1.      Original protocol, final protocol, summary of changes.  
2.      Original statistical analysis plan, final statistical analysis plan, summary of changes

1. **Original protocol, final protocol, summary of changes.**

**The Original protocol has been published:** BMJ Open 2018 Jun 30;8(6):e020873

**Final protocol**

**INTRODUCTION**

Since the 1960’s, intraoperative administration of opioids is considered a keystone of anaesthesia as well as hypnotics and muscle relaxants. Synthetic opioids were introduced to achieve hemodynamic stability during anaesthesia. They allow an inhibition of the sympathetic system without cardiovascular collapse and histamine release. Since then, anaesthesia has changed from inhalation to multimodal anaesthesia with lower doses of hypnotic. In 2017, the intraoperative objectives of hypnosis, hemodynamic stability, immobility and anticipation of postoperative analgesia can be achieved without opioids. Moreover, opioid administration consequences are neither scarce nor benign for the patient. Perioperative opioids are

associated with nausea and vomiting [[1](#_ENREF_1)], sedation [[2](#_ENREF_2)], ileus [[3](#_ENREF_3)], confusion/delirium [[4](#_ENREF_4)], respiratory depression [[5](#_ENREF_5)], increased postoperative pain and morphine consumption [[6](#_ENREF_6)], immunodepression [[7](#_ENREF_7)], hyperalgesia and chronic postoperative pain [[8](#_ENREF_8) [9](#_ENREF_9)]. Among these complications, hypoxemia, ileus and confusion/delirium are the most frequent. They are associated with a significant morbidity, can increase the length of stay and slow postoperative rehabilitation:

- Postoperative hypoxemia is frequent in post anaesthesia care unit (PACU) [[10](#_ENREF_10)]. It appears within minutes after tracheal extubation and the incidence is maximal 30 minutes after the arrival in PACU. The incidence of postoperative arterial hypoxemia after abdominal surgery varies between 20 to 40 % in the literature [[11](#_ENREF_11) [12](#_ENREF_12)]. The residual effect of anaesthetic drugs plays a major role in the genesis of early postoperative hypoxemia, especially opioids [[13](#_ENREF_13)]. Postoperative opioid-induced respiratory depression is a cause of death and brain damage. Amongst 357 acute pain claims registered in the USA between 1990 and 2009, 92 were respiratory depression of which 77% resulted in severe brain damage or death. The vast majority (88%) of respiratory depression occurred within 24 hours of surgery [[5](#_ENREF_5)].

- Postoperative ileus (POI) is a well-known consequence and complication of gastrointestinal, pelvic, and some non-abdominal surgeries (i.e. spine), resulting in significant morbidity and patient discomfort and dissatisfaction. More serious complications can include gastrointestinal perforation, nosocomial infections, malnourishment and muscular atrophy. These sequelae make POI one of the most important factors of prolonged hospitalization following abdominal surgery. The development and consequences of POI following abdominal surgery is further complicated by the need for opioids to manage moderate to severe pain. Opioids are

associated with bowel dysfunction, POI in non-abdominal procedures, and can exacerbate and prolong recovery from ileus following abdominal surgeries. A recent review revealed that, in selected surgeries, 10.3% of patients treated with opioids had ileus [[3](#_ENREF_3)]. Furthermore, higher doses of opioids were associated with higher incidence of POI.

- Delirium and postoperative cognitive dysfunction (POCD) are extremely common in

geriatric surgical patient. After elective major joint replacement or other types of major surgery, about 5% to 15% of elders develop delirium and 25% to 40% and 12% to 15% develop, respectively, early or late POCD. Delirium and POCD are associated with prolonged length of stay, discharge to a place other than home and higher 1-year mortality. In addition, delirium is associated with an accelerated trajectory of cognitive decline to dementia [[14](#_ENREF_14) [15](#_ENREF_15)]. Opioids are one of the risk factors of POCD. Patients receiving postoperative analgesia through a patient-controlled analgesia device that administer opioids intravenously were shown to be at significantly higher risk for the development of POCD [[4](#_ENREF_4)]. Moreover, fast-track set-up with multimodal opioid sparing analgesia is associated with a lack of delirium after elective hip and knee arthroplasty in elderly patients [[16](#_ENREF_16)].

Efficacious multimodal analgesia and anaesthesia are the basis of successful fast-track surgery. These multidrug regimens aim at decreasing postoperative pain, intra- and postoperative opioid requirements, and subsequently, opioid-related adverse effects and to fasten recovery. Opioid-free postoperative analgesia has been therefore recommended for more than 10 years [[17](#_ENREF_17)]. Based on the same principle of opioid sparing, opioid-free anaesthesia (OFA) is a multimodal anaesthesia associating hypnotics, NMDA antagonists, local anaesthetics, anti-inflammatory drugs and alpha-2 agonists. Hemodynamic stability can be achieved without opioids during anaesthesia in 2017. The first studies on OFA focused on bariatric surgery where respiratory complications are frequent. OFA with dexmedetomidine (Dex) significantly attenuated postoperative pain and reduced opioid requirements without causing respiratory depression in obese patients [[18](#_ENREF_18) [19](#_ENREF_19)]. OFA was then proposed for awake neurosurgery [[20](#_ENREF_20)] and various minor [[21](#_ENREF_21)] or major surgeries [[22](#_ENREF_22)]. Two meta-analyses have concluded that intraoperative Dex reduced postoperative pain, opioid consumption [[23](#_ENREF_23) [24](#_ENREF_24)]. One study showed a reduction of postoperative nausea and vomiting [[25](#_ENREF_25)]. Adverse effects were hypotension and bradycardia. Proofs of the effect of OFA on reducing opioid-related adverse events after major or intermediate non-cardiac surgery are still scarce. We hypothesized that the reduced opioid used during and after surgery allowed by OFA compared with standard of care will be associated with a reduction of postoperative opioid-related adverse events.

**METHODS AND ANALYSIS**

**Trial design**

The POFA study is an investigator initiated, national, multicentre, randomized, single-blind, parallel-group clinical trial with concealed allocation of patients scheduled to undergo elective intermediate or major non-cardiac surgery 1:1 to receive either a standard anaesthesia protocol or OFA. The trial will be conducted at 11 university and non-university centres. The study started in December 2017 and the recruiting period will be 24 months.

**Participant eligibility and consent**

Trial site investigators will identify consecutive eligible patients from the listed criteria. Eligible patients will receive written and oral information and will be included after investigators have obtained informed written consent.

Inclusion criteria

1. Adult (18 years or older) patients admitted to the participating centre
2. Undergoing a scheduled major or intermediate non-cardiac surgery [[26](#_ENREF_26)]
3. Benefiting from the health insurance system
4. Having signed an informed consent

Non-inclusion criteria

1. Pregnant or breast-feeding women
2. Allergy to dexmedetomidine or one of its excipients
3. Allergy to one of the drugs used for anaesthesia or one of their excipients
4. Urgent surgery
5. Intracranial surgery
6. Transplant surgery or transplanted patients
7. Surgery with planned regional anaesthesia
8. Outpatient surgery
9. Atrioventricular block, intraventricular or sinoatrial block
10. Adam-Stokes syndrome
11. Patients chronically treated with beta blockers and HR < 50 bpm
12. Cardiac insufficiency with a LVEF <40%
13. Epilepsy or seizures,
14. Acute cerebral pathology
15. Obstructive sleep apnoea syndrome
16. Severe hepatic insufficiency (Prothrombin Ratio < 15%)
17. Adults legally protected (under judicial protection, guardianship, or supervision), persons deprived of their liberty
18. Patients in whom the CAM-ICU cannot be performed (i.e. deaf patients)
19. Uncontrolled hypotension,

**Allocation and blinding**

Patients will be randomized in two groups (control group and Dex group). In order to ensure group comparability, a plan of randomization will be used. Randomization will be done by investigators as close as possible to the surgery. Each patient will be given a unique patient-number and a randomization number (patient code) will be computer generated. It will be a block-randomization. Randomization will be stratified on the centre and on the type of surgery: abdominal (digestive, urological, gynaecological) or non-abdominal. The primary evaluation criterion will be assessed blinded to the randomization group. During the study period, patients and outcome assessors will be kept blind to the randomization group. Nurses evaluating outcomes in PACU and in the ward will not participate to the anaesthesia and will not be aware of the randomization group. They will be blind to the treatment. The anaesthesiologist and the nurse anaesthesiologist (care providers) will be the only ones not blinded. They will not participate in the assessment of the patients at any time.

At each participating centre, data will be collected and entered into the electronic web-based case report form (eCRF) by trial or clinical trained personal (clinical research associate), blinded to the allocation group, under the supervision of the trial site investigators.

**Interventions**

All included patients will be allocated to one of the following two study groups:

* **Control group:** patients will receive a standardized anaesthesia protocol with remifentanil
* **Dex group:** patients will receive a standard anaesthesia protocol with dexmedetomidine

*Standardized intravenous induction of general anaesthesia will include:* Propofol: 1.5 - 2 mg/kg*,* Lidocaine: 1.5 mg/kg (IV bolus)*,* Ketamine: 0.5 mg/kg (IV bolus)*,* Cisatracurium: 0.15 mg/kg (IV bolus before tracheal intubation)*,* Dexamethasone: 8 mg (IV bolus) and target-controlled infusion (TCI) of remifentanil (3 - 5 ng/ml)**(Control group)**orIVdexmedetomidine 0.4-1.4 μg/kg IV (**Dex group).**

*Standardized maintenance of general anaesthesia will include:* Desflurane*,* IVLidocaine: 1.5 mg/kg/h *,*  IV Ketamine: 0.25 mg/kg/h, IV Cisatracurium as neededandTCIremifentanil (2 - 5 ng/ml) **(Control group)**or IV dexmedetomidine 0.4-1.4 μg/kg/h IV (**Dex group).** At the end of surgery, IV morphine (0.05 mg/kg) will be administered in the **Control group.** In both groups, intraoperative dose changes will be left to the anaesthesiologist in charge of the patient. Depth of anaesthesia (BISTM, Covidien, France) and analgesia (ANITM, Métrodoloris, France) will be monitored. The target of BISTM will range between 40 and 60 and ANITM between 50 and 70.

*Standardized postoperative protocol will include:*

*Extubation after verification of standard criteria:* Spontaneous breathing with VTe ≥ 5-8 ml/kg, respiratory rate of 12 to 25 c/min,absence of residual curarisation defined by T4/T1 ≥ 90% (train-of-four),SpO2 ≥ 95% with FiO2 ≤ 50%,verbal and motor response to simple orders,temperature ≥ 36°C.**Extubation defines the H0** for assessment of the primary and secondary criteria events.

*Postoperative treatment:* IV Lidocaine 1.5 mg/kg/h for 12 hours*,* Paracetamol (1g/6h IV and then oral)*,* Nefopam (20mg/6h IV and then oral), Morphine titration in PACU according to routine standard of care*,* Morphine IV PCA according to routine standard of care*,* Ondansetron as a rescue medication in case of PONV.Patients will leave the PACU when Aldrete score > 9.

Decisions about all other aspects of patient care will be performed according to the expertise of the staff at each centre and to routine clinical practice to minimize interference with the trial intervention. Nevertheless, to avoid extremes of clinical practice, trial investigators will be strongly encouraged to apply intraoperative normothermia, multimodal postoperative analgesia (without regional anaesthesia) and prevention of postoperative nausea and vomiting (PONV) based on Apfel score. Early postoperative resumption of fluids and solids will be encouraged.

**Outcome measures**

Primary composite outcome

The primary composite outcome will be the occurrence of a severe postoperative opioid-related adverse event within the first 48 hours after extubation defined as: postoperative hypoxemia or postoperative ileus (POI) or postoperative cognitive dysfunction (POCD). The onset of an opioid-related adverse event will be assessed blinded to the randomization group

**Postoperative hypoxemia** is defined as therapeutic oxygen supplementation to maintain SpO2 > 95% within the first 48h after extubation; the duration of oxygen treatment will also be recorded [[27](#_ENREF_27)].

**Postoperative ileus (POI)** is defined as an absence of flatus or stools within the first 48h after extubation.

**Postoperative cognitive dysfunction (POCD)** will be evaluated using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) by a care provider (either anaesthesiologist or nurse). The Confusion Assessment Method (CAM) [[28](#_ENREF_28) [29](#_ENREF_29)] has been validated in multiple settings and is a widely used standardized method for identifying delirium with a high sensitivity of 94% (95% CI, 91%-97%), high specificity of 89% (95%CI, 85%-94%). The CAM algorithm consists of 4 items: 1. Acute Onset or Fluctuating Course. 2. Inattention 3. Disorganized thinking. 4. Altered Level of consciousness. The diagnosis of delirium by CAM/CAM-ICU requires a positive response to features 1 and 2 plus either 3 or 4; in these cases, the patients will be considered as presenting a POCD.

Secondary outcomes

* Each component of the primary outcome measure will be analysed separately.
* Number of episodes of postoperative pain (numeric rating scale (NPS) ≥ 3) within 48 hours after extubation and at rest
* Opioid consumption during the 48 hours following extubation
* Time between the end of remifentanil or dexmedetomidine administration and an Aldrete score > 9 (when applicable)
* Time between the end of remifentanil or dexmedetomidine administration and extubation
* Rate of unscheduled admission in intensive care unit
* Number of PONV episodes during the 48 hours following extubation. Need for rescue antiemetic medication will be recorded
* Hospital length of stay (max 28 days) defined as the number of days after extubation before first hospital discharge
* Number of cardiac events during surgery (bradycardia defined as the number of episodes with atropine administration, hypotension defined as PAM < 65 mmHg, hypertension defined as PAM > 90 mmHg) and rescue medication

**Sample size estimation**

196 patients per group will be needed to have 80% power, at a two-sided alpha level of 0.05, to show a relative between-group difference of 40% in the composite primary outcome measure (30% to 18%), under the assumption of an overall incidence of 5% of postoperative ileus (from 5% to 20.6% after major or intermediate non-abdominal and abdominal surgery, respectively) [[10](#_ENREF_10) [11](#_ENREF_11)], 20% of postoperative hypoxemia (from 20% to 40% depending on the surgical site) [[12](#_ENREF_12) [13](#_ENREF_13)] and 5% of postoperative delirium (from 3.6% to 30% after elective surgery and abdominal surgery, respectively) [[3](#_ENREF_3) [5](#_ENREF_5) [14](#_ENREF_14)], thus 30% for the primary outcome measure. A total of 400 patients will be included to take into account non-evaluable patients. Patients undergoing a second surgery or dying within 48 hours without presenting the primary evaluation criteria will be kept considered as success in the analysis.

**Statistical analysis (cf. plan of statistics)**

**Missing values**

Missing data will not be replaced. Mixed models can be used in analysis of repeated data to avoid deleting subjects with any missing values.

**Data Registration**

Data will be entered into the web- based electronic case report form (eCRF) by trial or clinical personnel under the supervision of the trial site investigators at each participating centre. From the eCRF the trial database will be established. Data collection will be monitored by trained research coordinators.

The following data will be registered:

Baseline characteristics at randomization:

Demographic data (age, height, weight, gender and body mass index); American Society of Anaesthesiologists (ASA) physical status; type of surgery; significant comorbidities (cardio-vascular, respiratory, neurologic, psychiatric and /or abdominal disease, cancer, preoperative chemotherapy or radiotherapy).

Intraoperative data:

Date of surgery, total doses of anaesthesia medications, doses of rescue medication (atropine, norepinephrine, adrenaline, ephedrine, anti-hypertensive medications), BISTM and ANITM values, Ventilation data at the beginning and the end of the surgery (Vt, RR, Peep, inspired fraction of oxygen), duration of surgery and anaesthesia, intraoperative complications (episode of bradycardia with atropine administration, hypotension (MAP < 65 mmHg), hypertension (MAP < 90 mmHg), shock (haemorrhagic, septic, cardiac, anaphylactic), clamping of a major vessel (aorta, vena cava), cardiac arrest, death, oxygen desaturation (SpO2 < 90% during more than 5 minutes), necessity to interrupt the procedure).

Postoperative data:

Patients will be assessed once daily during until the end of day 2 (48 hours).

The following data will be collected:

* Post OR care pathway (PACU, scheduled intensive care unit (ICU) admission, unscheduled ICU admission)
* Duration to obtain Aldrete score ≥ 9
* Extubation time
* Post PACU care pathway (surgical ward, scheduled intensive care unit (ICU) admission, unscheduled ICU admission)
* Duration of stay in PACU
* Episodes of oxygen desaturation defined by SPO2 < 95 % with oxygen requirement during the first 48 hours after extubation
* Time to first flatus and first stool
* CAM-ICU daily during the first 48 hours after extubation
* Episodes of PONV
* Presence of a postoperative naso gastric tube. If yes, date and hour if withdrawal
* Postoperative pain: episodes of NRS ≥ 3
* Total morphine consumption during the first 24 and 48 hours after extubation
* Length of stay (max 28 days)
* Death (until day 28)

**Patient withdrawal**

A participant who no longer agrees to participate in the clinical trial can withdraw the informed consent at any time without need of further explanation. Participants who will withdraw from the study will be followed up, according to routine clinical practice in each participating centre. In order to conduct intention-to-treat analyses with as little missing data as possible, the investigator may ask the participant which aspects of the trial he/she wishes to withdraw from (participation in the remaining follow-up assessments, use of already collected data). Whenever possible, the participant will be asked for permission to obtain data for the primary outcome measure. All randomised patients will be reported, and all data available with consent will be used in the analyses. If appropriate, missing data will be handled in accordance with multiple imputation procedures if missing data are greater than 5%.

**Safety**

Every serious adverse event related to the studied treatment or not, expected or unexpected, must be reported within 24 hours by the investigator to the sponsor on a “Serious adverse event” form on which will be indicated the date of occurrence, criterion of severity, intensity, relationship with the treatment (or the study) evaluated, and the outcome. The period in which serious adverse events should be reported begins from the day of the written informed consent to the end of the follow-up (48 hours). Whenever a serious adverse event persists at the end of the study, the investigator must follow the patient until the event is considered resolved. The following events: postoperative hypoxemia, postoperative ileus and postoperative

cognitive dysfunction will be recorded as primary evaluation criterion in the case report form. In order to avoid collection duplication, they will not be reported on the “adverse event” page of the case report form. As planned in the study, they will be analysed at the time of interim analyses (two interim analyses after inclusion of 1/3 and 2/3 of the patients) which will permit to show potential difference between the two groups during the study.

In addition, serious adverse events will be submitted to the data monitoring and safety committee (DMSC). The DMSC is independent of the trial investigators and will perform an ongoing review of safety parameters and overall study conduct. The DMSC is comprised of three independent clinicians (anaesthesiologists), a physician pharmacologist and a methodologist. The DMSC will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. To contribute to enhancing the integrity of the trial, the DMSC may also formulate recommendations relating to the recruitment/retention of participants, their management, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control. Recommendations for pausing or stopping the study will be made by the DMSC in case of serious adverse reactions and suspected unexpected serious adverse reaction.

All adverse events for which the investigator or the sponsor considers that a causal relationship with the investigational medicinal products can be reasonably considered, will be considered as suspected adverse reactions. If they are unexpected, they are qualified as being Suspected Unexpected SAR (SUSAR) and will be notified in a report by the sponsor to Eudravigilance (European pharmacovigilance database) and to local regulatory agency within the regulatory time periods for reporting: Immediate declaration if seriousness criteria is death or life-threatening condition, declaration within 15 days for other seriousness criteria.

**Data handling and retention**

Data will be handled according to French law. All original records (including consent forms, reports of suspected unexpected serious adverse reactions and relevant correspondences) will be archived at trial sites for 15 years. The clean trial database file will be anonymised and maintained for 15 years.

**Patient and public involvement**

Patient and public were not involved in any of the phases of this study

**ETHICS AND DISSEMINATION**

**Ethical and legislative approvals**

POFA trial was approved by the French National Safety and Drug Agency (Agence Nationale de Sécurité du Médicament (July, 11th, 2017). By September 4, 2017, the study has been approved for all centres by a central ethics committee (Comité de Protection des Personnes Ile-de-France II, Paris, France). The POFA trial is registered in the European Clinical Trials Database (EudraCT 2017-001907-61) and at ClinicalTrials.gov with the trial identification number NCT03316339. Trial methods and results will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines [[31](#_ENREF_31)].

**Publication plan**

Scientific presentations and reports corresponding to the study will be written under the responsibility of the coordinating investigator of the study with the agreement of the principal investigators and the methodologist. The co-authors of the report and of publications will be the investigators and clinicians involved, on a pro rata basis of their contribution in the study, as well as the biostatistician and associated researchers. All trial sites will be acknowledged, and all investigators at these sites will appear with their names under ‘the POFA investigators’ in an Appendix to the final manuscript. Rules on publication will follow international recommendations [[32](#_ENREF_32)].

**Conclusion**

The POFA trial is the first prospective, randomized, parallel, single-blind, multicentre study evaluating the effect of OFA on severe postoperative opioid-related adverse events. If POFA yields positive results, it would bring strong data to promote OFA. Showing a benefit of OFA in terms of reduction of opioid-related adverse events, reduction of global morbidity, reduction of the economic burden associated with opioid-related adverse events and reduction in length of stay would result in a collective benefit for future patients and could lead to significant changes in the standard of care in anaesthesia.

**DMSC:** Prof Patricia Lavand’homme (Brussels, Belgium), Dr Emmanuel Marret (Paris, France), Prof Jean Joris (Liège, Belgium), Dr Theodora Bejan-Angoulvant (Tours, France), Marina Nguon (Lyon, France).

**Scientific committee:** Prof Emmnanuel Futier (Clermont-Ferrand, France), Prof Gerald Chanques (Montpellier, France), Prof Bruno Laviolle (Rennes, france), Prof Helene Beloeil (Rennes, France).

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The funding sources had no role in the trial design, trial conduct, data handling, data analysis or writing and publication of the manuscript.

**Trial sponsor:** CHU de Rennes, Direction de la recherche Clinique, 2 avenue Henri le Guilloux, 35033 Rennes Cedex, France. The sponsor had no role in the trial design, trial conduct, data handling, data analysis or writing and publication of the manuscript.

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**Summary of changes**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Date** | **version** | **modifications** | **Approval by promotor** | **Approval by EC** | **Approval by ANSM** |
| 05/15/2017 | V1.0 |  | 05/17/2017 | 07/11/2017 | 05/22/2017 |
| 09/27/2017 | V2.0 | Answers to EC’s questions |  |  | 09/04/2017 |
| 10/06/2017 | V3.0 | 2 centres added | 10/06/2017 | 11/06/2017 | 11/20/2107 |
| 11/20/2017 | V4.0 | New version sent to the centres |  |  |  |
| 03/06/2018 | V5.0 | Adding ancillary study on chronic pain | 03/07/2018 | 05/14/2018 | NA |
| 06/14/2018 | V6.0 | New version sent to the centres |  |  |  |
| 11/19/2018 | V7.0 | Modification of the dosage of dexmedetomidine | 11/19/2018 | 12/17/2018 | 12/14/2018 |
| 12/28/2018 | V8.0 | New version sent to the centres |  |  |  |
| 01/18/2019 | V9.0 | Recruitment suspended | 01/18/2019 | Non-authorized | Non-authorized |

ANSM= agence nationale de la sécurité du médicament = National agency for drug safety, EC = ethics committee

1. **Original statistical analysis plan, final statistical analysis plan, summary of changes**

**Original statistical analysis plan**

|  |
| --- |
| Writter : Maxime Esvan |

*Statistical analysis plan is written according to protocol V8.0 (December 28, 2018).*

*It follows discussions and e-mail exchanges on September 6, 2018; January 10, 2019; June 4,5 and 6, 2019.*

|  |  |
| --- | --- |
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1. Reminder on the protocol
   1. Study objectives

The primary objective is to compare the effects of an intraoperative opioid-free analgesia strategy with that of standard clinical practice on postoperative opioid-related severe adverse events after major or intermediate non-cardiac surgery.

The secondary objectives are described below:

* Determine if OFA is associated with a better postoperative analgesia;
* Determine if OFA can reduce postoperative opioid consumption;
* Determine if OFA can reduce the delay to obtain an Aldrete score ≥ 9 and the delay to extubation;
* Determine if OFA reduces postoperative rate of unscheduled admission in ICU;
* Determine if OFA reduces postoperative nausea and vomiting (PONV);
* Determine if OFA reduces the length of stay in the hospital;
* Evaluate the tolerance to Dexmedetomidine in OFA.
  1. Evaluation criteria
* Primary evaluation criteria

The primary outcome measure will be the occurrence of a severe postoperative opioid-related adverse event within the first 48 hours after extubation defined as: postoperative hypoxemia or postoperative ileus (POI) or postoperative cognitive dysfunction (POCD).

In addition, each component of the primary outcome measure will be analysed separately.

The onset of an opioid-related adverse event will be assessed blinded to the randomization group.

**Postoperative hypoxemia** is defined as a SpO2 < 95% with a need for oxygen supplementation within the first 48h after extubation; the duration of oxygen treatment will also be recorded.

**Postoperative ileus** is defined as an absence of flatus or stools within the first 48h after extubation.

**Postoperative cognitive dysfunction** will be evaluated using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) by a care provider (either anaesthesiologist or nurse).

The Confusion Assessment Method (CAM)[[1]](#footnote-1),[[2]](#footnote-2) has been validated in multiple settings and is a widely used standardized method for identifying delirium with a high sensitivity of 94% (95% CI, 91%-97%), high specificity of 89% (95%CI, 85%-94%).

The CAM algorithm consists of 4 items: 1. Acute Onset or Fluctuating Course. 2. Inattention 3. Disorganized thinking. 4. Altered Level of consciousness.

The diagnosis of delirium by CAM/CAM-ICU requires a positive response to features 1 and 2 plus either 3 or 4; in these cases, the patients will be considered as presenting a POCD.

* Secondary evaluation criteria
* Number of episodes of postoperative pain (numeric rating scale ≥ 3) within 48 hours after extubation, at rest;
* Opioid consumption during the 48 hours following extubation;
* Time between the end of remifentanil or dexmedetomidine administration and an Aldrete score ≥ 9 (when applicable);
* Time between the end of remifentanil or dexmedetomidine administration and extubation;
* Rate of unscheduled admission in intensive care unit;
* Number of PONV episodes during the 48 hours following extubation. Need for rescue antiemetic medication will be recorded;
* Hospital length of stay (max 28 days) defined as the number of days after extubation before first hospital discharge;
* Number of cardiac events (bradycardia defined as the number of episodes with atropine administration, hypotension defined as PAM < 65 mmHg, hypertension defined as PAM > 90 mmHg) and rescue medication, during surgery.
  1. Design

This is a multicentre, prospective, randomized, controlled, simple-blind, parallel group trial. Patients will be randomized in two groups:

* Control group: Standard anaesthesia protocol with remifentanil.
* Dex group: Standard anaesthesia protocol with dexmedetomidine (OFA).
* Conduct of the study

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|  | **D-30**  **to D-1** | **D-1 to D0** | **D0**  **Surgery** | **H0**  **extubation** | **H48** | **D2** | **D7 (or hospital discharge if < D7)** |
| Preoperative consultation / Information | X |  |  |  |  |  |  |
| Written informed consent |  | X |  |  |  |  |  |
| Selection criteria |  | X |  |  |  |  |  |
| Randomization |  | X |  |  |  |  |  |
| Administration of the treatment |  |  | X |  |  |  |  |
| Morphine consumption |  |  |  |  |  |  |  |
| NRS ≥ 3 |  |  |  |  |  |  |  |
| Cardiac events:  bradycardia (episodes with atropine)  hypotension (PAM<65 mmHg)  hypertension (PAM>90 mmHg) |  |  |  |  |  |  |  |
| PONV |  |  |  |  |  |  |  |
| Opioid-related adverse events: hypoxemia, ileus, POCD (CAM-ICU) |  |  |  |  |  |  |  |
| Ancillary study : 3 tubes of 5 ml of blood on agar-free lithium heparinate (green top) |  |  | X\* (morning before surgery) |  |  | X\* (morning) | X\* (morning) |

* Expected duration of participation of persons
* Recruitment period : 24 months
* Duration of patient follow-up : maximum 28 days
* Duration of data analysis : 6 months
* Estimated total duration of study : 31 months

Starting with inclusion of the first patient, the sponsor has to inform without delay the local health agency and the ethics committee of the actual date of start-up of the study. The actual date of start-up = date of signature of consent form by the first person who is a subject in the study.

The date of end of the study will be transmitted by the sponsor to the ethics committee and to the local health agency within 90 days or earlier according to local regulations. The date of end of the study corresponds to the last visit of the last person participating in the study.

* Randomization

Patients will be randomized in two groups (control group and Dex group). In order to ensure group comparability, a plan of randomization will be used. Randomization will be done online by investigators as close as possible to the surgery (D-1 or D0). Each patient will be allocated a unique randomization number (patient code).

Randomization will be stratified on the centre and on the type of surgery: abdominal (digestive, urological, gynaecological) or non-abdominal.

* Methods of blinding

The primary evaluation criterion will be assessed blinded to the randomization group.

During the study period, patients and outcome assessors will be kept blind to the randomization group. Nurses evaluating outcomes in PACU and in the ward will not participate to the anaesthesia and will not be aware of the randomization group. They will be blind to the treatment. The anaesthesiologist and the nurse anaesthesiologist (care providers) will be the only ones not blinded. They will not participate in the assessment of the patients at any time.

* Sample size

196 patients per group will be needed to have 80% power, at a two-sided alpha level of 0.05, to show a relative between-group difference of 40% in the composite primary outcome measure (30% to 18%), under the assumption of an overall incidence of 5% of postoperative ileus (from 5% to 20.6% after major or intermediate non-abdominal and abdominal surgery, respectively)[[3]](#footnote-3),[[4]](#footnote-4), 20% of postoperative hypoxemia (from 20% to 40% depending on the surgical site)[[5]](#footnote-5),[[6]](#footnote-6) and 5% of postoperative delirium (from 3.6% to 30% after elective surgery and abdominal surgery, respectively)[[7]](#footnote-7),[[8]](#footnote-8),[[9]](#footnote-9) , thus 30% for the primary outcome measure.

A total of 400 patients will be included to take into account non-evaluable patients. Patients undergoing a second surgery or dying within 48 hours without presenting the primary evaluation criteria will be kept considered as success in the analysis.

* 1. Planned analysis

Statistical analysis will be performed on all randomized and evaluated patients (intention to treat analysis).

* Descriptive analysis

A first overall descriptive analysis and analysis by group will be performed. This consists of separate estimates, numbers and percentages for qualitative variables, means, standard error, medians and interquartile intervals for quantitative variables. The normal feature of the distribution of quantitative variables is checked.

* Comparison of groups at baseline

Student’s t test or a Mann-Whitney test if necessary will be used to compare quantitative variables, and a Chi² or Fisher’s exact test if necessary will be used to compare qualitative variables between two groups at inclusion.

* Analysis of the primary criteria

The primary endpoint (composite endpoint) will be compared between the two groups with the Chi² test.

Two interim analyses after inclusion of 1/3 and 2/3 of the patients, and one final analysis are planned. Stopping rules will use the alpha spending function with the O’Brien-Fleming boundary. The cumulative values of alpha for each analysis are: 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, Cork, Ireland). The trial will be stopped early if the significance of the Chi² test is below these alpha values.

* Analysis of other criteria

For the analysis of the other endpoints, the same strategy as for baseline comparisons will be used.

In addition, censored endpoints (time to achieve an Aldrete score ≥ 9) will be compared using the log-rank test.

Continuous endpoints repeatedly measured during the study will be compared using a repeated measure two-way (time, group) analysis of variance.

For all these analyses, adjustments can be made in case of heterogeneity at inclusion.

* Analysis of adverse events

Possible adverse events are coded according to the MedDRA classification and are the subject of a descriptive analysis.

* Planned degree of statistical significance

Except for the interim analyses described above, a p value <0.05 will be considered as significant for all analyses.

* Method of management of missing, unused or invalid data

Missing data will not be replaced. Mixed models can be used in analysis of repeated data to avoid deleting subjects with any missing values.

* Choice of persons to include in the analysis

This trial is an intention to treat study, that is all randomized and evaluated patients will be analysed in their randomization group.

1. Changes to the protocol

* Primary evaluation criteria

Patients with a surgical recovery within 48 hours after extubation are evaluable and considered successful if they have not met the primary endpoint.

Patients whose resumption of transit is not notified in the file are "not assessable for transit" if the hospital discharge takes place from D3 onwards.

The systematic administration of O2 before desaturation should be noted as a deviation. An episode of hypoxemia will be reported if and only if SpO2 < 95%.

If CAM-ICU H48 is not performed because the patient is discharged before H48 post-extubation and has no other component of the primary endpoint, it will be considered successful for the primary endpoint.

Patients with absence of two components of the primary endpoint will be considered successful for the primary endpoint if hospital discharge takes place on D3.

* Secondary evaluation criteria

Time between the end of remifentanil or dexmedetomidine administration and an Aldrete score ≥ 9 (when applicable): if time when Aldrete score ≥ 9 is missing, it will be replaced with time when patients leave the PACU.

* End of the study

At the request of the sponsor and the ANSM (French National Agency for Medicines and Health Products Safety) on 10/01/2019, inclusions were suspended for urgent safety measures to the new fact that the information of bradycardia cases represents. Patient addition and randomization rights were removed on 11/01/2019. No inclusion and randomization took place between 10 and 11 January 2019.

1. Analysed populations
   1. Number of subjects included

316 patients were included and randomized: 158 in the control group and 158 in the Dex group.

* 1. Populations

314 patients are included in intent-to-treat population: 157 in the control group and 157 in the Dex group

312 patients have met the primary endpoint: 156 in the control group and 156 in the Dex group.

Flow-diagram of the POFA trial:

1 Discontinued intervention

* 1 Logistic reason (04008)

1 Discontinued intervention

* 1 Adverse event (01081)

157 Included in intent-to-treat analysisa

1 Excluded from intent-to-treat analysis

* 1 Consent withdrawal (09005)

157 Included in intent-to-treat analysisb

1 Excluded from intent-to-treat analysis

* 1 Consent withdrawal (06020)

158 randomized to receive remifentanil (Control Group)

157 Received remifentanil as randomized

1 Did not received remifentanil as randomized

* 1 Randomization mail not received (09005)

158 randomized to receive dexmedetomidine (Dex Group)

154 received dexmedetomidine as randomized

4 Did not received dexmedetomidine as randomized

* 1 Failure to comply with randomization for administration of clonidine (treatment contraindicated with dexmedetomidine but not indicated in the protocol) (06007)
* 1 Randomization mail not received (06020)
* 2 Anesthesiologist did not know that the patient was including (10006, 10010)

316 randomized

**Allocation**

**Follow-up**

**Analysis**

a One patient does not meet the primary criteria (04008)

b One patient does not meet the primary criteria (01081)

1. General information

Statistical analysis will be performed with SAS software V9.4 (SAS Institute, Cary, North Carolina, USA).

Presentation will be performed by treatment group (control group and Dex group).

The first interim analysis was performed on November 2, 2018 and the second on January 31, 2019.

1. Analysis of the evaluation criteria
   1. Primary evaluation criteria

See 1.2, 1.4 and 2

* 1. Secondary evaluation criteria

See 1.2, 1.4 and 2.

**Final statistical analysis plan (September, 17, 2019)**

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| Writter : Maxime Esvan |

*Statistical analysis plan is written according to protocol V8.0 (December 28, 2018).*

*It follows discussions and e-mail exchanges on September 6, 2018; January 10, 2019; June 4,5 and 6, 2019; August 5 and 21, 2019; September 4 and 6, 2019.*

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| **Methodologist :** | **Coordinating Investigator:** |
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1. Reminder on the protocol
   1. Study objectives

The primary objective is to compare the effects of an intraoperative opioid-free analgesia strategy with that of standard clinical practice on postoperative opioid-related severe adverse events after major or intermediate non-cardiac surgery.

The secondary objectives are described below:

* Determine if OFA is associated with a better postoperative analgesia;
* Determine if OFA can reduce postoperative opioid consumption;
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* Primary evaluation criteria

The primary outcome measure will be the occurrence of a severe postoperative opioid-related adverse event within the first 48 hours after extubation defined as: postoperative hypoxemia or postoperative ileus (POI) or postoperative cognitive dysfunction (POCD).

In addition, each component of the primary outcome measure will be analysed separately.

The onset of an opioid-related adverse event will be assessed blinded to the randomization group.

**Postoperative hypoxemia** is defined as a SpO2 < 95% with a need for oxygen supplementation within the first 48h after extubation; the duration of oxygen treatment will also be recorded.

**Postoperative ileus** is defined as an absence of flatus or stools within the first 48h after extubation.

**Postoperative cognitive dysfunction** will be evaluated using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) by a care provider (either anaesthesiologist or nurse).

The Confusion Assessment Method (CAM)[[10]](#footnote-10),[[11]](#footnote-11) has been validated in multiple settings and is a widely used standardized method for identifying delirium with a high sensitivity of 94% (95% CI, 91%-97%), high specificity of 89% (95%CI, 85%-94%).

The CAM algorithm consists of 4 items: 1. Acute Onset or Fluctuating Course. 2. Inattention 3. Disorganized thinking. 4. Altered Level of consciousness.

The diagnosis of delirium by CAM/CAM-ICU requires a positive response to features 1 and 2 plus either 3 or 4; in these cases, the patients will be considered as presenting a POCD.

* Secondary evaluation criteria
* Number of episodes of postoperative pain (numeric rating scale ≥ 3) within 48 hours after extubation, at rest;
* Opioid consumption during the 48 hours following extubation;
* Time between the end of remifentanil or dexmedetomidine administration and an Aldrete score ≥ 9 (when applicable);
* Time between the end of remifentanil or dexmedetomidine administration and extubation;
* Rate of unscheduled admission in intensive care unit;
* Number of PONV episodes during the 48 hours following extubation. Need for rescue antiemetic medication will be recorded;
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* Conduct of the study

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|  | **D-30**  **to D-1** | **D-1 to D0** | **D0**  **Surgery** | **H0**  **extubation** | **H48** | **D2** | **D7 (or hospital discharge if < D7)** |
| Preoperative consultation / Information | X |  |  |  |  |  |  |
| Written informed consent |  | X |  |  |  |  |  |
| Selection criteria |  | X |  |  |  |  |  |
| Randomization |  | X |  |  |  |  |  |
| Administration of the treatment |  |  | X |  |  |  |  |
| Morphine consumption |  |  |  |  |  |  |  |
| NRS ≥ 3 |  |  |  |  |  |  |  |
| Cardiac events:  bradycardia (episodes with atropine)  hypotension (PAM<65 mmHg)  hypertension (PAM>90 mmHg) |  |  |  |  |  |  |  |
| PONV |  |  |  |  |  |  |  |
| Opioid-related adverse events: hypoxemia, ileus, POCD (CAM-ICU) |  |  |  |  |  |  |  |
| Ancillary study : 3 tubes of 5 ml of blood on agar-free lithium heparinate (green top) |  |  | X\* (morning before surgery) |  |  | X\* (morning) | X\* (morning) |

* Expected duration of participation of persons
* Recruitment period : 24 months
* Duration of patient follow-up : maximum 28 days
* Duration of data analysis : 6 months
* Estimated total duration of study : 31 months

Starting with inclusion of the first patient, the sponsor has to inform without delay the local health agency and the ethics committee of the actual date of start-up of the study. The actual date of start-up = date of signature of consent form by the first person who is a subject in the study.

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* Randomization

Patients will be randomized in two groups (control group and Dex group). In order to ensure group comparability, a plan of randomization will be used. Randomization will be done online by investigators as close as possible to the surgery (D-1 or D0). Each patient will be allocated a unique randomization number (patient code).

Randomization will be stratified on the centre and on the type of surgery: abdominal (digestive, urological, gynaecological) or non-abdominal.

* Methods of blinding

The primary evaluation criterion will be assessed blinded to the randomization group.

During the study period, patients and outcome assessors will be kept blind to the randomization group. Nurses evaluating outcomes in PACU and in the ward will not participate to the anaesthesia and will not be aware of the randomization group. They will be blind to the treatment. The anaesthesiologist and the nurse anaesthesiologist (care providers) will be the only ones not blinded. They will not participate in the assessment of the patients at any time.

* Sample size

196 patients per group will be needed to have 80% power, at a two-sided alpha level of 0.05, to show a relative between-group difference of 40% in the composite primary outcome measure (30% to 18%), under the assumption of an overall incidence of 5% of postoperative ileus (from 5% to 20.6% after major or intermediate non-abdominal and abdominal surgery, respectively)[[12]](#footnote-12),[[13]](#footnote-13), 20% of postoperative hypoxemia (from 20% to 40% depending on the surgical site)[[14]](#footnote-14),[[15]](#footnote-15) and 5% of postoperative delirium (from 3.6% to 30% after elective surgery and abdominal surgery, respectively)[[16]](#footnote-16),[[17]](#footnote-17),[[18]](#footnote-18) , thus 30% for the primary outcome measure.

A total of 400 patients will be included to take into account non-evaluable patients. Patients undergoing a second surgery or dying within 48 hours without presenting the primary evaluation criteria will be kept considered as success in the analysis.

* 1. Planned analysis

Statistical analysis will be performed on all randomized and evaluated patients (intention to treat analysis).

* Descriptive analysis

A first overall descriptive analysis and analysis by group will be performed. This consists of separate estimates, numbers and percentages for qualitative variables, means, standard error, medians and interquartile intervals for quantitative variables. The normal feature of the distribution of quantitative variables is checked.

* Comparison of groups at baseline

Student’s t test or a Mann-Whitney test if necessary will be used to compare quantitative variables, and a Chi² or Fisher’s exact test if necessary will be used to compare qualitative variables between two groups at inclusion.

* Analysis of the primary criteria

The primary endpoint (composite endpoint) will be compared between the two groups with the Chi² test.

Two interim analyses after inclusion of 1/3 and 2/3 of the patients, and one final analysis are planned. Stopping rules will use the alpha spending function with the O’Brien-Fleming boundary. The cumulative values of alpha for each analysis are: 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, Cork, Ireland). The trial will be stopped early if the significance of the Chi² test is below these alpha values.

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For the analysis of the other endpoints, the same strategy as for baseline comparisons will be used.

In addition, censored endpoints (time to achieve an Aldrete score ≥ 9) will be compared using the log-rank test.

Continuous endpoints repeatedly measured during the study will be compared using a repeated measure two-way (time, group) analysis of variance.

For all these analyses, adjustments can be made in case of heterogeneity at inclusion.

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Possible adverse events are coded according to the MedDRA classification and are the subject of a descriptive analysis.

* Planned degree of statistical significance

Except for the interim analyses described above, a p value <0.05 will be considered as significant for all analyses.

* Method of management of missing, unused or invalid data

Missing data will not be replaced. Mixed models can be used in analysis of repeated data to avoid deleting subjects with any missing values.

* Choice of persons to include in the analysis

This trial is an intention to treat study, that is all randomized and evaluated patients will be analysed in their randomization group.

1. Changes to the protocol

* Primary evaluation criteria

Patients with a surgical recovery within 48 hours after extubation are evaluable and considered successful if they have not met the primary endpoint.

Patients whose resumption of transit is not notified in the file are "not assessable for transit" if the hospital discharge takes place from D3 onwards.

The systematic administration of O2 before desaturation should be noted as a deviation. An episode of hypoxemia will be reported if and only if SpO2 < 95%.

If CAM-ICU H48 is not performed because the patient is discharged before H48 post-extubation and has no other component of the primary endpoint, it will be considered successful for the primary endpoint.

Patients with absence of two components of the primary endpoint will be considered successful for the primary endpoint if hospital discharge takes place on D3.

RR and IC95% will be performed.

* Secondary evaluation criteria

Time between the end of remifentanil or dexmedetomidine administration and an Aldrete score ≥ 9 (when applicable): if time when Aldrete score ≥ 9 is missing, it will be replaced with time when patients leave the PACU.

* End of the study

At the request of the sponsor and the ANSM (French National Agency for Medicines and Health Products Safety) on 10/01/2019, inclusions were suspended for urgent safety measures to the new fact that the information of bradycardia cases represents. Patient addition and randomization rights were removed on 11/01/2019. No inclusion and randomization took place between 10 and 11 January 2019.

* Missing data

Because of missing data for the primary endpoint, we will use multiple imputation by chained equation.

* Subgroup analysis

Subgroup analyses will be performed on the primary evaluation criteria according to the type of surgery: abdominal (digestive, urological, gynaecological) or non-abdominal.

The primary evaluation criteria and bradycardia will be analysed by separating patients in the dex group according to the median dose of dexmedetomidine received.

1. Analysed populations
   1. Number of subjects included

316 patients were included and randomized: 158 in the control group and 158 in the Dex group.

* 1. Populations

314 patients are included in intent-to-treat population: 157 in the control group and 157 in the Dex group

312 patients have met the primary endpoint: 156 in the control group and 156 in the Dex group.

Flow-diagram of the POFA trial:

1 Discontinued intervention

* 1 Logistic reason (04008)

1 Discontinued intervention

* 1 Adverse event (01081)

157 Included in intent-to-treat analysisa

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* 1 Failure to comply with randomization for administration of clonidine (treatment contraindicated with dexmedetomidine but not indicated in the protocol) (06007)
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316 randomized

**Allocation**

**Follow-up**

**Analysis**

a One patient does not meet the primary criteria (04008)

b One patient does not meet the primary criteria (01081)

1. General information

Statistical analysis will be performed with SAS software V9.4 (SAS Institute, Cary, North Carolina, USA).

Presentation will be performed by treatment group (control group and Dex group).

The first interim analysis was performed on November 2, 2018 and the second on January 31, 2019.

1. Analysis of the evaluation criteria
   1. Primary evaluation criteria

See 1.2, 1.4 and 2

* 1. Secondary evaluation criteria

See 1.2, 1.4 and 2.

1. Change history

|  |  |  |  |
| --- | --- | --- | --- |
| **Date** | **Document name** | **Version** | **Modification/Context** |
| 06/06/19 | PAS\_POFA\_190606\_V1 | V1 | First version |
| 01/07/19 | PAS\_POFA\_190701\_V2 | V2 | Management of missing data updated |
| 17/09/19 | PAS\_POFA\_190917\_V3 | V3 | Primary evaluation criteria updated (RR and IC95%)  Addition of subgroup analysis |
| 26/09/2019 | PAS\_POFA\_190924\_V4 | V4 | Subgroup analysis updated |

1. Inouye SK et al. A chart-based method for identification of delirium: validation compared with interviewer ratings using the Confusion Assessment Method. J Am Geriatr Soc 2005; 53 : 312-18 [↑](#footnote-ref-1)
2. Inouye SK et al. Clarifying confusion: the Confusion Assessment Method: a new method for detection of delirium. Ann Intern Med 1990; 113: 941-48 [↑](#footnote-ref-2)
3. Canet J et al, Prediction of postoperative pulmonary complications in a population-based surgical cohort. Anesthesiology 2010;113:1338-50. [↑](#footnote-ref-3)
4. Xue fs et al. The influence of surgical sites on early postoperative hypoxemia in adults undergoing elective surgery. Anesth Analg 1999;88(1):213-9. [↑](#footnote-ref-4)
5. Reeder MK et al. Postoperative hypoxemia after major abdominal vascular surgery. Br J Anaesth 1992;68(1):23-6 [↑](#footnote-ref-5)
6. Canet J, et al. Early postoperative arterial oxygen desaturation. Determining factors and response to oxygen therapy. Anesth Analg  1989; 69: 207-12 [↑](#footnote-ref-6)
7. Lee LA et al, Postoperative opioid-induced respiratory depression: a closed claims analysis. Anesthesiology 2015;122:659-65. [↑](#footnote-ref-7)
8. Gan TJ et al. Impact of postsurgical opioid use and ileus on economic outcomes in gastrointestinal surgeries. Curr Med Res Opin. 2015 31(4):677-86 [↑](#footnote-ref-8)
9. Crosby G et al. Cognitive outcome of surgery: is there no place like home? Anesth Analg  2014; 118: 898-900 [↑](#footnote-ref-9)
10. Inouye SK et al. A chart-based method for identification of delirium: validation compared with interviewer ratings using the Confusion Assessment Method. J Am Geriatr Soc 2005; 53 : 312-18 [↑](#footnote-ref-10)
11. Inouye SK et al. Clarifying confusion: the Confusion Assessment Method: a new method for detection of delirium. Ann Intern Med 1990; 113: 941-48 [↑](#footnote-ref-11)
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16. Lee LA et al, Postoperative opioid-induced respiratory depression: a closed claims analysis. Anesthesiology 2015;122:659-65. [↑](#footnote-ref-16)
17. Gan TJ et al. Impact of postsurgical opioid use and ileus on economic outcomes in gastrointestinal surgeries. Curr Med Res Opin. 2015 31(4):677-86 [↑](#footnote-ref-17)
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