STUDY PROTOCOL

Impact of continuous intraoperative administration of esmolol on NOL-guided control of nociception. The EsmoNOL randomized controlled trial

Version: 3
February 26, 2024

ClinicalTrial : **NCT06291363**

This trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements

CONFIDENTIAL

Title

Impact of continuous intraoperative administration of esmolol on NOL-guided control of nociception. The EsmoNOL randomized controlled trial

Version 3, February 26th, 2024

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A. BACKGROUND

Opioid analgesic drugs have long been the gold standard treatment for perioperative pain relief, playing a crucial role in general anesthesia. Although opioids have a high perioperative analgesic efficacy, they typically cause short-term adverse effects and potentially severe long-term adverse effects as evidenced by the ongoing opioid epidemic in North America (Bohringer et al., 2020; Shanthanna et al., 2021). Opioids can also lead to another problematic condition known as opioid-induced hyperalgesia (OIH), a paradoxical response characterized by increased pain sensitivity in patients using opioids for pain relief (Angst and Clark, 2006; Colvin et al., 2019; Richebé et al., 2018). More specifically, it has been proven that high intraoperative doses of opioids cause hyperalgesia in patients after surgery (Fletcher and Martinez, 2014). Given this, two approaches were explored : opioid-free anesthesia and opioid-sparing anesthesia, employing a combination of analgesics and adjuvants via continuous infusions (Shanthanna et al., 2021).

Intraoperative beta-blockers as a opioid-sparing strategy

The use of esmolol as an adjuvant to general anesthesia has been suggested as an opioid-free potential alternative. Esmolol is an ultra-short acting cardioselective β1-adrenergic receptor antagonist that plays a crucial role in reducing sympathetic overload induced by numerous perioperative stimuli such as tracheal intubation, intraoperative events, and extubation (Asouhidou and Trikoupi, 2015). Since sympathetic overload generates physiological responses that reflect the patient's pain (Paloheimo et al., 2010), esmolol could serve as a viable alternative to opioids in maintaining hemodynamic stability during general anesthesia (Asouhidou and Trikoupi, 2015). Although esmolol lacks analgesic or anesthetic properties on its own, its combination with propofol or volatile-based anesthesia showed great promise in reducing the intraoperative and postoperative analgesic consumption (Celebi et al., 2014).

Previous studies assessing intraoperative esmolol and its administration based on vital signs have led to inconsistencies and controversies with some studies supporting its use and others disapproving it (Gelineau et al., 2018). However, relying solely on vital signs, such as blood pressure (BP) or heart rate (HR), as a guide for esmolol administration may influence the doses administered as esmolol can lower BP and HR. Thus, this approach might not be ideal as it

could overlook other essential factors and necessitates the adoption of a more comprehensive monitoring system that considers a larger range of parameters.

Nociception monitoring as a opioid-sparing strategy

With the advent of nociception monitoring, new devices can be used, especially the Physiological Monitoring Device PMD-200™. This device offers the multiparameter Nociception Level (NOL) index that integrates five parameters in a dimensionless index : HR, heart rate variation (HRV), photoplethysmographic pulse wave amplitude (PPGA), skin conductance level (SC), number of SC fluctuations . By continuously analyzing the incoming signals with an artificial intelligence algorithm, this monitor provides a real-time index to inform the clinician on the level of nociception felt by the anesthetized patient, thus guiding the administration of opioids. Even if the core signals reflect the activity of the sympathetic nervous system, this monitor has been validated to monitor nociceptive stimuli (Martini et al., 2015; Renaud-Roy et al., 2019; Shahiri et al., 2022), and has been demonstrated to reduce the intraoperative consumption of opioids by 20 to 30% while simultaneously reducing pain and opioids consumption in the PACU.

Combining beta-blockers to nociception monitoring

While it has been demonstrated that chronic usage of beta-blockers does not impair the intraoperative validity of the NOL Index (Bergeron et al., 2022), it remains unclear how acute administration of short-acting cardioselective β1-adrenergic blocker, such as esmolol, impacts the use of sympathetic system-based nociception monitors. Combining the two opioid-sparing strategies could either act synergistically, or could antagonize their respective benefits.

Therefore, this study aims to evaluate esmolol's perfusion impact during induction and maintenance of general anesthesia, using NOL-guided control of nociception, in adult patients undergoing laparoscopic and lower abdominal surgery, on intraoperative remifentanil consumption and postoperative pain in the PACU.

B. OBJECTIVES & HYPOTHESIS

Primary Objective

The main objective of the study is to evaluate the impact of continuous intraoperative infusion of esmolol on intraoperative remifentanil administration in patients undergoing general anesthesia with NOL-guided nociception management.

Secondary Objectives

Secondary objectives cover a wide range of concepts, including the hemodynamic impact of esmolol, the pain profile, and the incidence of opioid-related side effects. More specifically, we aim to :

1. compare NOL Index variation before and after orotracheal intubation and first surgical incision. NOL index will be evaluated 3 minutes after stimulations to record the maximum value and calculate the area under the curve ;
2. compare the mean intraoperative BP and HR;
3. compare the intraoperative requirements and time weighted average of norepinephrine, ephedrine, glycopyrrolate and atropine;
4. compare the total time and time weighted average with NOL value above > 25.
5. To compare the total time and time weighted average of hypotension and/or bradycardia during surgery;
6. compare the time to first analgesic requirement in PACU;
7. compare postoperative morphine equivalent consumption in the post anesthesia care unit (PACU);
8. compare the intensity of pain at rest and under stress, using a verbal rating scale (VRS), from arrival to discharge from PACU;
9. To compare Silvermann Integrated Approach (SIA) Score (combining pain score and opioid consumption);
10. assess postoperative outcomes such as postoperative nausea and vomiting (PONV) and amount of antiemetics used in PACU;
11. compare the time spent in PACU.

Hypotheses

The main hypothesis of this study is to show that patients receiving an intraoperative esmolol infusion during a NOL-guided general anesthesia, will consume a lower amount of intraoperative remifentanil (mcg.kg-1.h-1) with a reduction of 20 to 30% of intraoperative opioid consumption, without impacting hemodynamic parameters. Upon reproducible nociceptive stimulation such as orotracheal intubation and initial surgical incision, we expect a reduction of the deltaNOL with the administration of esmolol, while still capturing the event on the PMD-200. Finally, once the patient reaches the PACU, we expect a longer time to first opioid, a lower pain score on arrival, a lower opioid consumption, a reduced incidence of PONV, and a shorter PACU stay.

C. METHODS

Study design

The study design is a prospective randomized controlled double-blinded superiority trial, conducted at a single center : Maisonneuve-Rosemont Hospital, part of the Centre intégré universitaire de santé et des services sociaux (CIUSSS) de l'est de l'île-de-Montréal (CEMTL), located in Montreal, Quebec, Canada. The duration of this study is expected to be 1 year, from February 2024 to February 2025.

Patient population

We will screen and aim to recruit consecutive adult patients undergoing laparoscopic lower abdominal surgery expected to last between 60 to 180 minutes.

Inclusion criteria

- Fully consented, ASA 1-3 patients from 18yo to 65yo
- Undergoing laparoscopic surgery associated with sub umbilical mini-laparotomy. Eligible surgeries will be hysterectomy (excluding vaginal approach) and left hemicolectomy, of duration time expected under 180 minutes, under général anesthesia
- No allergy to one of the medications used in this study

Exclusion criteria

Contraindication to the use of the study drug (esmolol) is an exclusion criterion :

- Hypotension
- Sinus bradycardia
- Sick sinus syndrome
- Second and third degree A-V block
- Pulmonary hypertension
- Right ventricular failure secondary to pulmonary hypertension
- Decompensated heart failure
- Cardiogenic shock
- Nontreated pheochromocytoma
- Known hypersensitivity to esmolol or any of the inactive ingredients of the product
- Allergy to esmolol or other beta blockers (cross-sensitivity is possible)
- Renal dysfunction
- Airway disease such as asthma or COPD
- Thyrotoxicosis
- Myasthenia gravis
- Raynaud's disease or oeripheral circulatory disorder

Other situations leading to exclusion :

- Severe mental impairment
- Chronic use of opioids, β-adrenergic receptors antagonists
- High risk of conversion to laparotomy according to the surgical team (>25%)

Patients will automatically be excluded after recruitment if they withdraw their consent, or if laparoscopy is converted to laparotomy.

Recruitment

The research team will assess the elective surgical list of Maisonneuve-Rosemont Hospital's operating room to identify eligible patients at least one week before their scheduled surgery. Potential participants will be contacted by the research team via phone to provide an

explanation of the project. The communication form used during these calls will be approved by the CIUSSS EMTL Research Ethics Committee.

Patients who express interest will receive the information and consent form via email to obtain further details about the study protocol. They will also be informed about the potential risks of esmolol before agreeing to participate.

A thorough review of the patients' medical charts will be conducted to confirm that they meet the inclusion criteria and have no exclusion criteria. Subsequently, the research team will meet the candidates before the surgery to address any questions they may have. If the patients still wish to participate, informed consent will be obtained. Once approved, the patients will sign the consent form and undergo randomization.

Randomization and blinding

Electronic randomization will be performed by a statistician using a computer-generated randomized sequence with a variable block size unknown to the investigators, and then implemented in a RedCAP™ application. It will be sealed in an opaque envelope and handed to the dedicated research staff not involved in patient care and responsible to prepare the blinded syringe. The envelope will be opened at the patient's entry into the operating ward, after confirming that the surgery will be performed. Once the group is assigned to the patient, the research staff will prepare a syringe containing the randomized solution, either esmolol or saline. Each 10ml ampoule contains 100mg of esmolol. Syringe preparation will depend on the patient's adjusted body weight (ABW) and the expected duration of surgery (DOS) in hour as indicated on the surgical booking request. The number of ampoules required (NA) will be calculated according to the following formula (rounded up to nearest whole number):

$$NA = \frac{ABW \times \left(0.5 + (1.2 \times DOS)\right)}{100}$$

If a syringe recharge is needed during the surgery, a new blinded syringe containing the same substance as the previous one, will be prepared by the dedicated research staff and brought into the operating room.

The patient, the anesthesiologist, the surgeon, the PACU staff and the research team acting as outcome assessors, will all be blinded to the randomization.

Monitoring

Both groups will undergo routine monitoring according to the CSA guidelines, which will encompass non-invasive blood pressure, pulse-oximetry, EKG and a temperature probe. Invasive arterial pressure monitoring will be at the discretion of the anesthesiologist in charge of the patient. The monitoring will be conducted using the Dräger Infinity C700 (Dräger Medical, Lübeck, Germany) monitor. Additionally, all patients will have a unilateral BISTM EEG sensor (Medtronic, Canada) placed on their forehead to monitor the depth of anesthesia. A Train-of-four scan (TOF scan™; Draeger Medical Canada inc., Mississauga, Ontario, Canada) for monitoring neuromuscular function will also be used. It should be noted that this monitoring is not specific to research and is provided to all patients undergoing general anesthesia at our center.

Throughout the entire anesthesia duration, the NOL index finger probe (PMD-200™ device, Medasense Biometrics Ltd, Ramat Gan, Israel) will be applied for monitoring intraoperative nociception.

All intraoperative data and events will be recorded on the research computer, as further described in the dedicated section of the protocol.

Anesthesia Protocol

Anesthesia induction: All patients will receive 1g PO acetaminophen with 10mL of water prior to entering the operating room. Standardized general anesthesia (GA) protocol will be administered in both groups following theses procedures: induction with intravenous (IV) slow

boluses of lidocaine to numb the vein, propofol 1.5 to 2 mg.kg-1 (ABW), remifentanil with target controlled infusion (TCI) pump and Minto model to reach an effect-site concentration of 3ng.ml-1, rocuronium 0.8 mg.kg-1 total body weight (TBW), and dexamethasone 4 mg. Videolaryngoscopy (McGrath) and tracheal intubation will be done when TOF < 2/4 and remifentanil TCI plasmatic concentration (Cp) and effect-site concentration (Ce) will reach their target. Once intubated, remifentanil infusion will be reduced to a Ce of 1ng.ml-1. A no-touch period of 3 minutes will be observed. Patient's installation will then resume. This induction is part of a standard anesthesia and does not involve any research protocol. It is standardized to homogeneize our population.

Intervention: Patients will be randomized (1:1) in the intervention group and standard care (SOC) group. In the intervention group, intravenous esmolol will be given as a bolus (0.5mg.kg-1) over 5 minutes, and will be started simultaneously to the remifentanil initiation.

Once the bolus of esmolol is over, a perfusion of 20 mcg.kg-1.min-1 will be programmed and maintained until the end of the surgery and completion of skin sutures. In the SOC group saline will be used in place of esmolol. According to the latest meta analysis evaluating esmolol in an opioid-sparing strategy (Gelineau et al., 2018), in all opioids-controlled trials, it was given as a bolus followed by an infusion for the duration of surgery. Initial boluses ranged from 0.5 to 2 mg.kg-1. The infusion rate varied from 5 mcg.kg-1.min-1 to 300 mcg.kg-1.min-1 (mostly 5 to 50 mcg.kg-1.min-1). The dosages proposed in this protocol are based on these studies and meta-analyses that have used esmolol for morphine-sparing purposes, while maintaining minimal hemodynamic impact, hence the use of much lower dosages.

Anesthesia maintenance during surgery:

Nociception management: The remifentanil target controlled infusion will be set at 3 ng.ml-1 prior to the surgical incision, and will be modified according to the NOL index, as described in Figure 1. If the NOL index is > 25 for more than 1 min, we will increase remifentanil TCI by 0.5 ng.ml-1. This rate will be decreased by steps of 0.25 ng.ml-1 if the NOL index is < 10 for more than 3 min. The minimal remifentanil TCI concentration allowed in the protocol will be 1 ng ml-1, to ensure a minimal antinociception drug administration in case of inaccuracy of NOL

Index in either group. Furthermore, in the event of a TAM > 120% of its basal level, and despite a NOL Index between 10 and 25, remifentanil will be increased.

Only the **intervention** and **anesthesia maintenance** sections above differ from the usual management of patients under general anesthesia.

In both groups, IV hydromorphone 0.006 mg.kg-1 and ondansetron 4 mg will be administered once pneumoperitoneum is deflated and skin suture is started. Local anesthetic infiltration of the wounds will be performed by the surgical team using a maximum of 30 ml de bupivacaine 0.5%. Remifentanil infusion will be stopped and removed at the start of wound dressing.

Hemodynamic management**:** Baseline mean arterial blood pressure (MAP) will be defined as the average of three consecutive values taken 1 min apart and determined before the induction of general anesthesia. Intravenous (IV) infusion of norepinephrine will be adjusted to maintain +/- 20% of the baseline values of the pre-anesthesia MAP. Balanced crystalloids will be administered to patients at a rate of 3 ml.kg-1.h-1 (ABW) throughout the surgery. Intravenous fluid boluses will be administered at the discretion of the anesthesiologist in charge. Perioperative blood management will be done according to guidelines.

Depth of anesthesia management: The maintenance of anesthesia will rely on sevoflurane to reach [0.7–1.2] minimal alveolar concentration (MAC; MAC adjusted to the participant's age) and a BIS index of [40-60]. Sevoflurane will be discontinued when the wound dressing is completed, and participants will be extubated in the operating room and transferred to the post-anesthesia care unit (PACU).

Neuromuscular blockade management: The TOF ratio will be maintained at 0/4 with repeated boluses of 0.1 $mg.kg^{-1}$ rocuronium. The patient's neuromuscular blockade will be reversed by sugammadex 2 $mg.kg^{-1}$ to and 4 $mg.kg^{-1}$ (TBW) according to TOF response, to obtain a minimum ratio of 0.9.

Patient management in PACU: patients will be transferred to the PACU, and as soon as sufficient contact is obtained by the PACU nurses the pain level will be assessed. In the PACU, all the postoperative criteria of the study will be assessed until time of readiness for discharge. According to standard practice, the attendant nurse will administer IV hydromorphone in PACU.

D. ENDPOINTS

Primary endpoint

The primary endpoint is the intraoperative amount of remifentanil in mcg.kg-1.h-1, administered between the first surgical incision and its discontinuation at wound dressing.

Secondary endpoints

- The NOL Index variation before and after orotracheal intubation and first surgical incision. NOL index will be evaluated 3 minutes after stimulation to record the maximum value and calculate the area under the curve;
- The mean intraoperative BP and HR;
- The intraoperative doses and time weighted average of norepinephrine (mg); ephedrine (mg), glycopyrrolate (mg) and atropine (mg);
- Total time and time weighted average with NOL value above > 25;
- The total time and time weighted average of hypotension (< 20% of the baseline values of the pre-anesthesia mean arterial pressure (MAP) and/or bradycardia (HR < 60 beats/min, or HR < 50 beats/min for a profound bradycardia)) during surgery;
- The time to first analgesic requirement in PACU;
- The amount of morphine equivalent consumption for postoperative pain relief in the post anesthesia care unit (PACU) in both groups.
- The intensity of pain at rest and under stress, using a verbal rating scale (VRS), from arrival to discharge from PACU.

- The Silvermann Integrated Approach (SIA) Score (combining pain score and opioid consumption);
- Postoperative outcomes such as postoperative nausea and vomiting (PONV) and amount of antiemetics used in PACU;
- The time spent in PACU (in minutes);

Data Collection Procedures

Electronic data from medical monitoring devices, including BIS™ and PMD-200™, will be collected. Before collecting any data, all device times will be time-synchronized. The time of anesthesia induction, intubation, surgical incisions, and other intraoperative events will be manually recorded. This computer gathers all the data electronically and uses the integrated events tag system of the Medasense PMD-200™, or the BetterCare software (provided by Dräger, Lübeck, Germany) connected to the Dräger anesthesia workstation.

All anesthesia and surgery-related events, like the type and amount of vasopressor used, will be recorded separately on a Case Report Form (CRF). The CRF will be built using RedCap software (Vanderbilt University), which will be accessed via electronic tablets by the research team in the operating room. Once the anesthesia is complete and the patient extubated, all the electronic data will be exported.

The data from various monitor devices (anesthesia workstation, ventilator, BIS Index, NOL Index), as well as raw waves form of specific signals (BP, pulse-oximetry, plethysmography, EKG), will be electronically extracted under a unique identification number assigned at randomisation, to a secured, offline research computer, insuring patient anonymization. Patient identity will only be mentioned on the consent form, which will be kept in a locked closet in the Department of Anesthesiology at Maisonneuve-Rosemont Hospital for as long as required by the law (15 years).

Pain intensity is recorded according to a verbal numerical rating scale (0 = absence of pain, and 10 = unbearable pain).

Opioid requirements, pain scores, and post-operative events such as PONV and critical respiratory events will be documented on the PACU record.

E. STATISTICAL PLAN

Sample Size Determination and Power

Based on a recent unpublished trial (MERK study) recently held at our center focusing on colorectal surgeries, we assumed a mean intraoperative remifentanil consumption of 5.59 mcg.kg-1.h-1 and 7.98, respectively in the intervention and control group, with a combined standard deviation of ± 3.24. This data is aligned with recently published international data (Sabourdin et al., 2022). With an alpha risk of 5%, a power of 80.0%, a two-tailed test, and an estimated dropout ratio of 10.0%, it was calculated that 32 patients would be required in each group, to detect a 30% reduction in intraoperative remifentanil administration.

Statistical Methods

Descriptive statistics will be presented by groups using mean and standard deviation, or median and interquartile range if the distribution is skewed or not normal for continuous parameters (according to the skewness of the distribution of each parameter). Frequency (%) will be used for categorical parameters. According to the nature of the analyzed endpoints, confidence intervals (CIs) between proportions or between means/medians differences will be presented. Missing data will be replaced by the maximum value observed (worst-case scenario). Risk differences or mean differences with 95% confidence intervals will be reported for all outcomes. The alpha value will be set at 0.05 to establish statistical significance. All data will be analyzed by the intention to treat principle. All statistical analysis will be performed using SAS, SPSS software or python programmation langage via VS Code or Jupyter notebook software.

Primary Outcome

Total dose of remifentanil in mg.kg-1.h-1 will be compared using Wilcoxon Mann-Whitney test (assuming data will not necessarily follow a normal distribution).

Secondary Outcome

Intraoperative and postoperative data collected in the groups will be compared using parametric (Student t-test) or nonparametric tests (Mann-Withney U test) depending on the type of variables and their distribution, and a chi-square test will be used for proportion. Data collected over time on categorical variables or on those which are not normally distributed will be analyzed with non-parametric tests.

Drug Perfusion trajectories

We will calculate Z scores for remifentanil and norepinephrine rates of perfusion with the mean and standard deviation (SD) of all participants calculated at the same time point - in the following approach:

$$Z_{individual} = \frac{x_{individual} - \mu_{global}}{\sigma_{global}}$$

where χ corresponds to the individual rate of perfusion registered, μ and σ correspond to the mean and SD of all participants at the same time.

We will use nociception Z scores to define the level of the importance of intraoperative opioid and norepinephrine administration needed to maintain adequate NOL index. Intraoperative administration will be classified as mild or major:

- None : a decrease in Z score < 1 SD,
- Minor: a decrease in Z score ≥ 1 SD,
- Major: a decrease in Z score ≥ 1.96 SD.

F. SAFETY AND ADVERSE EVENTS

Safety And Compliance Monitoring

Ensuring participant safety is a top priority for the research team and hospital staff. In the unlikely chance of an unexpected adverse event, the principal investigator, Dr. Pascal Laferrière-Langlois, will be immediately notified. Prompt actions will be taken to provide appropriate care.

The devices used in this study include standard anesthetic monitoring, with the addition of a non-invasive finger probe for NOL analysis. Classical monitoring will always be recorded and serve as the reference for anesthesia guidance.

Patients experiencing adverse reactions will be closely monitored by the appropriate doctor until discharged from the PACU. If necessary, they will be hospitalized for further observation.

Medical Monitoring

The study has a low level of risk. The Principal Investigator (PI) or designated personnel will regularly review all data, such as study completeness, enrollment, protocol deviations, dropouts, and adverse events, on a weekly or bi-weekly basis.

Definition Of Adverse Events

An adverse event is any unfavorable and unintended sign, symptom or disease temporarily associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure. Adverse events will be graded as Mild, Moderate or Severe, and as Related / Possibly Related / Not Related to study procedures.

Follow-up of subjects after adverse events

In the event of beta-blocker overdose or intoxication, the first line of treatment is to administer treatments to accelerate heart rate: atropine, glycopyrrolate or isoprenaline. If these treatments are not effective in treating cardiovascular symptoms, glucagon can be used. Glucagon activates myocardial adenylcyclase, stimulates cyclic AMP synthesis and increases contractility and heart rate, even in the presence of high concentrations of beta-blockers.

Patients included in the research project will be continuously monitored and standardized for general anesthesia. Emergency drugs for rapid treatment of bradycardia or hypotension will be ready and available throughout the patient's stay in the institution. Anesthetists, respiratory therapists and nurses will also be on standby at all times should any of these side effects occur and require urgent treatment. Dealing with these side effects is an integral part of our day-to-day work in the operating theatre and recovery room.

Patients experiencing adverse reactions will be closely monitored by the appropriate doctor. Since esmolol has a 30-minute clearance time, they will benefit from prolonged monitoring for at least 2 hours until discharged from the PACU. Observations during this time wil be add to the patient’s medical record.

If necessary, they will be hospitalized for further observation. In collaboration with the surgical team, a member of the anesthesia department will visit the patient before he or she is discharged home.

Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses

In the event of an adverse event, all clinical information and developments concerning the patient will be recorded on the anesthetic and/or postoperative monitoring sheet. These will be integrated into the patient's medical record, along with any subsequent potential clinical assessments.

We'll notify Health Canada within 15 days or 7 days if the reaction is life-threatening or results in death. A detailed report and assessment within the next 8 days, in accordance with Food and Drug Regulations, subsection C.05.014.

An adverse event report will be also be made to CIUSSS EMTL Research Ethics Committee.

Administration of the intervention drug : esmolol

The onset of action of esmolol is short, around 30 seconds, as is its duration of action which revolves between 10 and 30 minutes maximum. Patients will be closely monitored throughout this period, and the risk of adverse effects beyond this point is extremely low.

Standard Canadian Anesthesiologists' Society (CAS) monitoring will be installed before the start of esmolol perfusion and will be maintained until transfer to the recovery room where the patient will also be closely monitored. Emergency medication will be available at the patient's bedside if an adverse reaction occurs.

The use of Esmolol (Brevibloc) has been associated with the following adverse reactions :

- Hypotension : symptomatic hypotension (hyperhidrosis, dizziness) and asymptomatic hypotension
- Bradycardia
- Pulmonary edema
- Bronchospasm
- Administration site reactions some serious in nature. They include signs and symptoms of infusion site irritation and inflammation but also severe reactions (thrombophlebitis , necrosis and blistering) , in particular when associated with extravasation.

Although esmolol has been used in several studies aiming to reduce intraoperative opioid administration, this indication is not included in the product monograph. Therefore, we sought and received approval (no objection letter) from Health Canada on 2024/02/23.

Subject safety will be guaranteed by research and hospital staff at all times during the completion of the study procedures. All adverse effects will be recorded and patients at risk of serious side effects will be screened and excluded from the present study.

G. PROPER HANDLING OF SUBJECTS

Ethical Considerations

No undiagnosed conditions should be identified in the context of this study. In the inadvertent diagnosis of a new condition, the participant might be excluded, per our exclusion criterias, or remain enrolled based on the manifestation and disease severity. We will file a consultation request to the appropriate physician, for example a vascular surgeon. We will ensure that the required clinical care is appropriately provided to the participant.

Subject Withdrawal

Early Withdrawal of Patients

We will track the number of withdrawn subjects. Possible reasons a subject may withdraw is a desire to discontinue their participation.

When and How to Withdraw Patients

A withdrawal occurs when a participant voluntarily chooses to leave or is no longer able to participate in the research study (impossibility to obtain stable NOL Index signal, conversion to laparotomy). We will remove a participant if they mention to the research personnel that they no longer wish to continue with the study. Withdrawal of consent can occur either before the anesthesia, or after once the patient reaches the post-anesthesia care unit (PACU). The research personnel will keep all personal health information secured in the database.

Data Collection and Follow-up for Withdrawn Patients

We will not store data after participant withdrawal.

Breach of protocol

Three distinct events can lead to a forced breach of protocol during anesthesia : impossibility to obtain stable NOL index signal despite optimization attempts for at least 20 minutes, conversion to laparotomy, or hemodynamic instability. In the improbable event of a major hemodynamic instability potentially attributable to or worsened by the administration of one of the study drugs, the anesthesiologist can decide to stop the protocol.

In all three scenarios, the blinding will be lifted and the perfusion of the research medication will be stopped. These events will be collected and analyzed subsequently.

Risks

There is very little risk involved with participation in this study. Both groups will benefit from all best practices concerning their anesthetic management, as well as the strategies usually used to optimize perioperative opioid sparing. Side effects that may be associated with the use of esmolol are described in the section "Safety and adverse events".

H. DATA HANDLING AND RECORD KEEPING

Confidentiality and Security

Protected health information will not be re-used or disclosed to a third party except as required by law, for authorized oversight of the research, or as permitted by an authorization signed by the research subject.

Electronic Data

Data will be stored on a password-protected laptop which has been assigned to Dr Pascal Laferrière-Langlois. He will maintain primary responsibility for this computer and the data it contains.

Hard Data

Paper copies (consent form) of patient information will be stored in a locked file cabinet in a locked office in the Department of Anesthesiology.

Coding Data

Data are confidential. Data will be assigned a unique study code (P1, P2, and so on up until PX) and the codes will be linked to the subject's identities. The link will be kept separately from the data so that no patient can be identified in the event of loss or theft.

Accessibility

Only the PI and the co-investigators will have access to all the data during the study and study analysis. All records relating to this clinical trial will be retained for a period of 15 years.

Training

Every person involved in this study will receive appropriate training and abide by confidentiality guidelines to protect the subject's privacy.
All Health Information Protection Act rules and regulations will be strictly followed.

Linked Data

There will be no linked data.

I. STUDY MONITORING, AUDITING, AND INSPECTING

Study Monitoring Plan

Every week the PI will check the recruitment and data collection.

Auditing and Inspecting

There will be no formal plan for auditing or inspecting.

J. STUDY ADMINISTRATION

Organization and Recruiting Site

The operating schedule will be reviewed in advance. Eligible patients will be contacted by phone to discuss their possible inclusion in the study. The investigator team will meet with them the day prior to or on the day of surgery. If they give their consent to participate, it will be collected, and time will be allocated to answer any questions they may have. They will be given a copy of the information and consent form .

Study Timetable

Depending on validation by the ethical authorities, inclusions should begin in February or March 2024. Given the study population, we estimate that we will be able to include a target number of subjects by September or October 2024. Data consolidation will be completed one month following the last enrollment.
Analysis and publication should follow shortly thereafter.

K. PUBLICATION PLAN

We plan to publish the results of this trial in a high-impact factor journal in the field of anesthesia, for example Anesthesiology or the Canadian journal of anesthesia.

L. BUDGET

This study will be supported by funds from Dr Pascal Laferrière-Langlois at the CR-HMR and the Department of Anesthesiology and Pain Medicine. The usual resources of the anesthesia research department will be solicited.

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N. ANNEXES

Drug preparation:

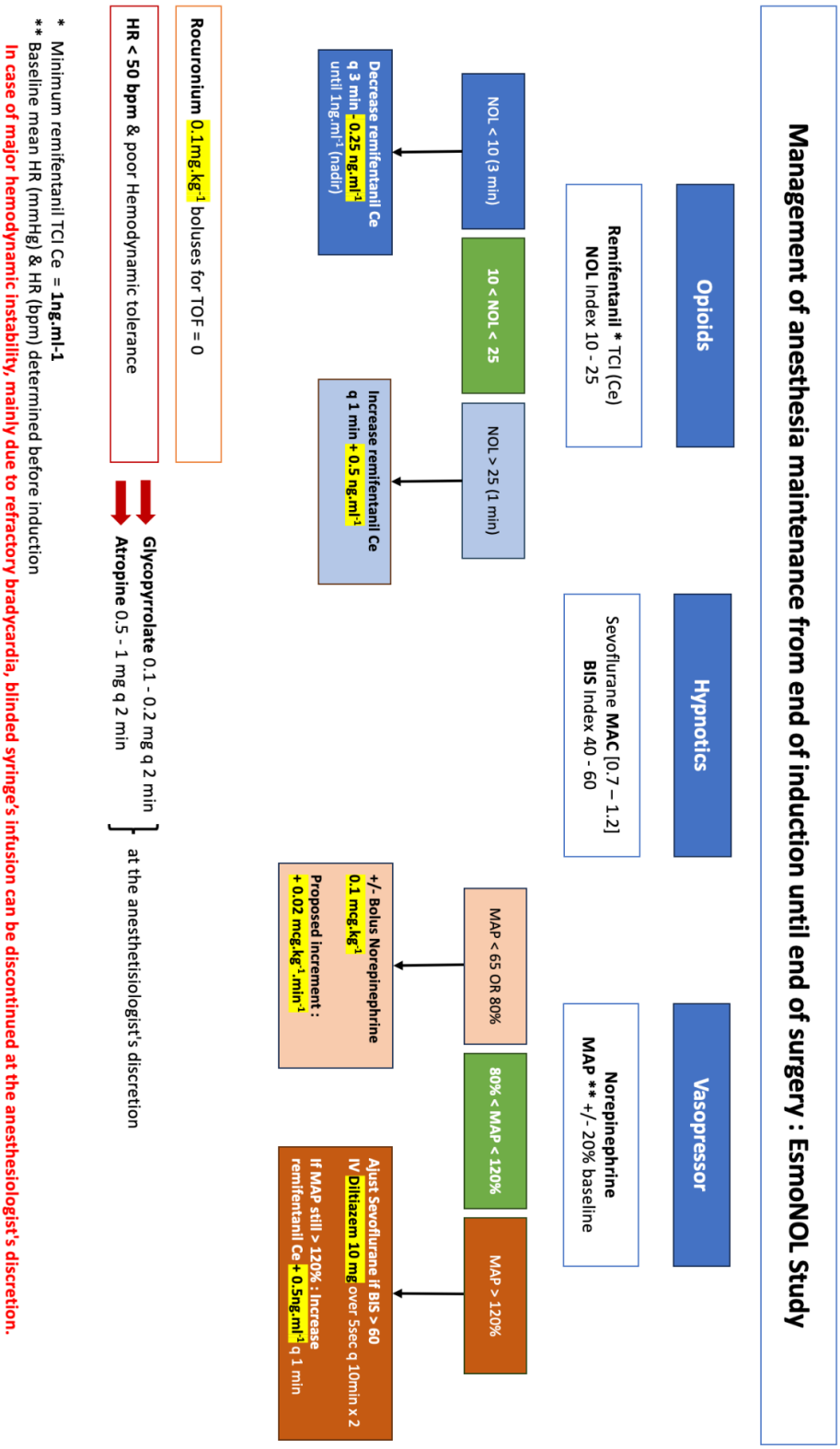
Groupe Esmolol : 4 amp. BREVIBLOC of 10ml (10mg.ml^{-1}) in a 50ml syringe. Groupe SOC : 40 ml of saline in a 50ml syringe.

- Initial bolus : 0.5mg.kg^{-1}
- Infusion : 1.2mg.kg^{-1}.h^{-1} (= 20mcg.kg-1.min^{-1})

PMD-200 homologation

PMD-200 medical device homologation number used for research: **99488.** It is to be used in accordance with its approved indications for use.

O. FIGURE 1


Management of anesthesia maintenance from end of induction until end of surgery : EsmoNOL Study
Opioids
Remifentanil * TCI (Ce)
NOL Index 10 - 25
NOL < 10 (3 min)
10 < NOL < 25
NOL > 25 (1 min)
Decrease remifentanil Ce
q 3 min - 0.25 ng.ml-1
until 1ng.ml-1 (nadir)
Increase remifentanil Ce
q 1 min + 0.5 ng.ml-1
Hypnotics
Sevoflurane MAC [0.7 – 1.2]
BIS Index 40 - 60
Vasopressor
Norepinephrine
MAP ** +/- 20% baseline
MAP < 65 OR 80%
80% < MAP < 120%
MAP > 120%
+/- Bolus Norepinephrine
0.1 mcg.kg-1
Proposed increment :
+ 0.02 mcg.kg-1.min-1
Ajust Sevoflurane if BIS > 60
IV Diltiazem 10 mg over 5sec q 10min x 2
If MAP still > 120% : increase
remifentanil Ce + 0.5ng.ml-1 q 1 min
Rocuronium 0.1mg.kg-1 boluses for TOF = 0
HR < 50 bpm & poor Hemodynamic tolerance
Glycopyrrolate 0.1 - 0.2 mg q 2 min
Atropine 0.5 - 1 mg q 2 min
at the anesthetisiologist's discretion
* Minimum remifentanil TCI Ce = 1ng.ml-1
** Baseline mean HR (mmHg) & HR (bpm) determined before induction
In case of major hemodynamic instability, mainly due to refractory bradycardia, blinded syringe's infusion can be discontinued at the anesthesiologist's discretion.