · kg^{-1} · h^{-1}), neuromuscular blockade, and dexamethasone (8 mg, IV bolus; Supplemental Digital Content 1, http://links.lww.com/ALN/C541). Enrolled patients were assigned to intraoperatively receive either IV remifentanil, using effect site target-controlled infusion mode (3 to 5 ng/ml corresponding to 0.1 to 0.25 μg · kg^{-1} · min^{-1}; remifentanil group) or IV dexmedetomidine administered at the infusion rate of 0.4 to 1.4 μg · kg^{-1} · h^{-1} (dexmedetomidine group). In both groups, intraoperative dose changes were left to the anaesthesiologist in charge of the patient. For dexmedetomidine, investigators were instructed to adapt the dosage of the continuous infusion according to the heart rate of the patient. Because of an increased incidence of bradycardia in the dexmedetomidine group, the independent data and safety monitoring board made the recommendation to lower the maximal dose of dexmedetomidine to 1 μg · kg^{-1} · h^{-1} starting on December 28, 2018, after 153 dexmedetomidine patients had been enrolled.

Dexmedetomidine or remifentanil were stopped at the end of surgery. In patients assigned to the remifentanil group, a bolus of IV morphine of 0.05 mg/kg was administered at the end of surgery.[13] Depth of anesthesia was individually adjusted to achieve and maintain a Bispectral Index between 40 and 60 (Covidien, France) and an analgesia nociception index between 50 and 70 (MétroDoloris, France) using drugs selected at the discretion of the supervising physician throughout the surgical procedure in each group. Standardized postoperative treatment involved IV lidocaine 1.5 mg · kg^{-1} · h^{-1} for 12 h, paracetamol (1 g/6 h IV and then orally), nefopam (20 mg/6 h IV and then orally), and morphine titration in PACU followed by morphine IV patient-controlled analgesia both according to routine standard of care. Ondansetron was used as a rescue medication for postoperative nausea and vomiting. All patients received oxygen supplementation only when Spo_2 was lower than 95%. The patients were discharged from the PACU when their Aldrete score was higher than 9.[8] All other perioperative care was performed according to the discretion and practices of local clinicians.

Primary Outcome

The primary outcome was a composite of postoperative opioid-related adverse events within the first 48 h after extubation. Components of the composite primary outcome were postoperative hypoxemia, defined as an Spo_2 level of less than 95% with a need for oxygen supplementation[14]; postoperative ileus, defined as an absence of flatus or stools; and postoperative cognitive dysfunction, evaluated using the Confusion Assessment Method.[11,12] The Confusion Assessment Method algorithm consists of four items: (1) acute onset or fluctuating course, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. The diagnosis of delirium by the Confusion Assessment Method requires a positive response to features 1 and 2 plus either 3 or 4; in these cases, the patients were considered as presenting a postoperative cognitive dysfunction. Each of the components of the primary outcome was also analyzed separately. Spo_2 was assessed continuously in PACU and every 6 h for 48 h in the ward. The Confusion Assessment Method was assessed on days 1 and 2.

Secondary Outcomes

Secondary outcomes were episodes of postoperative pain (defined as any episode with numeric rating scale greater than or equal to 3) within 48 h after extubation, opioid consumption during the 48 h after extubation, time to reach an Aldrete score greater than 9 after the discontinuation of remifentanil or dexmedetomidine, time to extubation, unplanned intensive care unit (ICU) admission, postoperative nausea and vomiting, need for rescue antiemetic medication, and the duration of hospital stay. Timepoints for pain and postoperative nausea and vomiting assessment were performed according to routine clinical practice in each center to minimize interference associated with the trial intervention. Safety elements included intraoperative cardiac events during surgery (number of episodes of bradycardia requiring atropine administration, hypotension defined as mean arterial pressure lower than 65 mmHg and hypertension defined as mean arterial pressure higher than 90 mmHg) and rescue medication.

Statistical Analysis

The study was designed as a superiority trial. Assuming a 5% rate of postoperative ileus,[15] a 20% rate of postoperative hypoxemia,[16–19] and 5% rate of postoperative delirium[20–22] (thus 30% for the primary outcome), we calculated that 196 patients/group would be needed to have 80% power at a two-sided α level of 0.05 to show a relative between-group difference of 40% in the composite primary outcome measure (30% to 18%). To allow for the potential unevaluable patients, the number of patients to be enrolled was increased to 400 patients.

We conducted all analyses before the breaking of the randomization code on an intention-to-treat basis. The primary endpoint (composite endpoint) was compared between the two groups with the chi-square test. Two interim analyses after inclusion of one third and two thirds of the patients and one final analysis were planned and realized. Stopping rules were the α spending function with the

O'Brien–Fleming boundary. The cumulative values of α for each analysis were: 0.00021 at the first analysis, 0.01202 at the second analysis, and 0.04626 at the final analysis (nTerim, V1.1, Statistical Solutions Ltd., Ireland). The trial would have been stopped early if the significance of the chi-square test was below these α values. For the analysis of the other endpoints, independent samples *t* test or a Mann–Whitney test if necessary was used to compare quantitative variables. Normality was assessed using Q–Q plots. Variables normally distributed were presented as means and SD; non-normally distributed variables were presented as median and interquartile range. A chi-square or Fisher exact test if necessary was used to compare qualitative variables. Except for the interim analyses described above, a two-sided *P* value < 0.05 was considered as significant for all analyses. After examination of the data, adjustment for confounding variables was not necessary. Multiple imputation by chained equation was used to replace missing data for the primary endpoint. Subgroup analyses were performed on the primary endpoint according to the type of surgery: abdominal (digestive, urologic, gynecologic) or nonabdominal. Statistical analysis was performed with SAS software V9.4 (SAS Institute, USA).

Results

Patients

Of the 1,522 screened patients from March 2017 through January 2019, 316 patients underwent randomization, and 314 patients (157 patients per group) were included in the analysis (fig. 1). The patients were included in 10 centers as follows (remifentanil/dexmedetomidine): Rennes (54/54), Nantes (1/2), Nimes (25/24), Lille (45/46), Metz (7/7), Périgueux (11/10), Clichy (3/3), Toulouse (4/4), Clermont-Ferrand (5/5), and Saint-Brieuc (3/3). Because of missing data on two patients, data on primary outcome were finally available for 312 patients (156 patients/group).

Because of increased incidence of bradycardia, the doses of dexmedetomidine were lower starting on December 28, 2018, after recommendation of the independent data and safety monitoring board. At the time, 309 patients were already included (156 in the remifentanil group and 153 in the dexmedetomidine group). After warnings made by the French Healthcare Safety Agency (Agence Nationale de Sécurité du Medicament, Paris, France), the independent data and safety monitoring board met again on January 18, 2019, and decided to stop the trial; the decision was accepted by the POFA steering committee. Only seven patients were included between December 28, 2018, and January 18, 2019. The reason for stopping the trial was severe bradycardia in five patients associated with asystole for three of them in the dexmedetomidine group. All of these bradycardias happened before the reduction of dexmedetomidine doses decided on December 28, 2018. None of these bradycardias/asystoles led to postoperative complications or sequelae (table 1).

The demographic and clinical characteristics of the two groups were similar at baseline (table 2). Intraoperative data were also similar with the exception of higher doses of propofol in the dexmedetomidine group (table 3).

Primary Outcome

The composite primary endpoint occurred in 122 of 156 (78%) patients in the dexmedetomidine group and in 105 of 156 (67%) of the patients in the remifentanil group (relative risk, 1.16; 95% CI, 1.01 to 1.33; $P = 0.031$ without imputation of missing data; $P = 0.027$ with imputation of missing data [1 in each group]). Hypoxemia occurred in 110 of 152 patients (72%) in the dexmedetomidine group (109 at day 1 and 1 at day 2) and in 94 of 155 patients (61%) in the remifentanil group (91 at day 1 and 3 at day 2; relative risk, 1.19; 95% CI, 1.02 to 1.40; $P = 0.030$). Mean duration of hypoxemia was not different between groups (343 ± 575 min in dexmedetomidine group *versus* 406 ± 606 min in remifentanil group; $P = 0.370$). The incidence of postoperative ileus (33 of 149 patients in the dexmedetomidine group (22%) and 28 of 151 patients in the remifentanil group (18%; relative risk, 1.19; 95% CI, 0.76 to 1.97; $P = 0.473$) or cognitive dysfunction (2 of 141 patients in the dexmedetomidine group at day 1 [1.4%] and 0 of 140 patients [0%] in the remifentanil group; $P = 0.498$) were not different between groups. Within the dexmedetomidine group, the primary outcome occurrence was analyzed according to the dosage of dexmedetomidine (lower or higher than the median value of the whole population 0.9 $\mu g \cdot kg^{-1} \cdot h^{-1}$), and these two subgroups were not different (table 4).

Secondary Outcomes

The cumulative 0 to 48 h postoperative morphine consumption (11 mg [5 to 21] *versus* 6 mg [0 to 17]; median difference, 3.3 mg; 95% CI, 0.8 to 5.7) and postoperative nausea and vomiting (58 of 157 (37%) *versus* 37 of 157 (24%); relative risk, 0.64; 95% CI, 0.45 to 0.90) were both statistically significantly less in the dexmedetomidine group, where analgesia measures were not different between groups (table 5). A total of 58 patients did not need any morphine administration after surgery (40 of 157 in the dexmedetomidine group and 18 of 157 in the remifentanil group; relative risk, 2.22; 95% CI, 1.33 to 3.70; $P = 0.0014$). The mean time to extubation and time to achieve an Aldrete score higher than 9 were longer in the dexmedetomidine than in the remifentanil group (table 5). Unplanned ICU admission and duration of hospital stay were not different between groups.

Subgroup Analysis

Patients who underwent abdominal surgery reported similar results as the whole population of the study: hypoxemia was more frequent in the dexmedetomidine group than in the remifentanil group (relative risk, 1.19; 95% CI, 1.02 to

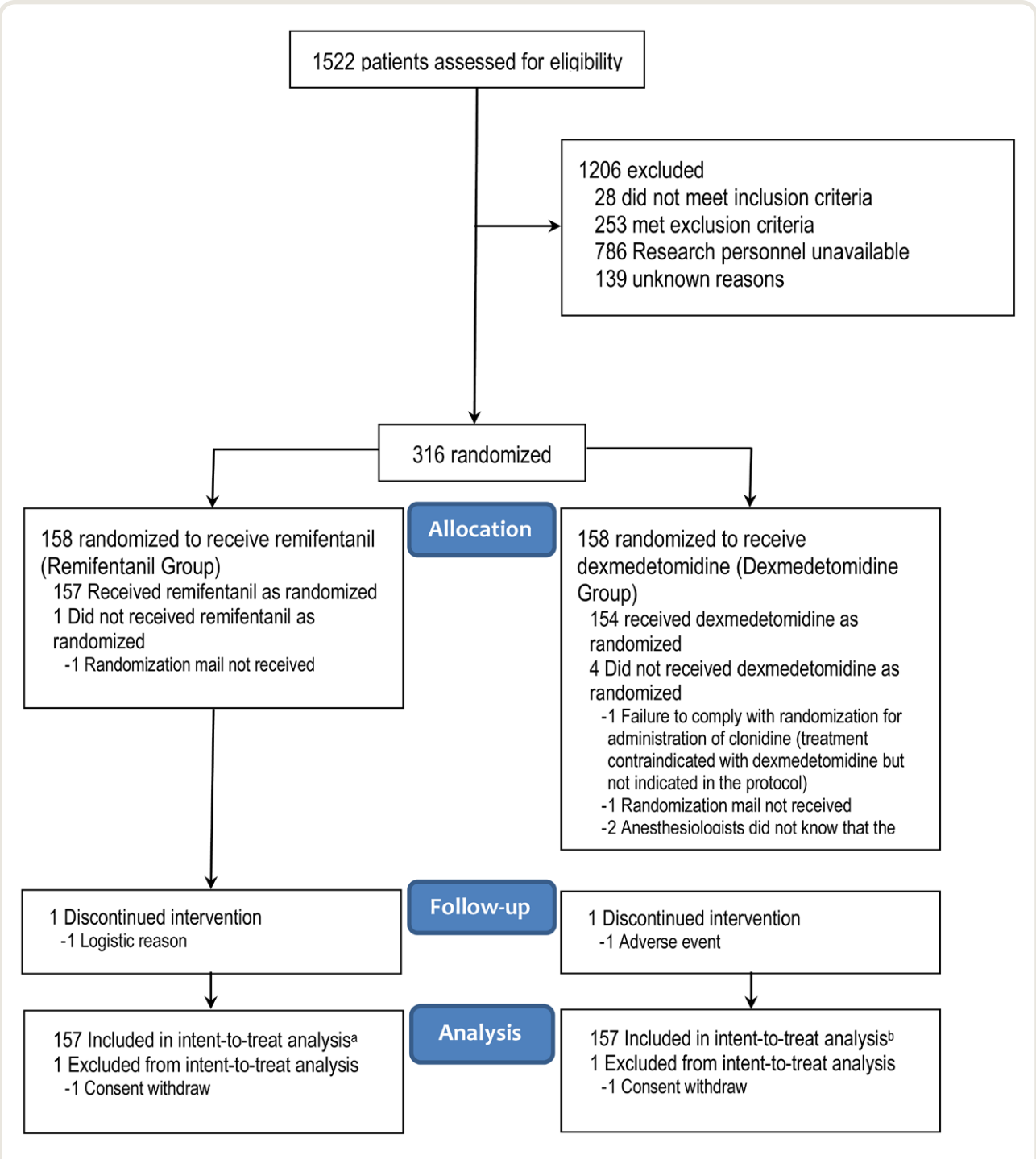

Fig. 1. Flow of participants through the study.

1.40; $P = 0.030$), and no difference was observed for ileus or postoperative cognitive dysfunction

Adverse Events

Bradycardia requiring atropine administration was more frequent in the dexmedetomidine group than in the remifentanil group (relative risk, 2.14; 95% CI, 1.18 to 3.88; table 5). Out of the five cases of profound bradycardia in the dexmedetomidine group, three occurred during the gas insufflation before laparoscopy (table 1). Within the dexmedetomidine group, complications were analyzed according to the dosage of dexmedetomidine (lower or higher than the

Table 1. Description of the Five Cases of Profound Bradycardia in Dexmedetomidine Group

Baseline Characteristics	Dex Dosage	Description	Comments
Female, 44 kg, scheduled for pancreatic surgery; no noticeable preoperative condition	1 μg · kg^{-1} · h^{-1}	40 min after induction and before surgical incision: Profound bradycardia (heart rate, 15 beats/min) and asystolia Resuscitation including atropine and epinephrine to restore a rhythm; dexmedetomidine administration was stopped Because of the administration of IV lidocaine, IV intralipids were administered Patient transferred in intensive care unit without surgery No complication, no sequalae, and surgery rescheduled 1 week later	The weight was overestimated by the investigator; low weight of the patient was not considered
Male, 85 kg, scheduled for robot-assisted laparoscopic prostatectomy; no noticeable preoperative condition	0.6 μg · kg^{-1} · h^{-1}	During surgical carbon dioxide insufflation: bradycardia (heart rate, 38 beats/min) followed by asystolia for 15 s Dexmedetomidine administration and insufflation were temporarily stopped; atropine was administered Normal hemodynamic restored and surgery completed No complication, no sequalae	Diagnosis: bradycardia secondary to vagal stimulation during carbon dioxide insufflation
Male, 76 kg, scheduled for robot-assisted laparoscopic prostatectomy; no noticeable preoperative condition	0.53 μg · kg^{-1} · h^{-1}	During surgical carbon dioxide insufflation: bradycardia (heart rate, 42 beats/min) followed by asystolia for 15 s Dexmedetomidine administration and insufflation were stopped; ephedrine and resuscitation maneuvers were administered Normal hemodynamic restored and surgery completed No complication, no sequalae	Diagnosis: bradycardia secondary to vagal stimulation during carbon dioxide insufflation
Female, 124 kg, scheduled for laparoscopic gastrectomy; no noticeable preoperative condition	0.9 μg · kg^{-1} · h^{-1}	15 min after carbon dioxide insufflation: bradycardia (heart rate, 10 beats/min) Dexmedetomidine administration was stopped; atropine was administered Normal hemodynamic restored and surgery completed No complication, no sequalae	Diagnosis not clear
Male, 84 kg, scheduled for laparoscopic prostatectomy. No noticeable preoperative condition.	0.48 μg · kg^{-1} · h^{-1}	During surgical carbon dioxide insufflation: bradycardia (heart rate, 30 beats/min): Dexmedetomidine dosage was lowered and insufflation is stopped; atropine and resuscitation maneuvers were administered Normal hemodynamic restored and surgery completed No complication, no sequalae	Diagnosis: bradycardia secondary to vagal stimulation during carbon dioxide insufflation

median value of the whole population: 0.9 μg · kg^{-1} · h^{-1}), and no differences were observed. Other severe unexpected events were not related to the group (table 5).

Discussion

In this multicenter randomized, open-label trial, opioid-free balanced anesthesia with dexmedetomidine resulted in a greater incidence of postoperative opioid-related serious adverse events compared with balanced anesthesia with remifentanil in patients undergoing elective intermediate or major noncardiac surgery. Patients in the opioid-free balanced anesthesia with dexmedetomidine group had more postoperative hypoxemia, delayed extubation, prolonged PACU stay, and intraoperative bradycardia. Five cases of severe bradycardia in the dexmedetomidine group led to the early termination of the study. Balanced opioid-free anesthesia was associated with less morphine consumption and fewer incidences of postoperative nausea and vomiting.

Altogether, our results reflect a prolonged sedation in the opioid-free balanced anesthesia group. In our study, we chose not to administer a bolus of dexmedetomidine to avoid bradycardia. In the absence of validated monitors of nociception and depth of anesthesia during opioid-free anesthesia, investigators were asked to adapt the dosage of the continuous infusion according to the heart rate of the patient (with an upper limit of 1.4 and then 1 μg · kg^{-1} · h^{-1}). The objective was to administer a dose allowing hemodynamic stability without bradycardia or hypotension. The resulting mean dosage of the continuous infusion (1.2 ± 2 μg · kg^{-1} · h^{-1}) in our study can be considered high, and we could hypothesize that the increased sedation and the high incidence of severe bradycardia observed in our study are a consequence of this high dosage. When analyzing the five cases of severe bradycardia in our study, one case was related to an overestimation of the patient's weight, whereas the other four cases all happened during carbon dioxide insufflation for laparoscopic surgery. Establishing artificial pneumoperitoneum and therefore increasing intraabdominal pressure can lead to unexpected cardiovascular changes including bradycardia. The addition of dexmedetomidine in this specific situation could then be at risk. These four cases of bradycardia raise questions regarding the use of dexmedetomidine during carbon dioxide insufflation for laparoscopic surgery.

Further, significantly more patients did not need any opioid administration within the 48 h after surgery in the balanced opioid-free anesthesia with dexmedetomidine group. They also experienced less postoperative nausea and vomiting. One can hypothesize that morphine sparing might not be the only reason for the reduction of postoperative nausea and vomiting. Dexmedetomidine could have a prolonged antiemetic effect, as previously suggested.[23]

Table 2. Characteristics of the Patients at Baseline

Characteristic	Remifentanil Group (N = 157)	Dexmedetomidine Group (N = 157)	Standardized Difference (95% CI)
Age, yr	60.6 ± 13.3	58.8 ± 13.3	–0.13 (–0.36 to 0.09)
Female sex	60 (38)	48 (31)	0.16 (–0.06 to 0.38)
Weight, kg	79 ± 20	81 ± 19	0.09 (–0.14 to 0.31)
Body mass index, kg/m^2	27 ± 7	27 ± 6	0.04 (–0.19 to 0.26)
ASA physical status*			0.30 (0.07 to 0.52)
I	56/153 (37)	41/155 (26)	
II	83/153 (54)	102/155 (66)	
III	14/153 (9)	11/155 (7)	
IV	0/153 (0)	1/155 (1)	
Type of surgery			0.08 (–0.14 to 0.30)
Abdominal surgery	146 (93)	149 (95)	
Digestive	66 (45)	58 (39)	
Urologic	70 (48)	83 (56)	
Gynecologic	10 (7)	8 (5)	
Other surgeries	11 (7)	8 (5)	
Orthopedics	5 (46)	5 (63)	
Ear, nose, throat	1 (9)	1 (12)	
Vascular	3 (27)	1 (12)	
Other	2 (18)	1 (12)	
Heart rate, beats/min	77 ± 15	75 ± 13	–0.10 (–0.32 to 0.12)
Arterial blood pressure, mmHg			
Systolic	138 ± 20	134 ± 17	–0.21 (–0.43 to 0.01)
Diastolic	79 ± 12	78 ± 12	–0.09 (–0.31 to 0.13)
Mean	99 ± 13	97 ± 12	–0.16 (–0.38 to 0.06)

The data are presented as means ± SD for continuous variables and frequency (%) for categorical variables. Heart rate and blood pressure were assessed during the preoperative consultation.

*The American Society of Anesthesiologists (ASA) criteria for physical status include a classification for normal health (I), mild systemic disease (II), severe systemic disease (III), and severe systemic disease that is a constant threat to life (IV).

Smaller studies have already shown that opioid-free anesthesia allows postoperative opioid sparing. After bariatric surgery[1] and spine surgery,[7] opioid-free anesthesia protocols allowed better postoperative analgesia with less morphine consumption and lesser risk of postoperative nausea and vomiting with opioid-free anesthesia during bariatric surgery.[3] However, our findings differ from those of previous smaller studies that reported benefits of opioid-free anesthesia on postoperative outcomes. Indeed, in our study, patients experienced more adverse events, despite a lower

Table 3. Intraoperative Data

Variable	Remifentanil Group (N = 157)	Dexmedetomidine Group (N = 157)	Mean Difference (95% CI)	*P* Value
Ventilator parameter (end of surgery)				
Respiratory frequency per min	17 ± 3	17 ± 3	0 (–1 to 1)	0.634
PEEP, cm H_2O	6 ± 1	6 ± 2	0 (0 to 0)	0.709
Tidal volume, ml	462 ± 59	475 ± 73	13 (–3 to 28)	0.110
FIO_2, %	50 ± 17	52 ± 17	2 (–2 to 6)	0.160
Duration of surgery, min	168 ± 80	169 ± 83	1 (–17 to 19)	0.888
Duration of anesthesia, min	257 ± 140	268 ± 154	11 (–22 to 44)	0.511
Anesthetic drugs				
Dose of propofol, mg	185 ± 65	231 ± 86	46 (29 to 63)	< 0.0001
Dose of lidocaine, mg	447 ± 273	443 ± 266	–3 (–64 to 57)	0.91
Dose of ketamine, mg	74 ± 36	76 ± 37	2 (–6 to 11)	0.57
Dose of remifentanil, µg)	1,403 ± 713			
Dose of remifentanil, µg · kg^{-1} · min^{-1}	0.09 ± 0.04			
Dose of dexmedetomidine, µg · kg^{-1} · h^{-1}		1.2 ± 2		

The data are presented as means ± SD.

FIO_2, inspiratory fraction of oxygen; PEEP, positive end-expiratory pressure.

Table 4. Primary Outcome and Its Components

Variable	Remifentanil Group (N = 157)	Dexmedetomidine Group (N = 157)	Risk Difference (95% CI)	*P* Value
Composite primary endpoint	105 (67%)	122 (78%)	11 (1 to 20)	0.031
Postoperative hypoxemia	94 (61%)	110 (72%)	12 (1 to 22)	0.030
Postoperative ileus	28 (18%)	33 (22%)	4 (–6 to 13)	0.473
Cognitive dysfunction	0 (0%)	2 (1%)	1 (–1 to 3)	0.498

The components of the composite primary outcome (within the first 48 h after extubation) were postoperative hypoxemia defined as an oxygen saturation level of less than 95% with a need for oxygen supplementation, postoperative ileus defined as an absence of flatus or stools, and postoperative cognitive dysfunction evaluated using the Confusion Assessment Method.

Table 5. Secondary Outcome Analyses and Adverse Events

Outcome	Remifentanil Group	Dexmedetomidine Group	Mean/Median/Risk Difference (95% CI)	*P* Value
Morphine consumption, mg*	11(5 to 21)	6 (0 to 17)	–3.3 (–5.7 to –0.8)†	0.002
Number of episodes with numerical rate scale ≥ 3‡	2 (1 to 3)	2 (1 to 3)	0 (0 to 0)†	0.618
Time for extubation, h§	0:40 ± 1:28	1:09 ± 1:45	0:29 (0:07 to 0:51)‖	0.009
Duration of PACU stay, h#	1:53 ± 1:47	2:28 ± 2:11	0:35 (0:09 to 1:02)‖	0.010
Unplanned admission‡	0 (0)	1 (0)	0 (0 to 0)**	1.000
Postoperative nausea and vomiting‡	58 (37)	37 (24)	–13 (–23 to –3)**	0.010
Use of rescue antiemetic drugs‡	41 (26)	21 (13)	–13 (–21 to –4)**	0.005
Duration of hospital stay, days‡	5.1 ± 4.5	5.4 ± 5.6	0.2 (–0.9 to 1.4)‖	0.664
Adverse events	n = 157	n = 157		
Hypertension	117 (75)	125 (80)	5 (–4 to 14)**	0.283
Hypotension	94 (60)	97 (62)	2 (–9 to 13)**	0.728
Bradycardia	14 (9)	30 (19)	10 (3 to 18)**	0.009
Bradycardia with heart rate < 45 beats/min	9 (6)	25 (16)	10 (3 to 17)**	0.004
Other severe unexpected events	5 (3)	5 (3)	0 (–4 to 4)**	1.000

The data are presented as means ± SD for continuous variables except for morphine consumption and number of episodes with numeric rating scale of at least 3, for which data are presented as median (25th percentile; 75th percentile) and frequency (%) for categorical variables. Bradycardia was defined as the number of episodes with atropine administration, hypotension was defined as mean arterial blood pressure lower than 65 mmHg, and hypertension was defined as the mean arterial blood pressure higher than 90 mmHg. Other severe unexpected events were hemorrhagic shock, surgical complications, inhalation, myocardial infarction, and colic ischemia.

*Data were available on 156 patients in each group. †Median difference. ‡Data were available on 157 patients in each group. §Data were available on 157 patients in the remifentanil group and 154 patients in the dexmedetomidine group. ‖Mean difference. #Data were available on 156 patients in the remifentanil group and 154 patients in the dexmedetomidine group. **Risk difference.

overall opioid consumption. Mulier *et al.*[24] reported, in a small randomized controlled trial, that opioid-free anesthesia was associated with a better recovery, better comfort, and less postoperative pain, while patients consume less postoperative morphine and experience less postoperative nausea and vomiting and less postoperative oxygen desaturation when compared with opioid-based anesthesia during bariatric surgery. A retrospective study, performed in 9,246 patients who underwent bariatric surgery, also reported that opioid-free anesthesia was associated with less postoperative complications.[4] Meta-analyses have also reported benefits with opioid-free anesthesia.[25,26] However, the results have to be analyzed with caution because the heterogeneity of the studies included was high. In addition, all these meta-analyses included some studies in which dexmedetomidine was administered at the same time as opioids; that is, the protocol was not strictly avoiding opioids.

Previous studies have led to conflicting results regarding the effect of opioid-free anesthesia on sedation. Indeed, some studies reported a reduction in extubation delay[1] or in desaturation,[24] whereas others reported a prolonged extubation time and PACU stay[27] and prolonged postoperative sedation.[27,28] These discrepancies could be due to the different dosages of dexmedetomidine administered. Indeed, the efficient dosage of dexmedetomidine during general anesthesia that allows for hemodynamic stability with the least side effects has not yet been determined. Doses vary from one study to another: some investigators administered a bolus followed by a continuous infusion (0.5 to 1 μg/kg followed by 0.2 to 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$),[1,29] others administered only a bolus (0.75 to 4 μg/kg),[28,30] and some administered a continuous infusion without a bolus (0.6 to 1.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$).[7] With these doses, most previous studies on dexmedetomidine administered intraoperatively during opioid-free anesthesia[25] or even when administered in ICU[31] have reported bradycardia. A

meta-analysis including 4,868 patients reinforced this warning and showed a high-confidence evidence for a risk of bradycardia.[32] Finally, the association of dexmedetomidine with propofol was shown to increase the risk of hypotension and bradycardia when compared with propofol alone during colonoscopy.[33]

Analyzing the incidence of hypoxemia in our study, many hypotheses can be formulated. One can hypothesize that the combination of lidocaine, ketamine, and dexmedetomidine in the opioid-free balanced anesthetic with dexmedetomidine group could have participated in the higher incidence of serious adverse events. Indeed, the sedative effect of dexmedetomidine and/or effects of other administered drugs cannot be ruled out in the incidence of hypoxemia. Moreover, postoperative hypoxemia is not solely a consequence of opioid administration. However, opioids contribute to hypoxemia, and patients who received greater opioid doses were shown to be more likely to experience at least one episode of postoperative hypoxemia.[34] Postoperative opioid-induced respiratory depression has been associated with devastating consequences such as death and brain damage.[35]

There are several limitations to our study. Because of the lack of validated nociception and depth of anesthesia monitors during opioid-free anesthesia, the trial design based the dosage of dexmedetomidine on the patient's heart rate. This might have led to higher dosages and side effects such as sedation and bradycardia; the latter finally led to the premature interruption of the study. However, as stated above, the optimal dosage of dexmedetomidine under general anesthesia has not yet been determined. The premature interruption of the study for safety concerns is obviously a limitation. The choice of dexmedetomidine could also be questioned. Despite the different definitions of opioid-free anesthesia that can be found in the literature or in practice (with or without α2 agonists/ketamine/local anesthetics), previous studies have suggested that α2 agonists especially dexmedetomidine, could provide the hemodynamic stability traditionally provided by intraoperative opioids.[24] However, our definition of opioid-free anesthesia (multimodal anesthesia including ketamine, lidocaine, and dexmedetomidine) is not definitive, and other ways to administer opioid-free anesthesia have to be explored. Another limitation is the high frequency of hypoxemia that occurred in our study, which was higher than expected. The incidence of postoperative hypoxemia varies between 20 and 40% in the literature,[16,18,19] which is less than the 70% observed in our study. However, the definition of postoperative hypoxemia is neither consensual nor clear in the literature. Indeed, the Spo_2 threshold for the definition of hypoxemia varies from 90 to 95%.[14,24] By choosing 95%, we observed more hypoxemia than some previous studies. Moreover, in our study patients did not receive preemptive oxygen therapy. Indeed, Mulier *et al.*[24] reported less hypoxemia with opioid-free anesthesia, but all patients received systematic postoperative oxygen therapy. In our study, we probably observed more hypoxemia because oxygen was delivered only when Spo_2 was lower than 95%. Finally, the collection of pain scores and postoperative nausea and vomiting measures was not standardized, and we did not assess the quality of postoperative recovery.

The choice of using lidocaine and ketamine in both groups and not only in the opioid-free balanced anesthesia group reflects some common practices based on international literature.[36,37] Such a combination of drugs has rarely been previously studied, even if they are used in daily practice in some countries. Indeed, in previous studies showing a benefit of opioid-free anesthesia without complications or side effects, patients in the control group received only intraoperative opioids.[24]

In summary, among patients undergoing elective intermediate or major noncardiac surgery, more patients having opioid-free anesthesia with dexmedetomidine had serious adverse events compared with those receiving remifentanil. Despite less postoperative opioid consumption and nausea and vomiting, patients receiving opioid-free anesthesia with dexmedetomidine had more intraoperative severe bradycardia and hypoxemia in PACU, longer time to extubation, and longer PACU stay. These results suggest that opioid-free balanced anesthesia is not as outstanding when compared with intraoperative opioids and raises questions about the benefit of eliminating intraoperative opioids and using dexmedetomidine when lidocaine and ketamine are already used.

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Competing Interests

Dr. Beloeil reported receiving fees as a speaker from Abbvie (Rungis, France) and Aspen (Rueil-Malmaison, France) and as member of an expert board Orion Pharma (Issy-les-Moulineaux, France). Dr. Asehnoune received fees from LFB (Les Ulis, France), Baxter (Guyancourt, France), Fisher and Paykel (Illkirch-Graffenstaden, France), and Edwards Lifescience (Guyancourt, France). Dr. Chanques received fees as a speaker from Aspen Medical (Rueil-Malmaison, France) and Orion Pharma and as member of an expert board from Orion Pharma. Dr. Roquilly received consulting fees from Merck (Fontenay-sous-bois, France) and bioMerieux (Bruz, France). Dr. Futier reported consulting fees from Drager Medical (Anthony, France), GE Healthcare (Velizy-Villacoublay, Farnce), Orion Pharma, and Edwards Lifesciences; personal fees for lectures from Fresenius Kabi (Sevres, France) and Getinge (Massy, France); and nonfinancial support from Fisher and Paykel Healthcare. The other authors declare no competing interests.

Reproducible Science

Full protocol available at: helene.beloeil@chu-rennes.fr. Raw data available at: helene.beloeil@chu-rennes.fr.

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