Safety in cardiovascular profile for the use of Propranolol as co-analgesic treatment in non-cardiac surgery, a pilot study.

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Submitted in August 2017

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science.

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Abstract

Background: Perioperative alternatives to treat pain are still mostly limited to the delivery of systemic opioids. Recently animal and clinical studies have suggested β2-receptors as a possible target to back up analgesia performed by opioids. Co-administration of opioid agonists with β-blockers resulted in substantial synergetic analgesia in animal pain behavioral models. Thus, co-administration of β2-blockers with opioids might be a resourceful synergic combination able to maximize opioids analgesia while minimizing their adverse effects. Despite encouraging results from preclinical studies, a clear understanding of the role of β2-receptor role in human analgesia is still lacking. Thus a randomized controlled trial to clarify the role of β2-blockers as co-analgesic adjuvants was designed and initiated at the McGill University Health Centre (NCT02511483). The hypothesis of the study was that Propranolol would be able to reduce Morphine consumption after surgery without impacting the hemodynamic stability of the patients. However, particularly, concerns related to the hemodynamic effects of β2-receptor blockage prevent their usage. To address this concern, we performed a planned interim-analysis from data of the ongoning randomized control trial to determine the hemodynamic safety of β2-adrenergic antagonist administration in the perioperative setting.

Methods: Data from patients recruited in this ongoing, randomized controlled trial were analyzed. Patients undergoing abdominal and gynecological laparoscopic surgery were randomized to receive either Propranolol (Propranolol group) or Placebo (Placebo group) in combination with Morphine as co-analgesic adjuvants. Perioperative blood pressure and heart rate were recorded. Postoperative analgesia, morphine consumption, opioid side-effects, were also measured.

Results: Systolic blood pressure (SBP) during the induction and emergency from anesthesia was higher in Propranolol Group versus the Placebo Group (induction of anesthesia: 121 mmHg ±21.5 vs 110 mmHg ±23.7; p-value: 0.04; emergence of anesthesia 117 mmHg ±12.5 vs 108 mmHg ±10.8; p-value: <0.01). No significant difference was find for diastolic blood pressure (DBP). Heart rate (HR) was lower in patients treated with Propranolol at the emergence from anesthesia (61 ±7.4 bpm vs 74 ±6.5 bpm, p-value: <0.01) and continued to be lower during the stay in PACU (67 ±7.1 bpm vs 90 ±21.9 bpm; p-value: 0.05) and on the surgical ward (66 ±6.4 bpm vs. 86 ±12.3 bpm, p-value: 0.02) on the day of the surgery (day 0).

Conclusions: The results of this interim analysis suggest that perioperative administration of propranolol as co-analgesic adjuvant at this dosage and regimen is feasible, and does not significantly affect blood pressure and heart rate. Although, few statistically significant differences were observed between the 2 groups, the clinical relevance of these findings is questionable as blood pressure and heart rate always remained within the safety range in the first 24 hours after surgery. On the other side, analgesic benefits related to the administration of Propranolol were not observed. Recruitment of future patients will to better define the analgesic role of administering Propranolol as co-analgesic adjuvant in the context of multimodal analgesia.

Résumé

Contexte: Les alternatives périopératoires pour traiter la douleur sont toujours surtout limitées à la livraison d'opiacés systémiques. Récemment, des études expérimentales et cliniques ont suggéré les ß2-récepteurs comme une cible possible pour améliorer l'analgésie exécutée par des opiacés. La coadministration d'opiacés avec des ß-bloqueurs a abouti à une analgésie synergétique dans les modèles animaux. Ainsi, la coadministration de ß2-bloqueurs avec des opiacés pourrait être une combinaison synergique ingénieuse capable de maximiser l'analgésie d'opiacés en minimisant leurs effets indésirables. Bien que les résultats d'études précliniques soient encourageants, une compréhension claire du rôle des ß2-récepteurs dans l'analgésie humaine manque toujours. Ainsi, une étude randomisée en double aveugle a été conçue et amorcée au Centre de santé Universitaire McGill (NCT02511483) pour clarifier le rôle des ß2-bloqueurs comme adjuvant co-analgésique. L'hypothèse de l'étude était que le Propranolol pourrait réduire la consommation de Morphine après la chirurgie sans avoir un impact sur la stabilité hémodynamique des patients. Cependant, les préoccupations liées aux effets hémodynamiques de blocage des ß2-récepteurs empêchent leur utilisation. Pour adresser cette préoccupation, nous avons fait une analyse provisoire planifiée des données de l'étude clinique pour tester la sécurité hémodynamique d'administration d'antagoniste ß2-adrénergique dans l'arrangement périopératoire.

Méthode: Les données des patients recrutés dans l'étude randomisée contrôlée ont été analysées. Les patients subissant la chirurgie laparoscopie abdominale et gynécologique ont été randomisés pour recevoir ou le Propranolol (le groupe Propranolol) ou le Placebo (le groupe de Placebo) en combinaison avec de la Morphine comme adjuvant co-analgésique. La tension périopératoire et

la fréquence cardiaque ont été enregistrées. L'analgésie post-opératoire, la consommation de Morphine et les effets secondaires opioïdes ont été aussi mesurés.

Résultats: la pression artérielle systolique (PAS) pendant l'induction et l'émergence de l'anesthésie était plus haute dans le Groupe traité avec le Propranolol contre le Groupe de Placebo (l'induction d'anesthésie : 121 mmHg ±21.5 contre 110 mmHg ±23.7; p-valeur : 0.04; émergence d'anesthésie 117 mmHg ±12.5 contre 108 mmHg ±10.8; p-valeur : 0.01). Aucun différence significative n'a été observée pour la tension diastolique (PAD). La fréquence cardiaque (HR) était inférieure chez les patients traités avec le Propranolol pendant l'émergence de l'anesthésie (61 ±7.4 bpm contre 74 ±6.5 bpm, la p-valeur : 0.01) et continuait à être plus basse pendant le séjour dans le PACU (67 ±7.1 bpm contre 90 ±21.9 bpm; p-valeur : 0.05) et le reste de la journée de la chirurgie (jour 0) (66 ±6.4 bpm contre 86 ±12.3 bpm, p-valeur : 0.02).

Conclusion: Les résultats de cette analyse provisoire suggèrent que l'administration périopératoire de Propranolol comme co-analgésique adjuvant à ce dosage et à ce régime soit faisable et n'affecte pas significativement la tension et la fréquence cardiaque. Bien que peu de différences statistiquement significatives aient été observées entre les 2 groupes, la pertinence clinique de ces découvertes est douteuse étant donné que la tension et la fréquence cardiaque restaient toujours dans la gamme de sécurité pendant toute la durée du séjour à l'hôpital. De l'autre côté, des avantages analgésiques liés à l'administration de Propranolol n'ont pas été observés. Le recrutement de futurs patients pourra mieux définir le profil analgésique de l'administration de Propranolol comme co-analgésique adjuvant dans le contexte d'analgésie multimodale.

Acknowledgments

I would like to thank my supervisor, Dr. Luda Diatchenko, for her support along these years. Her mentorship has meant a lot to me.

I would like to thank Dr. Franco Carli, Dr. Thomas Schricker and Dr. Albert Moore for their wise advices and the time reserved to me.

The writing of this manuscript would have not be possible without the invaluable support and guidance of the following people. Not only for reading this work and teaching me about science, but for sharing their friendship with me during these two incredible years.

Pavel Gris, Rodrigo Benavides, Anne-Julie Chabot-Doré, Samar Khoury, Ryan Lichtenwalter, Carol Meloto, Alexander Samoshkin, Katerina Zorina-Lichtenwalter, Marjo Piltonen, Marc Parisien

Finally, I would like to thank the Canadian Excellence Research Chairs (CERC) Program (grant CERC09) to have kindly provided the funding for this project.

Introduction

The impact of surgical procedures on the medical care system is often underappreciated. At the same time it is not easy to find an accurate updated estimate for the total volume of surgical operations in Canada. Nevertheless, it is possible to approximate it, rounded by defect, considering the record for the number of inpatient surgical discharges. For example, during the year 2011-2012 in Canada there has been 823,618 discharge of surgical inpatients[1]. On different terms this means that in one year 2.3% of Canadian population experienced at least once the surgical environment in one of its forms. Notably, the number of surgical discharge has grown at a rate of 42% over a decade (Figure 1).

This phenomenon is not limited to an historical phase, as market studies on the volume of surgeries suggest that the growth rate in surgical procedures is unlikly to stop soon given the over-medicalization of society and the increase in life expectancy. These changes also pervades in our daily experience, such as the public opinion still perceived surgical procedures as exceptional events in their life, although nowadays it is fairly common that a citizen will undergo at least one surgical procedure, of any kind, during the course of his/her life. This transformation brings with itself major repercussions on the structure of the health system in general. Interestingly an aspect that often passes unnoticed is that, following this surgical epidemic, 10 to 50% of patients will experience mild to severe acute post surgical pain[2,3] and, consequently, will need to be treated for it.

After all, pain after surgery is the primary factor that causes an increase in the length of hospital stay (LOS). For example, the data from the top ten surgeries (32% of the total surgeries) performed in Canada between 2014-2015 display how the average length of stay after the

procedure is comprised between 2.6 and 9.6 days[4]. At the same time data from the year 2014-2015 show how the average cost for one day of convalescence after surgery was estimated at 1,717 US$[5]. From this it easy to recognize the economic repercussion of undertreated pain after surgery. This without considering the economic burden related to the use of opioids, the most prescribed treatment for post-surgical pain. Acknowledging these developments oblige us to reflect on how the treatment of postoperative acute pain will play an increasing role in the future. It could be speculated that postoperative pain treatment will overcome the limits of moral or clinical obligation to acquire a status even in the public health domain. Consequently, the research aimed to optimize treatment of pain after surgery, pointing to fully satisfy the patient's expectation and the social commitments (biological responsibility) holds a pivotal role in this transformation. Nowadays adequate acute pain treatment has exceeded the basic humanitarian and clinical obligations, to become a standard of quality of care in public health.

Post-Operative Pain

The International Association for the Study of Pain (IASP) defines pain as: 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage'. Pain as "the normal, predicted physiologic response to an adverse chemical, thermal, or mechanical stimulus…associated with surgery, trauma, and acute illness" [6] is usually referred as acute pain. Acute pain is a short-lived (less than 3 months) response temporally related to tissue damage. The pain, initially severe, tends to subside as the healing process takes place and it responds well to conventional analgesia. Biologically speaking, the perception of acute pain requires an intact nervous system and is associated with hyperactivity of the autonomic system (expressed by the appearance of vasoconstriction, with hypertension, tachycardia, sweating, and vasoconstriction). Postoperative pain is a particular type of acute pain,

referred also as nociceptive pain after surgery, where patients complain of two different types of pain: one constant ongoing pain at rest and a second sharp, intense pain with movement that is more difficult to treat.[7] In his review Brennon[8] examines the specific pathophysiological mechanisms sustaining surgical pain. During a surgical procedure, the tissue manipulation performed by the operator activates specific nociceptors (pain receptors) as well as free nerve endings. This tissue damage is associated with the release of inflammatory mediators, such as bradykinin, serotonin, and histamine, which contribute to the peripheral sensitization. The underlying mechanism involves peripheral sensitization of primary afferent nociceptors by algogenic mediators locally released. Clinically, the increasing of sensitization manifests as "hyperalgesia" that is a reduction of the noxious threshold to signals that physiologically are not perceived as painful. A surgical injury produces two types of hyperalgesia: a "primary hyperalgesia" around the wound and a "secondary hyperalgesia" in the adjacent tissues. Secondary mechanical hyperalgesia results from enhanced response of dorsal horn neurons to peripheral inputs as consequence of central sensitization. Once the peripheral nociceptors are stimulated, the dorsal horn of the spinal cord convey the signal via the A-δ (myelinated) fibers and the C (unmyelinated) fibers. If hyperalgesia develops A-α and A-β fibers are also susceptible to the stimulation. The signals then pass through the second order spinal neurons travelling on the neospinothalamic and paleospinothalamic tracts. The signal enters in the central nervous system with an increased amplitude and duration, a phenomenon known as "wind up" or central sensitization. Finally, once they have reached the thalamic cells the signals are finally redirected to the somatosensory cortex, where the stimulus is perceived and localized.[9]

After surgical procedure, an average of 80% of people experience acute pain, and 75% of them score their level of pain as moderate or severe[10]. Nevertheless, short-term pain is not the only

kind of pain that could be experienced after surgery. In some case, a local unresolved inflammation, or lesions to the peripheral nerves, or a state of hyperactivity of the adrenergic system can sustain the perception of pain over the limited time of the surgical trauma promoting the insurgence of postoperative chronic pain (POCP)[11,12]. Up to now epidemiologic data about POCP are limited and the scientific community has still not found unanimous consensus about its clinical relevance, on the other hand, as the numbers of surgical treatments have exponentially grown interest in understanding POCP is gaining more and more relevance[13]. It is indeed alarming that depending on the kind of surgical procedure taken in consideration, from 5 to 80% of the patients are at risk to develope some sort of chronic pain[14].

Management of Post-operative Pain

With the introduction in the 1995[15] of the concept of pain as the 5th vital sign, control of pain after surgery has gained more attention. To meet the task, hospitals have established dedicated acute pain postoperative services to guarantee optimal level of pain control[16]. These improvements seem to be insufficient as postoperative pain still remains largely undertreated[17]. The research group guided by Apfelbaum performed 2 administrative retrospective studies on postsurgical pain 10 years apart one from the other[2,3]. The disheartening results from the 2 surveys showed no real amelioration in the level of pain of the patients after surgery, or at least in its perception from the patients. Even if the study cohorts were limited in the number, the scenario depicted is still not reassuring.

The importance of an adequate postoperative pain relief raises from the identification of its biological benefits rather than a humanitarian, but morally obligatory, act. The primary goal of

acute pain treatment to make the patient feel comfortable achieving in this way important surgical milesetones, such as early mobilization, early feeding to mobilize the person associated with faster recovery. On the opposite, if not appropriately controlled, acute pain may results amongst other in an increase of catabolism and cardiorespiratory work, and determine a state of immunosuppression and hypercoagulability (please refer to Table 2 for complete list of side effects associated with uncorrelated acute pain). Finally, high levels of postoperative pain result in poor patient satisfaction, a suboptimal recovery phase and finally an increase of health care costs.[18]

For these reasons, optimal pain therapy after surgery is mandatory. The principle behind analgesic techniques is to counteract the activation of nociceptors either in the periphery or centrally. For now the best postoperative pain relief has emerged through the concomitant use of different drugs, to target in more efficient way different types of receptors involved. This approach is also known as "multimodal" or "balanced" analgesia and is defined as: "the technique of using more than one group of analgesics or technique to provide additive or synergistic effects while minimizing individual side effects."[19] The concept of multimodal analgesia was introduced more than a decade ago and it has allowed a reduction in the doses of individual drugs used, reducing consequently the incidence of side effects related to each of them. Multimodal analgesia techniques have been shown to shorten hospitalization time, to improve functional recovery and to decrease healthcare costs. For these reasons the recent "Guidelines on the Management of Postoperative Pain" published by the American Pain Society in 2016 recommend the use of multimodal analgesia including: medications, and non-pharmacological approaches for the treatment of post-surgical pain (strong recommendation, high quality of evidence). Between possible adjuvant listed, the panel strongly recommend the

use of anti-inflammatory drugs (NSAID's high quality evidence), and gabapentin or pregabalin (moderate quality of evidence), whereas the use of ketamine (weak recommendation, moderate quality evidence) and intravenous lidocaine (weak recommendation, moderate quality evidence) is recommended weakly and supported by moderate evidence[20].

There are a plurality of biological and psycho-sociological factors backing postoperative pain. Health professionals need to be aware that two patients, even if they are having the same surgical intervention, will experience different levels of pain. This makes challenging to reach a standardization between the analgesic techniques. Identification of patient's genetic profile and implementation of pharmacogenomics approach will to meet this challenge in the futre[21]. Postoperative pain management can be really effective only if well planned, delivered in a consistent, evidence based and procedure specific manner[22] and taking into account the patients' assessment of their own pain experience.

The role of opioids in postoperative pain management

Even after the integration of multimodal analgesia approach in clinical practice, the administration of opioids after surgery still covers the lion's share in postoperative analgesia. Opioids are indeed highly effective analgesics to treat acute pain at rest after surgery. Beside their efficacy, the sides effects associated with administration of opioids remain a major limitation for their use. Among the most common side effects associated to a moderate dosage are: nausea, vomiting, drowsiness, urinary retention, and constipation[23,24]. In this way ORADEs hamper the achievement of important surgical milestones such as early feeding (nausea and vomiting), mobilization and physiotherapy (sedation and respiratory depression), urinary

retention (early removal of Foley catheter), early recovery of bowel function (constipation). When used at higher dose, opioids may lead to more serious side effects as respiratory depression[25] or a long-term potentiation of nociceptive pathways[26]. The latter is a decrease of pain threshold in patients under opioid treatment and it is referred as opioid induced hyperalgesia (OIH). Even if clinical consensus about its clinical relevance it is not univocal among the scientific community[27], the development of OIH has been described also in the surgical setting[26] and in particular after the administration of Remifentanil and Fentanyl[28,29]. Clinical documentation of a decrease in nociceptive threshold induced by opioids has been reported as early as in the late XIX century by Albutt, and Rossbach[30], however the recent increase in opioid prescription has attracted renovate attention on its consequences. Although usually the major considerations related to opioid administration focus on short-term adverse effects, potential long-term risks are also present. Despite animal experiment showing a low probability for the beginning of addictive behavior after the use of opioid to treat acute pain, longitudinal studies on humans report a considerable percentage of patients (6 to 10%) who continue to consume opioids long after the surgery [31]. In this case it is more difficult to establish a direct correlation with the exposure to opioids, nonetheless long term side effects should also be taken into consideration when considering opioid therapy on a global perspective.

A large retrospective claims-based study (n=36529) documented that about 98.6% of the patients received opioid after surgery. In 13.6% of this population at least one opioid related adverse effect (ORADEs) was reported.[32] A second retrospective study[33] on administrative data in 2014 confirmed the previous percentages as opioids were used up to 99.8% of the total number of major surgical procedures (n=6285) and 11% of the patients treated with opioids experienced adverse effects. Patient experiencing ORADEs are more likely to have longer (almost doubled)

LOS, an increased risk (36-71%) of readmission within a month after the surgery, and an average cost of care 86% higher than the rest of the surgical population. It easy to acknowledge that ORADEs already have a major impact on the health care system draining an astound expense teetering between 17 and 29 billion of US$/year. Current clinical guidelines[20] for postoperative pain already suggest, where it possible, to avoid perioperative opioid therapy. Because the adverse effects related to the consumption of opioids have been shown to be dose dependent[34], the necessity for clinical research to look for other multimodal analgesic approaches able to achieve an opioid sparing effect is granted. For these reasons perioperative medicine is going through an important renew process trying to minimize use of opioids during hospital stay. This will result also in an economical advantage as studies comparing opioid-only techniques with various non-opioid and opioid-sparing therapies have demonstrated relevant economic benefits[35].

Moreover, it is highly probable that following the current surge in opioid prescriptions for chronic pain conditions[36] there will be an increase in patients that will be already under opioid therapy or in a opioid abuse state at the time of surgery. In these subgroups of patients, standard opioid therapy after surgery is been shown ineffective to control pain[37]. At the same time, the medical care system will experience an absolute increase in the number of surgical procedures together with a relative increase of surgical procedures on older patients as result of the population aging and perioperative technological progresses. Elderly patient are at higher risk of developing opioids adverse effects as consequence of concomitant comorbidities. Considering all these aspects combined we can expect in the future from one side a decrease in the efficacy of opioid-based therapy and on the other an increase in ORADEs in the surgical setting.

In the end, ORADEs not only are dangerous and costly, but also hinder surgical recovery. At the same time the efficacy of opioid-based analgesia is clearly sub-optimal. In fact, despite 99% of

patients receive postop opioids to treat acute pain, still up to 80% of patients report moderate-severe acute postop pain[32]. Finally, the choice of analgesia must always consider the surgical technique. In the last years advancements of surgical care, such as the introduction of minimal invasive procedures (ex. lap surgery-robotic surgery), have significantly reduced the severity of surgical pain. Postoperative opioid administration might be not only ineffective and disadvantageous, but also not necessary. These considerations should encourage researchers to find more effective and less disadvantageous analgesic interventions than administering solely opioids, especially in an era of advanced surgical care who is rapidly evolving. As the quality standard of postoperative analgesia will be set higher and higher, new strategies need to be addressed to meet these forthcoming challenges.

ß-blockers as possible alternative in the multimodal approach to reduce opioid consumption

β-adrenergic receptors (βAR) have been largely used during the intraoperative period to attenuate cardiovascular morbidity and mortality. Current AHA guidelines for β-blocker therapy to reduce cardiovascular risk in surgical setting discourage to begin a treatment with β-blocker before a non-cardiac surgery, in patients not already treated with β-blocker.[38] This recommendation is mainly influenced by the results of POISE study in which perioperative extended-release Metroprolol (β1 antagonist) administered to surgical patients at risk, or with cardiovascular disease, at a relatively high dosage (100 mg twice a day) and for long period of time (until 30 days after the surgery), increased the risk of stroke and mortality.[39] On the other hand, up to know there is no evidence from other studies of an increase in morbidity or mortality associated to short-term administration of low doses of β-blocker during the perioperative period. In contrast, the results of a Cochrane's meta-regression analysis showed that treatment with β-

blocker to prevent surgery related morbidity and mortality, lasting from 2 to 7 days, showed a reduction for all-cause of mortality 30 days after non-cardiac surgery [RR of 0.82, CI95% 0.40,1.67] [40].

Given the clinical necessity to improve postoperative analgesia and find possible opioid-sparing analgesic co-adjuvant, in the last years a multitude of clinical trials has tested the analgesic efficacy of many different molecules in an unprecedented quest. Amongst many options being studied, β-adrenergic receptors (βAR) antagonists have slowly conquered their own spotlight. Moreover, in multiple cases β-blockers have been used as a valid alternative to opioid during general anesthesia (opioid free anesthesia). Several randomized controlled trials (RCT) investigating these potentialities have reported a concomitant opioid sparing effect.

In the placebo controlled study, Chia and colleagues,[41] investigated the effect of intravenous (iv) Esmolol on postoperative pain in 97 patients after total abdominal hysterectomy. The group of subjects given iv Esmolol, (bolus of 0.5 mg/kg followed by an infusion at rate 50 μg/kg/min) needed 32% less rescue morphine than the patients in the placebo group during the first 3 days of hospitalization [37 (8) vs. 55 (11) mg; p = 0.005].

Ozturk and colleagues [42] treated 40 laparoscopic cholecystectomy patients with Desflurane-Alfentanil anesthesia either with iv Esmolol (bolus of 1 mg/kg followed by an infusion of 5–10 μg/kg/min) or saline. Also in this case iv Esmolol showed an opioid sparing effect, as almost 33% of the subjects in Esmolol group did not require rescue analgesics during the stay in the Post-anesthesia care unit (PACU).

In a control versus placebo study, Hwang and colleagues[43], treated 28 subjects undergoing laparoscopic gynecological surgery with an iv Esmolol infusion (bolus of 0.5 mg/kg followed by

30 μg/kg/min) and other 28 subject with an identical volume of saline. Patients in the Esmolol group received 50% less rescue Fentanyl then patients in the control group in the early postoperative period [median 25 (range, 25–50) μg vs. 50 (25–75) μg; p = 0.008]. Concomitantly, the average pain intensity, measured with NRS scale was 20% lower in the Esmolol group (p < 0.005).

In a cohort of patients undergoing septorhinoplasty, Celebi and colleagues (article in Portuguese) [44] treated 30 patients with a combination of iv Remifentanil and Esmolol (bolus of 0.5 mg/kg followed by an infusion at a lower rate of 5 μg/kg/min, Esmolol group) and a second group (n=30) with iv Remifentanil and saline (Control group). The Esmolol group needed less Remifentanil during the surgical procedure and it required 45 % less Morphine during the stay in the PACU. Pain (VRS, 0 to 10) was lower during the first hour after surgery in Esmolol group, but the LOS in PACU were similar between the 2 groups [7.1 (8.4) vs. 12.9 (8.7) mg; p = 0.011].

Teimoori and colleagues [45] investigated instead the effect of Propranolol (40 mg administered orally half hour before the surgery) on postoperative pain in patients anesthetised with iv Propofol, Nitrous Oxide and iv Remifentanil. The study was conducted in 73 patients undergoing laparoscopic hysterectomy in which postoperative pain (VAS, 0 to 10) was treated with Morphine. During the early postoperative period, the subjects given Propranolol rated their pain levels lower than the placebo group [1.0 (0.6) vs. 2.8 (0.8); p < 0.001] and the time to receive the first rescue Morphine dose was 13 hours longer in the Propranolol group [17 (1) vs. 4 (2) h; p < 0.001). Moreover morphine consmption was decreased by 72% during the first 24 postoperative hours [2.9 (2.5) vs. 10.4 (2.2) mg; p < 0.001]. The results of this study are remarkably positive as it not only showed an important reduction in morphine consumption in the group treated with Propranolol, but also a 4 times increase in time lapse to request the first bolus of Morphine (16

hours vs 4 hours). Unfortunately these positive results are questionable as the study design was sub-optimal. In fact, the bouls of Morphine after surgery was not administered by a patient controlled device, but by a nurse according the pain of the patient. Being the scheme for Morphine dosage administration rigidly compartmented, it is difficult to refer the difference in opioid consumption only to the synergic effect of Propranolol.

The clinical trials described until now studied the comparison between a group treated with β-blockers against a group treated with placebo. Even if this is an essential exercise to perfect our pathophysiological understanding, its benefit diminishes when contextualized in the current clinical practice. As described previously, with the introduction of multimodal analgesia nowadays it is rare that the management of postoperative pain lies only on the administration of opioids. It is therefore imperative to compare the β-blockers therapeutic option against other active analgesic coadjutants already prescribed in the clinical setting. Several studies have explored this horizon and they confirmed again a significant opioid-sparing effect related to the administration of Esmolol.

In 2007 Collard and colleagues[46] randomized 90 patients undergoing ambulatory laparoscopic cholecystectomy in three equal groups. One group received 1 μg/Kg of iv Fentanyl followed by intermittent Fentanyl boluses (Fentanyl group), the second group received iv Esmolol (1mg/Kg followed by an infusion of 5-15 μg/kg/min, Esmolol group) and no supplemental opioids during surgery, and a third group received iv Remifentanil (1 μg/Kg followed by an infusion of 0.1-0.5 μg/kg/min, Remifentanil group). The amount of iv Fentanyl used to treat postoperative pain was lower in the Esmolol group, compared with the Remifentanil and Fentanyl groups, (91.5 +/- 42.7 vs 237.8 +/- 54.7 vs 168.1 +/- 96.8 μg respectively, $p < 0.0001$). Patients treated with iv Esmolol recovered faster and left the hospital earlier than patients in the other groups ($p < 0.004$).

Kavak and colleagues (article non indexed on PubMed)[47] compared a cohort of patients treated with iv Esmolol (1 mg/kg bolus followed by an infusion of 50 μg/kg/min, Esmolol group) or with iv Lidocaine (1.5 mg/kg bolus followed by an infusion of 2 mg/kg/min, Lidocaine group) or with iv Remifentanil (10 μg bolus followed by a saline infusion, Remifentanil group). The need for Fentanyl in the Esmolol group was 45% lower compared to the Lidocaine group and 39% lower compared to the group of patient treated with Remifentanil [402 (72) μg - 728 (86) μg - 663 (84) μg; $p < 0.001$]. Pain scores were lower in the Esmolol group compared to the Remifentanil group during the early postoperative period.

In the study of Said-Ahmed[48], a comparison was made between the treatment with iv Esmolol (infusion rate of 5–15 μg/kg/min, Esmolol group) versus iv Fentanyl (initial bolus 1 μg/kg followed by 50 μg bolus every 30 min, Fentanyl group) in patients undergoing laparoscopic inguinal hernia reparir. A 42% reduction in postoperatively iv Fentanyl consumption was observed in patients treated with intraoperative iv Esmolol compared to patients receiving iv Fentanyl [96 (35) vs. 165 (88) μg; $p < 0.05$].

López-Álvarez and colleagues[49] studied the postoperative Morphine sparing effect of iv Esmolol after laparoscopic cholecystectomy. During surgery patients were treated with iv Esmolol (initial bolus of 0.5 mg/kg followed by infusion of 5-15 μg/kg/min, Esmolol group, n=30) or with a combination of iv Ketamine (0.5 mg/kg) and iv Remifentanil (0.5 μg/kg/min followed by an infusion of 0.1–0.5 μg/kg/min, Control group, n=30). The results showed a reduction in median morphine consumption for the groups treated with Esmolol compared to the Control group [0 (range, 0–2) vs. 5 (4–6) mg, respectively; $p > 0.001$]. Again, the pain scores in the Esmolol group were lower (difference in maximum NRS, −1.1; 95 % CI, −1.9 to −0.3) during the early postoperative period than those in the Control group.

Lee and colleagues[50] studied 60 patients undergoing laparoscopic cholecystectomy randomly assigned into three groups. The first group was treated with iv Esmolol (an initial bolus of 0.5 mg/kg followed with a continuous infusion of 10 μg/kg/min, Esmolol group, n = 20). The second group with Ketamine (an initial bolus of 0.3 mg/kg followed with a continuous infusion of 3 μg/kg/min, Ketamine group, n = 20) and the third group received an initial bolus and continuous with an equal amount of normal saline (Control group). Patients treated with Esmolol needed 43% less rescue Fentanyl than patients in the placebo group [38 (SD33) μg vs. 67 (SD37) μg; $p < 0.05$] during the first 6 hours after surgery. Fentanyl consumption was not different between the Esmolol and Ketamine groups

In contrast, there are also examples of clinical trials which demonstrated that Morphine consumption after perioperative βAR blockage is increased. Smith and colleagues[51] compared the effects on postoperative pain of intraoperative administration of iv Esmolol (bolus of 2.0 mg/kg followed by an infusion of 25–100 μg/kg/min) versus the administration of iv Alfentanil (16 μg/kg followed by an infusion of 0.8 μg/kg/min) 97 patients scheduled for arthroscopic elective surgery. In this case the rescue analgesics during the early postoperative period were requested by 57% of the subjects treated with Esmolol and by 34% of those treated with Alfentanil ($p < 0.05$). In addition, the subjects in the Esmolol group rated their pain intensity higher than those receiving Alfentanil during the early postoperative period ($p < 0.05$).

In a study by Coloma and colleagues[52], 53 patients scheduled for laparoscopic tubal ligation were treated either with iv Esmolol (bolus of 1.0 mg/kg followed by an infusion of 5–15 μg/kg/min, Esmolol group) or with iv Remifentanil (bolus 1.0 μg/Kg followed by an infusion of 0.025– 0.125 μg/kg/min, Control group). In the postoperative period the need for analgesics was higher in Esmolol group. In detail, during the first 24hrs after surgery more than half of the

patients in the Esmolol group required Hydrocodone as rescue analgesia compared to the number of patients in the Control group (14/27 vs. 6/26 patients; $p < 0.05$). However, the incidence of postoperative nausea and vomiting was lower in the Esmolol group.

At first glance, it is striking to note that Esmolol (a selective ß1-blokers) was used in all RCTs described, except than in one RCT. In this study Propranolol (a non-selective ß-blockers) was instead administered (Table 2). This choice can be easily justify by considering the pharmacokinetics proprieties and the conventional use of the 2 drugs. The distribution and elimination half-life of Esmolol are 2 and 9 minutes, respectively. These pharmacokinetic properties allow from one hand a rapid start of action and, critical feature for a dynamic process as the intraoperative period, and on the other hand they guarantee a transient pharmacological action. Moreover, Esmolol is already largely considered by the community of anesthesiologists as a valuable agent to use during surgical procedures to treat tachycardia and hypertension and provide cardiac protection. In contrast, Propranolol has features that make its manipulation more nettlesome in the surgical setting. In its oral formulation as immediate release tablets, Propranolol reaches the onset of action in 1-2 hours and it lasts until 6-12 hours. This does not allow dose adjustments and titration during surgery.

In a meta-analysis published in 2015, Harkanen and colleagues have summarized the current knowledge about the effect of intra-operative ß-AR antagonist on perioperative analgesia and opioid consumption[53]. The authors completed a systematic research for key words and Boolean operators for studies published until February 2015 on the major clinical database (CENTRAL, CINAHL, EMBASE, and MEDLINE). The results of the overall analysis confirmed that patients treated with low dose of intraoperative iv Esmolol infused during surgery consumed 32 to 45% less opioids than patients not treated with iv Esmolol in the immediate postoperative

period. To describe the results the authors used standardized mean difference (SMD as difference between the mean of two groups divided by the standard deviation) showing that the amount opioid consumption was in favor of intervention group with ß-blockers [SMD −1.7, 95% CI −2.5 to −0.9]. These results were partially confirmed by grouping the studies based on the comparison group either comparing ß-blockers with placebo [SMD -1.6, 95%CI -2.5 to -0.9] and with the active control [SMD -2.0, 95% CI -3.6 to -0.4]. However, in this sub-grouping analysis the need for rescue analgesia showed no significant difference in favor of the treatment with ß-blockers. These results should be interpreted by considering the high level of clinical heterogeneity reported in this meta-analysis (I^2>90%, p <0.05), despite the authors used of a random effect model. The same authors report this limitation in their manuscript and they acknowledge that "it prevents to reach a conclusive understanding about the role of ß-blockers as adjuvants in perioperative analgesic management"[53]. Nonetheless the meta-analysis has the undebatable value to approach systematically for the first time the role of ß-blockers to treat pain after surgery and their potentiality to reduce opioid consumption. Although the magnitude of the effect described can be questioned, overall these findings confirm the presence of a opioid sparing effect correlated with concomitant administration of β-blockers.

If Harken's results point to confirm the clinical value of βAR blockage to reduce opioid consumption after surgery, the mechanisms thorough which βAR blockage produce this effect remain obscure. Several hypothesis have been proposed. A simplistic, but very effective way to explain the opioid sparing effect of β-blockers points to their cardiovascular proprieties. Propranolol is able to modify the pharmacokinetics parameters of other intravenous anesthetic co-administered [54]. When administered, β-blockers decrease the cardiac output, increases the vascular resistance and finally it reduces the hepatic blood flow. As opioid molecules and other

anesthetics are metabolized in the liver, a decrease in blood flow will decrease their rate of extraction and clearance and increase their elimination half time, thus prolonging their analgesic effect. A model on healthy volunteers showed that administration of Propranolol doubled the area under the curve (AUC) for antipyrine, a surrogate of lipophilic drug, during the first three minutes of infusion. As stated by the authors[54], this difference was clinically equivalent to giving a double dose of the antipyrine from the beginning. Another possible pharmacokinetic interaction between β-blockers and opioids is their relationship with the P-glycoprotein ATP-binding cassette sub-family B member 1 (ABCB1). ABCB1 is a permeability glycoprotein involved in the transport of a multitude of molecules. In particular Propranolol is a ABCB1 inhibitors while Morphine is a P-glycoprotein ABCB1 substrate, therefore the interaction between these two drugs may increase the serum concentration of Morphine, and magnify its analgesic efficacy. A further hypothesis recalls the possible role of catecholamine in the signaling pathway of pain. It is known that in physiologic conditions nociceptors do not respond to stimulation from the sympathetic nerves. On the contrary, during an inflammatory process catecholamines are able to activate nociceptors and to trigger the neuroinflammation, a process recognised important for the development of primary and secondary hyperalgesia[11]. In this case, β-blockers would be able to prevent the catecholamine-mediated sensitization. The role of the autonomic system could be of interest also from another perspective. It is well documented that autonomic system is part of the descending system which modulates pain. The adrenergic receptor antagonist would block the excitatory effect of norepinephrine on pain signaling. The role of β-AR in nociception is confirmed by the fact that the injection of epinephrine and isoproterenol into the rat's paw induces mechanical hyperalgesia[55], phenomenon probably mediated by the activation of the β2-AR[56].

The central noradrenergic system is a neuromodulatory structure that can be considered a neuroanatomical analog of the peripheral sympathetic system. Centrally, noradrenaline is located in the locus coeruleus (LC). The LC is activated by important physical or psychological stresses as state of anxiety, fear or pain. The LC has multiple input and output connections. It both installs bidirectional pathways with other brain nuclei such as the amygdala or the hippocampus (regions of the brain involved in emotional processes), and on the other side it projects descending fibers to the spinal cord. Since these circuits also uses noradrenaline as one of the neurotransmitters, by blocking the ßAR present in these pathways can decrease the activity of the LC and decrease the perception of pain[57]. Additionally, experiments on rats have shown that Esmolol, dissolved in brain slices merged in artificial cerebrospinal fluid is able to directly modulate directly the release of neurotransmitters in the nuclei of the central nervous system through the activation of calcium currents, although in this case the effect was independent from the activation of β1 receptors, but probably mediated by GABAnergic receptors[58]. Moreover, β-blockers and in particular Propranolol could work similarly to local anestetics[59]. In fact Propranolol is able to block Na+ channels decreasing the cellular neuronal excitability[60]. Rat experiments show that the analgesic effect of intracutaneous Propranolol (area under the curve (AUC) of analgesia 5788 ± 421) is more potent and last longer than intracutaneus administration of Lidocaine (analgesic AUC 1979 ± 331)[61]. Also intrathecal administration of Propranolol produces equipotent analgesia than Lidocaine, but the analgesic effect lasts last longer [62]. Finally, β-blockers seem to have preventive analgesic properties. In fact the analgesic effect observed with the administration of β-blockers goes beyond the elimination half-life of the molecule itself. For example, the half-life of Esmolol is just of several minutes but its opioid sparing effect persists until the first postoperative days. A possible explanation of this prolongation of the

effect could be found in the partial contribution of β2-adrenergic receptors in the neuro-adaptive processes following the administration of opioids. Opioid tolerance, opioid dependence and opioid induced hyperalgesia seems to share common mechanisms and pathways and β-AR have been reported to play a meaningful role in their processing. Genetic association analysis and animal studies confirmed the association between OIH and β2-AR in mice[63] and showed that chronic opioid administration is followed by an up-regulation of β2-AR signaling pathways[56]. Tolerance and dependence processes induce by Morphine in mice are reversed after the administration of Butoxamine (a selective β2-AR antagonist), but not after administration of non-selective ß-blockers[64]. This model is also confirmed on a cellular level. As mentioned before, DRGs are the first station for the peripheral sensory afferents and substance P (SP) and calcitonin related peptide (CGRP) are shown to be important mediator for dependence, tolerance, and hyperalgesia related to opioid administration[65]. In Liang's study the levels of mRNA for peptide C and CGRP in DRG was reported to be related with opioid administration, and in particular the chronic administration of morphine was followed by an increase of their expression. At the same time β2 blockage was able to reduce their mRNA expression levels.[66] A clinical confirmation for this hypothesis came from a clinical trial performed by Chu in 2012. Intradermal electric stimulation was used to excite an area of secondary hyperalgesia on 10 healthy volunteers. The area of hyperalgesia augmented 140% after the administration of Remifentanil. On the contrary, the concomitant administration of Propranolol with Remifentail maintained the dimension of the hyperalgesic area unchanged[67].

Despite all these hypothesis confirmed by limited data, a real understanding of the role and mechanisms behind analgesic and the opioid sparing effect of ß-blockers it is still missing. Furthermore, it is difficult to establish the real connection between the selectivity of ß-adrenergic

antagonist and opioid-sparing effects from clinical trials. This because dosages used in clinical practice are often different from those used in experimental trials and thy are unlikely to guarantee the perfect selection of the receptors activated. It could be speculated that ß-receptors exert a wider anesthetic-sparing effects, and that the specific opioid sparing effect is just one of this more general actions. It has been known for a long time that Esmolol provides a general anesthetic sparing effect. Additionally, the primary hypothesis behind the use of Esmolol in the RCTs mentioned above was the substitution of Remifentanil (or other anesthetic opioids) instead of the study of synergic analgesic interaction with opioids. For now, evidence from clinical data is not strong enough to recommend the use of β-blockers as possible co-analgesic adjuvants. Besides this, the β2AR contribution could be slightly different from the general effect on β-AR, as the opioid-sparing effect could be mediated by a more direct modulation of the opioid molecular pathways.

An updated molecular model on how ß-blockers could affect the opioid receptor pathway

Opioid molecules exert their activity through opioid receptors. Until now, four different opioid receptors have been characterized: Mu opioid receptor (μ - MOR), Delta opioid receptor (δ – DOR), Kappa opioid receptor (κ – KOR), and opioid receptor like-1 (ORL1). Since most of opioid drug agonists have been developed as morphine analogs, and morphine being mostly a MOR agonist, it is not surprising that MOR is considered as more clinically relevant receptor. Opioid receptors are 7-transmembrane spanning proteins coupled to inhibitory G-proteins (GPCR), the largest membrane protein family in the human genome. Their molecular structure consists of 7-transmembrane-spanning α-helices (7-TM) with an extracellular amino (N) terminus, a ligand binding site, a G protein- binding site, and an intracellular carboxyl (C)

terminus. Following MOR activation by an agonist drug, Gα and Gβγ subunits dissociate and act on various intracellular effector pathways, for example altering the activity of adenylate cyclase and the level of the second messenger: cyclic adenosine monophosphate (AMP)[68]. The final and perhaps most important step in opioid signal transduction is the modulation of calcium and potassium ion currents. Once Gα is dissociated, the subunit interacts with potassium channel, (Kir3) causing cellular hyperpolarization, that is biologically reflected as an inhibition of tonic neural activity[69]. At the same time Gβγ subunit interacts with $Ca2^{+}$ channel inhibiting their calcium conductance, probably through a reduction in the voltage of activation of the channel pore opening[70]. Moreover, cAMP-dependent Ca^{2+} influx is reduced as consequence of the reduced level of cAMP. This is the most common and classical pathway for the signal transduction, but it is not the only one. Of note, there are also concomitant alternative pathways (for example through β-arrestin) that act slower but consistently with the cAMP-dependent Ca^{2+} pathway[71]. To summarize, the activation of an opioid receptor inhibits the tonic activity of the neuron and prevents the transmission of the signal. Since opioid receptors are expressed in modulating descending pathways, their activation inhibits spinal cord pain transmission[72].

Opioid gene expression normally results in a multiplicity of messenger RNAs (mRNA)[73]. In its first form, after DNA transcription, RNA contains introns and exons (pre-RNA). It is only during the splicing process that introns are removed to produce the mature mRNA that will be translated later. Even if a major transcript form of the mRNA exists, the exonics composition in the final mRNA can also be edited differently. It is indeed common that multi-exonic genes are spliced in several alternative ways, allowing a broad proteinomic variability in the receptor structure and their biological function. So, although MOR represents the most common receptor variant, Opioid receptor mu 1 (OPRM1) pre-mRNA can also be spliced differently, and opioid receptors

are physiologically present in many alternative variants. One of these is MOR1K, whose mRNA encodes for a final proteins with only 6TM domains rather than the canonical 7[74]. In detail, the receptor lacks the first extracellular N-terminal domain. When MOR docks on the surface of the plasma membrane, MOR1K is instead stored in intracellular compartments. Interestingly, the activation of 6TM-MOR isoform produces an increase in intracellular excitatory mediators, particularly in levels of cellular Ca^{2+} and nitric oxide (NO) release, and it is finally associated with the excitation of the cell[74]. These molecular events are of great interest as they rephrase the classic paradigm for the opioid signaling as a balance between two opposite pathways one, major, inhibitory and the other excitatory. The recognition of an excitatory pathway regulated by the activation of opioid receptors is also able to explain clinical behavior as opioid-induced hyperalgesia (OIH)[75].

GPCRs exist in dynamic protein complexes, interacting and combining with other receptors. In particular, GPCRs can couple with other receptors in a process called oligomerization[76,77]. Oligomerization happens essentially with two modalities: the formation of homodimers (a combination with the same receptor) or heterodimers (when the combined receptor is of a different type). Classic opioid receptors and their splice variants are not an exception to this rule. Here I will focus only on one among many of MOR oligomerizations:, the 6TM-MOR, as it is able to dimerize with β2AR. β2ARs are also GPCRs susceptible to catecholamine stimulation and coupled with G stimulatory subunits (Gs)[78]. The interaction between the two receptors is indeed a critical step for the activation of the excitatory opioid pathway since it allows the 6TM receptor to reach the membrane and be activated by an opioid agonist. On the contrary, blocking β-2AR prevents the development of dimers and interrupts 6TM migration to the membrane surface. This mechanism has been confirmed in *in vitro* experiments. In cells expressing the

dimer β2-AR-6TM-MOR pretreatment with ICI 118,551 (a selective β2-AR antagonist) was able to reduce intracellular Ca2+ elevation normally exhibited by the receptor dimer in the opioid dependent manner[78]. The molecular model is consistent also in vivo experiments. One of the most widely used animal models of acute pain is the injection of formalin into the paw of a mouse. The animal pain behavior is displayed afterward by the licking of the paw and measuring the time that the animal spends to lick its paw is a validated pain assessment in the mouse. In mice injected in the paw with formalin (5%), either morphine or ICI 118,551 administered alone were able to induce an analgesic behavior (the time spent licking the paw was diminished compared to the saline control). Moreover, the co-administration of opioid drug together with the β2-AR blocker (ICI 118,551) showed a positive synergy in decreasing pain assessed by analysis with isobolograms. Finally, the blockage of β2AR is even able to reverse the OIH in mice treated with opioids for four days to develop a state of hyperalgesia. Hyperalgesia in the animal is assessed measuring the time that the animal can remain on a hot or cold plate (plate test). Notably, in mice in which OIH has been induced the time spent on the plate is reduced. Once again, administration of ICI 118,551 is able to reverse the time to pre-OIH values either on the hot either on cold plate tests [78].

From what has been discussed until now emerges how β2-blockers appear to be a potential analgesic co-adjuvant which act synergistically opioids, and that co-administration of β2-AR with opioids could decrease the opioid need after surgery. Despite this even if the effect is present and described in the clinical literature, the evidence is often blurred from unclear clinical phenotypes and the lack of solid biological markers. At the same time the practicality to employ a largely used ß1-blocker drug, as Esmolol, has been constantly privileged over the experimental

evidence that instead suggest the adrenergic receptor β2 as the ideal target to obtain a maximal synergic effect.

Designing a clinical trial to establish the potential analgesic efficacy of perioperative ß-blockers, and understanding their underling mechanisms: scientific rational, objectives and hypothesis of a randomized controlled trial .

Considering the state of the art about the implementation of ß-blocker in perioperative pain treatment, we have decided to design and performed a randomized clinical trial with the objectives of intestigate the clinical effect of ß-blockers on opioid reduction and at the same time collect biological data to improve our understanding of the mechanisms underlying their efficacy. As mentioned before experimental data consistently suggest that β2AR, primary and selective target of ß-blockers, play a pivotal role in determining the analgesic and opioid sparing activity observed with the use of these medications. Unfortunately, purely selective ß2-blockers are not currently in Canada. For these reasons we were obliged to fall back on to use of Propranolol, a largely used nonselective β-blocker. As this drug has been shown to be effective in a previous clinical trial[45], we have decided to administer Propranolol at similar dosage used in this study in order to obtain comparable results. tried to pair to the dosage used in the previous study to have comparable outcomes. It is hypothesized that the implementation of a β2AR blocker as co-analgesic adjuvant in the treatment of acute surgical pain will contribute to decrease pain intensity, and the amount of opioid administered during the perioperative time, and therefore decrease the incidence of ORADEs and shorten hospital LOS.

Objectives and hypothesis of the manuscript presented in this thesis

The manuscript presented in this thesis will focus on determining the feasibility and safety profiles of RCT, by analyzing the results obtained from the first 10 patients enrolled. No analysis will be performed on the biological samples obtained as the sample size is too small to obtain meaningful results. Since cardiovascular stability might be the major concern for the use of Propranolol in perioperative setting when used in non-tachicardic or non-hypertensive patients, the current interim analysis will specifically determine its cardiovascular safety when it administered with the ultimate goal to provide analgesia. Our primary objective is to investigate if low doses of Propranolol administered before and after surgery significantly lower blood pressure and heart rate complications that could hamper the continuation of the ongoing RCT.

Methods

This prospective, double blind, randomized control trial was commenced in 18th May 2016 at McGill University Health Centre. After Health Canada approval for the use of Propranolol per os in surgical setting administered as co-analgesic adjuvant (No-objection letter: HC6-24-C186555), the study was approved by the McGill University Health Centre Ethics Board (15-169 MUHC CT2), and recorded on clinicaltrial.gov (NCT02511483). Patients scheduled for elective laparoscopic abdominal and gynaecological surgeries were recruited by a research assistant at the preoperative clinic. Exclusion criteria were: age less then 18 yr, American Society of Anesthesiologists (ASA) physical status III and more, history of hepatic failure (defined as levels of alanine aminotransferase and aspartate aminotransferase more than 2 times upper limit of normal), renal failure (defined as eGFR < 60 ml/min 1.73m2 or dialysis), patients with uncompensated congestive heart failure, severe sinus bradycardia, sick sinus syndrome, second and third heart block, heart rate less than 45 bpm, mean blood pressure <60 mmHg during the preoperative visit, chronic use of opioids or propranolol, history of asthma or reactive airway disease, allergic rhinitis during pollen season, allergy to opioids or β-blockers, alcohol use disorder within the past 6 months or abuse of psychoactive recreational drugs (MDMA, Ketamine, hallucinogens such as LSD and/or sympathomimetic such as Cocaine), history of major depressive disorders, and severe mental impairment, or inability to comprehend pain assessment. After signature of the written consent form subjects were instructed how to use the numerical rating scale (NRS). During the preoperative visit vital signs were checked and baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), respiration rate (RR) were recorded. If blood pressure and heart rate were satisfying, patients were randomly

assigned to receive Propranolol per os. (Propranolol Group) or placebo (Placebo group). This interim analysis determining the feasibility and safety of the study medication includes patients recruited between May 2017 and October 2017 .

Study drug, blinding and randomization

Propranolol is the first successful β-blocker commercially developed in the 1960's[79]. It interacts with equal affinity to β1 and β2 receptors, it lacks of intrinsic sympathomimetic activity and does not block α adrenergic receptors. Propranolol has a large volume of distribution (4 L/kg) and achieves high concentrations in the central nervous system, thanks to the high lipophilicity of its molecule. It almost completely absorbed after oral administration, however inter individual variation in presystemic clearance by the liver contributes to a high variability in plasma concentration after oral administration. Propranolol tablets have a half-time of 3 to 6 hrs, with onset of action for oral formulation of 1 to 2 hrs and duration of the effect (for immediate release tablets) of 6 to 12 hrs.

Clinically it is referred as nonselective β-adrenergic blocker (class II antiarrhythmic). The competitive block of response from β1- and β2-adrenergic stimulation results in decreases in heart rate, myocardial contractility, blood pressure, and myocardial oxygen demand. Moreover, producing splanchnic vasoconstriction (a phenomena β2AR mediated) it reduces the portal blood flow, and therefore the portal pressure.

Given the different scenario for its clinical use, the effective dosing of Propranolol is also significantly variable, for most indications starting doses are 40-80mg/day *per os*, but typical effective doses range from 120 to 320mg/day, *per os*. For analgesic purposes Propranolol has been already used for variety of morbid conditions. In particular Propranolol has been

occansionlay used to treat pain, for example with a dosage included between 60 and 320 mg/day to treat migraine or with a dose of 40mg/day for the treatment of temporal mandibular disorder (TMD)[80]. Evidences in literature about the optimal analgesic dosage are still limited. Common side effects associated with the use of Propranolol include light headedness, bradycardia, hypotension, insomnia, fatigue, nausea, diarrhea and bronchospasm. Possible side effects resulting from the co-administration of Propranolol and Morphine has been evaluated at Risk C (or Monitor therapy: meaning that evidence shows that the two drugs may interact with each other in a clinically significant manner, but the benefits of concomitant use usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects. To Physician are invited to consider dosage adjustments of one or both agents and monitor the patient to identify potential negative effects) for the risk of hypotension[81].

Propranolol group: Propranolol was administered *per os* at different dosages along the hospital stay. Drug's schedule was planned as follows: a first dose of 20 mg PO 30 min before the beginning of the surgery followed by the administration of an equal dose 12 hours after. Then, after other 12 hours the dose was increased to 30 mg PO every 12 hours and administered daily at this dosage for the remaining length of the hospital stay.

Placebo group: Placebo was administered at the same study points, for the entire duration of the trial.

For blinding purposes, Propranolol and Placebo tablets were over-encapsulated into a fully white capsule presentation, fitted with microcrystalline cellulose to avoid movement or translucency. The randomization sequence was prepared by a research assistant not participating in the study by using a computer-generated block randomization schedule predefined to produce 10 balanced

groups (version 3.0; http://www.randomizer.org/). The medication was stored at the hospital central pharmacy. The hospital central pharmacy was in charge of preparing and dispensing the single kit of medication according to the randomization log provided to the blinded researchers involved in the study.

Anesthesia, Analgesia, and Surgical Care

All patients were anesthetized by experienced anesthesiologists who were instructed to follow the study design, but were not involved in the preoperative and postoperative assessment. After premedication with midazolam 0.03 mg/kg iv and standard moniotring, anesthesia was induced with Propofol 2 mg/kg iv and Fentanyl 1.5 mg/kg iv. Orotracheal intubation was facilitated by Rocuronium 0.6 mg/kg iv. Anesthesia was maintained in both groups with with Desflurane adjusting the end-tidal concentration between 4% and 8% and the minimal alveolar anesthetic concentration (MAC) between 0.7 and 1.2. The lungs were mechanically ventilated with a mixture of air in oxygen (Fio2 40%) to maintain normocapnia. Intravenous Fentanyl (50 µg iv bolus) was used to maintain adequate analgesia during surgery based on standard hemodynamic monitoring and clinical judgment of the treating anesthesiologist. Episodes of hypertension and tachycardia, and hypotension and bradycardia, were managed as per standard of care by the treating anesthesiologist. Intraoperative normothermia (core temperature> 36.0) were maintained by positioning a thermal blanket over the exposed parts of the body and warming intravenous fluids when clinically indicated. Prophylaxis of postoperative nausea and vomiting was achived with dexamethasone at the induction of anesthesia and Zofran 4 mg at the end of the surgery. If clinically required, intraoperative hypotension (mean arterial blood pressure lower than 60 mm Hg) and bradycardia (heart rate lower than 40 bpm) were treated in all groups with a fixed dose of intermittent Ephedrine 40 mg or Atropine 0.4 mg, respectively. Desflurane was discontinued

after the last skin suture. Residual neuromuscular block was antagonized with Neostigmine 0.05 mg/kg and Glycopyrrolate 0.01 mg/kg. Patients were tracheally extubated on the operating table and then transferred to the postanesthesia care unit (PACU). Throughout all the intraoperative time a research assistant blinded to the study drug monitored the heart rate (HR) and systolic and diastolic blood pressure (respectively SBP and DBP) every 5 minutes. All patients were operated by surgeons highly experienced in laparoscopic approach or robotic surgery.

Postoperative Care and Evaluations

Patients were transferred to the PACU where the arterial blood pressure, heart rate, respiration, and temperature were monitored by nurses unaware of the research question every 10 minutes. The nursing staff did not interact with the anesthesiologists or the research assistant and used a standardized prescription for all patients. At the end of surgery Morphine 3 mg IV every 5 min was administered by the PACU nurse if needed to maintain NRS less than 4 (0-10, where 0 is no pain and 10 excruciating pain), until the subject was able to self-administered morphine bolus independently. Once the patients were enough awake, Morphine was delivered via IV-PCA pump (bolus 1 mg, lock out 7 minutes, with no background infusion) for the following 48 hours, except in the case of earlier discharge. Post-operative pain management was integrated with oral analgesics (acetaminophen 650 mg and naproxen 500 mg) as part of the multimodal analgesic treatment. Finally, Ondansetron 4 mg IV was prescribed for persistent nausea (lasting >5 min) or vomiting and could be repeated up to three times over a 3-h period if necessary.

When patients met the institutional standardized PACU discharge criteria, they were moved to the clinical ward. During the hospital stay on the surgical ward SBP, DBP and HR were monitored every 8 hours by a research assistant blind to the study medicatin. Hypotension

requiring treatment was considered a value of mean arterial blood pressure lower than 60 mm Hg, and bradycardia as a value of heart rate lower than 40 bpm. Furthermore, the research assistant collected data about: level of pain (NRS), amount of morphine consumed (mg), postoperative nausea and vomit (PONV) on a numerical scale from 0 to 3 (0 = absent; 1 = feeling nauseous; 2 = vomiting requiring treatment; 3 = vomiting that persisted despite treatment), level of sedation assessed using the Pasero Opioid -Induced Sedation Scale (POSS, S=sleep easy to awake, 1=Awake and alert, 2 Slightly drowsy, easly aroused, 3= Frequently drowsy, arousable, drifts off to sleep during conversation, 4= somnolent, minimal or no response to verbal or physical stimulation). Patients were also asked to record their desire to receive opioids through the opioid craving scale (OCS).

Outcomes and Statistical Analysis

The primary objective of this interim-analysis is to document SBP, DBP and HR during the study period, between the Propranolol and Placebo groups. Secondary objectives included the postoperative morphine consumption, and common ORADEs such as the presence of PONC, POSS and OCS in the PACU and during the stay in the clinical ward.. All data are reported as means and standard deviation, absolute values (percentage), or relative number of patients, when appropriate. Comparisons for each quantitative demographic and clinical variable among the two groups were performed by using an independent Student's t test and factorial ANOVA for repeated variables for any period of time. All reported p-values are two tails with the exception of difference between blood pression and heart rate in which one-tail test was chosen as the direction of the effect was known a priori. The level of significance for all the analysis was

set at $p < 0.05$ for all analysis. Statistical analysis was performed using Excel 2013 analytical and statistical package.

Results:

Patients' Characteristics

In the period between 18th May and 30th October 2016, 116 patients were screened for eligibility at the Montreal Royal Victoria Hospital. Of the 116 patients approached, 58 did not meet the inclusion criteria, and 38 patients refused to participate in the study, leaving 10 patients suitable to be enrolled in this study (Figure 2). Among these 10 subjects, two were excluded by the study as the anesthesia technique or the surgical approach were changed, leaving only 8 patients suitable for the analysis. In detail, in one case the responsabile anesthesist opted for spinal anesthesia instead of general anesthesia as from protocol. In the second case the planned laproscopic surgery was converted to laparotomy. Demographic, clnical and surgical features of each were similar between the 2 groups (Table 3). Baseline in SBP, DBP, and HR did not aslo differ (Table 4).

Intraoperative period

Intraoperative HR, DBP, and SBP of the patients recruited were similar between the 2 groups (Figures 3-5). Duration of surgery in the Propranolol Group was longer than in the Placebo Group, but this difference did not reach statistical significance (Table 5). SBP during the induction and emergency from anesthesia was higher in Propranolol Group versus the Placebo Group (induction of anesthesia: 121 mmHg ±21.5 vs 110 mmHg ±23.7; p-value: 0.04; emergence of anesthesia 117 mmHg ±12.5 vs 108 mmHg ±10.8; p-value: <0.01). However these differences were not clinically relevant. DBP was not different between the 2 groups neither during the induction nor during the emergence from anesthesia. HR was similar between the 2 groups at

time of induction, but it was lower in patients treated with Propranolol at the emergence from anesthesia (61 ±7.4 bpm vs 74 ±6.5 bpm, p-value: <0.01). It needs to mention that during surgery two boluses of Glycopirrolate were required to maintain HR above 50 bpm in one patient of the Propranolol group.

Postoperative Care

PACU

SBP, DBP were similar between the 2 groups also in PACU (Table 6, Figures 6-8). However the HR in Propranolol Group continued to be significantly lower than those in the Placebo Group (67 ±7.1 bpm vs 90 ±21.9 bpm, respectively; p-value: 0.05), but still within an acceptable clinical range. No difference in sedation were observed. Patient in Propranolol Group consumed more Morphine than patients in the Placebo group (29 ± 14.3 mg vs 18 ±7.3 mg, repectively; p-value: >0.05). Pain control was optimal in both groups (3.7 and 3.8 on NRS scale). There was no difference in sedation between the two groups, and no patient had episodes of nausea or vomit. Finally, length of stay in PACU was significantly shorter in patient of the Placebo Group (2hrs 17mins vs. 3hrs 44mins; p-value: <0.01).

Surgical ward

BP and RR were similar between the 2 groups and within a normal range throughout all the time spent on the srugical ward (Table 7). However, HR remained significantly lower in patients treated with Propranolol (66 ±6.4 bpm vs. 86 ±12.3 bpm, p-value: 0.02) on the day of the surgery (day 0), but not on day 1 (67 ±11.4 bpm vs. 77 ±9.3 bpm, p-value: >0.05). In both groups the average HR was above 60 bpm throughout the postoperative period. Postoperative pain was well controlled, and its intensity similarly between the 2 groups. Despite patients in the Propranolol Group used more Morphine than patients in the Placebo group, this difference was not

statistically significant. PONV, POSS, and OCS were also similar between the 2 groups. Coronary artery syndrome or cerebrovascular ischemic events did not occur in any of the patients included in this interim analysis.

Discussion:

The results of this interim analysis suggest that perioperative administration of Propranolol as co-analgesic adjuvant at this dosage and regimen is feasible, and does not significantly affect blood pressure and heart rate. Although few statistically significant differences were observed between the 2 groups, the clinical relevance of these findings is questionable as blood pressure and HR always remained within a normal range for the entire duration of hospital stay. Analgesic benefits associated with the use of Propranolol were not observed.

The primary hypothesis tested in the original RCT is that the synergistic cooperation of β2-AR antagonists and opioid agonists might produce better analgesia and concomitantly reduce the need of opioids after surgery. If these analgesic benefits are confirmed β2-AR blockers might routinely be integrated as analgesic co-adjuvant in the context of a perioperative multimodal analgesia regimen. However, side-effects caused by β2-AR antagonists such as decrease in myocardial contractility, hypotension, and bradycardia can significantly limit its use in the perioperative setting. In this interim analysis, we assessed the safety of administering Propranolol in the perioperative period. Specifically, we investigate weather low dose of Propranolol before and after the surgery could significantly decrease HR and BP, and therefore prevent the continuation of this RCT. It was found that blood pressure and heart rate were minimally affected by the administration of Propranolol. Only one patient in the Proprnolol Group needed a pharmacological intervention to guarantee the successful preservation of hemodynamic values. In this patient glycopirrolate was required to maintain HR above 50 bpm during surgery. During surgery blood pressure was similar in the 2 groups. Despite SBP was significantly higher in Propranolol group at the induction and the emergence from anesthesia,

this difference was clinically irrelevant. In contrast, DBP did not differ between the 2 groups during the induction or the emergence from the anesthesia, during the stay PACU, and once the patient returned to the surgical ward. HR was more affected by Propranolol than blood pressure. In fact, HR was lower in patients treated with Propranolol than those in the Placebo group, during the emergence from the anesthesia, during the stay in PACU and during first night of stay on the surgical ward (day 0). In this case, the decrease in HR was also clinically irrelevant.

Our results are in keeping with what observed in other clinical trials and in a recent meta-analysis[53], despite not all the studies accurately reported hemodynamic data[44,50]. In one study co-administration of Propranolol (to reach a final plasmatic concentration of 15 ng/mL) and Remifentanil in healthy volunteers did not decrease mean arterial pressure but instead reduced HR[67]. Interestingly, Schweinhardt *et al.* reported even an inverse relationship between the decrease in blood pressure and the heat sensibility to Propranolol (0.035 mg/kg body weight i.v.) in healthy volunteers[82]. In our pilot study, Clinically significant hemodynamic differences between the two groups were not observed, and HR and BP remained within normal values. Despite the hemodynamic data reported in this interim-analysis seem to confirm the cardiovascular safety of ß-blockers, these preliminary results don't allow to determine the impact of beta-blockers on adverse clinical outcomes associated with their use, such as stroke and coronary artery syndrome.

These preliminary data did also not show any difference in Morphine consumption between the 2 groups. Nausea and sedation were also similar. Even if the sample size was not large enough to reveal statistically significant results, the absence of a difference should be considered attentively. In fact, similar pilot studies with similar sample size reported a statistically and clinically significant difference[49]. It could be speculated that, hypothesizing a difference of the

same magnitude as those shown by Teimoori[45], this preliminary report should have sufficient statistical power to discern a difference, if present, between the 2 groups. Differently from Teimoori's study, the patients recruited in this trial were treated in the context of multimodal analgesia as per standard of care. It is probable that the presence of other analgesics drugs could have minimized the consumption of morphine in both groups, resulting difficult to appreciate any statistically and clinically meaningful difference. Moreover, for safety purposes we decided to use a low dose of Propranolol during the first day of hospitalizaiton. It could be also possible that the dose used in this trial is too low to show an opioid sparing effect, but adequate enough to don't compromise hemodynamics during surgery and in the immediate postoperative period.

Our pilot study pointed out the difficulties in recruiting patients for this RCT. Over a period of 6 months only 10 patients were recruited and this could have been due to several reasons. First, the informed consent was seek at the preoperative clinic, a complex structure that involve different medical professionals with limited amount of time to evaluate surgical patients. Almost forty percent of the patients who were excluded refused to participate in the study. Moreover, researchers conducting other clinical trials in the same surgical population were simultaneously seeking consent at the preoperative clinic. It might be possible that seeking consent in another clinical endeavour, with more time to explain in details the study and reassure patients about its safety, might have increased the recruitment rate. Second, exclusion criteria might have been too strict and this might have limited the potential number of patient to recruit. In fact, exclusion criteria such as, asthma and use of β-blockers, that are very common in the surgical population have greatly affected the recruitment process. In our study only these 2 exclusion criteria alone were responsible for almost 60% of patients excluded from the study. Based on these limitations and preliminary results we recommend the following modifications to the study protocol. Way of

administration of Propranolol *per os* should be changed from 20 mg every 12 hours to 40 mg once a day at long releases. Exclusion criteria related to the presence of asthma should be modified, and allow the recruitment of patients with non-asthmatic respiratory disease and those with mild or well controlled for of asthma. Moreover, ASA class III patients should also be included.

The possible analgesic efficacy and opioid sparing-effect resulting from the co-administration of β2-AR receptor antagonists with MOR agonist remains a valuable clinical question that deserves to be further investigated with basic-science and clinical research. Propranolol has the advantage to be a cheap and already available drug available in the Canadian market. Since β2-AR antagonist seems to play a pivotal role in determining analgesia and spare opioids, future development of selective β2-AR antagonists could facilitate the understanding of clinical relevance of administering these medications for analgesic purposes, and at the same time limit side-effects related to ß2-AR blockade. It is also important to recognize that it is unlikely that the use of Propranolol will attire the favours of anesthesiologists when a short term, easy-titratable β-blocker as Esmolol is available. Whether β2-antagonists could be recommended as co-adjuvant analgesic medications, and weather the probable negative hemodynamic effects overweight their positive analgesic effects remains to be further established by larger and more consistent trials. If the analgesic efficacy and safety of β-blockers will be confirmed, these medications might represent a clinical silver bullet expendable in a future nearer than expected, especially considering that the use of systemic opioids is becoming a major public-health problem , and that ongoing and upcoming changes in surgical care will significantly reduce the need of administering systemic opioid to treat acute surgical pain.

Conclusions:

The results of this interim analysis suggest that perioperative administration of Propranolol as co-analgesic adjuvant at this dosage and regimen is feasible, and does not significantly affect blood pressure and heart rate. Although few statistically significant differences were observed between the 2 groups, the clinical relevance of these findings is questionable as blood pressure and HR always remained within a normal range for the entire duration of hospital stay. Moreover analgesic benefits related to the administration of Propranolol were not observed.

Modifications to the original study protocol might facilitate the continuation of the study and guarantee the success of the trial.

Figures, Tables:

Figure 1

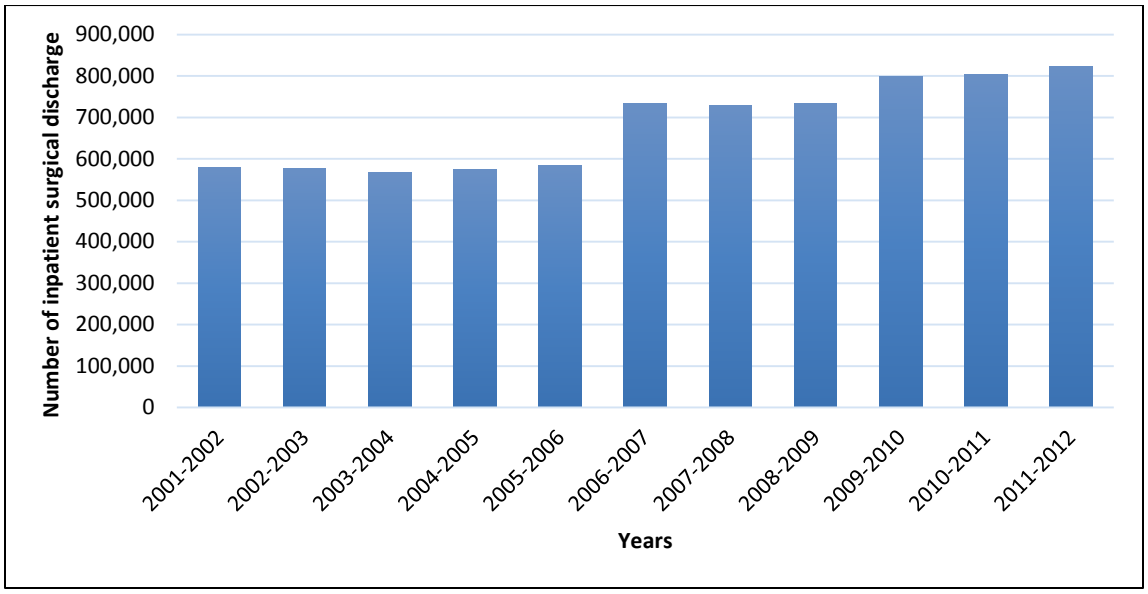

Figure 1. Number of hospital discharges after surgical procedures in Canada during the decade from 2001 to 2011[1].

Table 1

Ranks:	Surgical interventions	Number of inpatients discharges	LOS
1	Caesarean section delivery	100,963	3.2
2	Knee replacement surgery	60,607	4.1
3	Fractures	54,506	9.6
4	Hip replacement surgery	51,799	7.3
5	Coronary artery angioplasty	51,133	4.6
6	Hysterectomy	41,270	2.6
7	Removal of appendix	36,762	3.1
8	Removal of gallbladder	28,315	4.6
9	Pacemaker insertion	26,291	9.1
10	Prostatectomy	24,956	3.5

Table 1. Top ten surgical procedures in Canada in the year 2014-2015[4]. (LOS= length of stay)

Table 2

Cardiovascular effects
• Increased heart rate • Increased blood pressure • Increased stroke volume • Increased myocardial oxygen demands, reduced myocardial oxygen supply and possible myocardial ischemia • Reduced blood flow to viscera and skin causing delayed wound healing
Respiratory effects
• Stimulation of respiration causing initial hypocapnia and respiration alkalosis • Diaphragmatic splinting and hypoventilation, atelectasis, hypoxia and ensuing hypercapnia • Development of chest infection
Endocrine effects
• Catabolic and anabolic changes • Decreased in insulin production • Reduction in testosterone level • Fluid retention
Metabolic effects
• Raised blood sugar levels
Gastro-intestinal effects
• Delayed gastric emptying • Nausea • Reduced gastro-intestinal motility and ileus
Hemostasis
Psychological effects

Table 2. List of the clinical consequences associated with untreated acute pain[83].

Figure 2

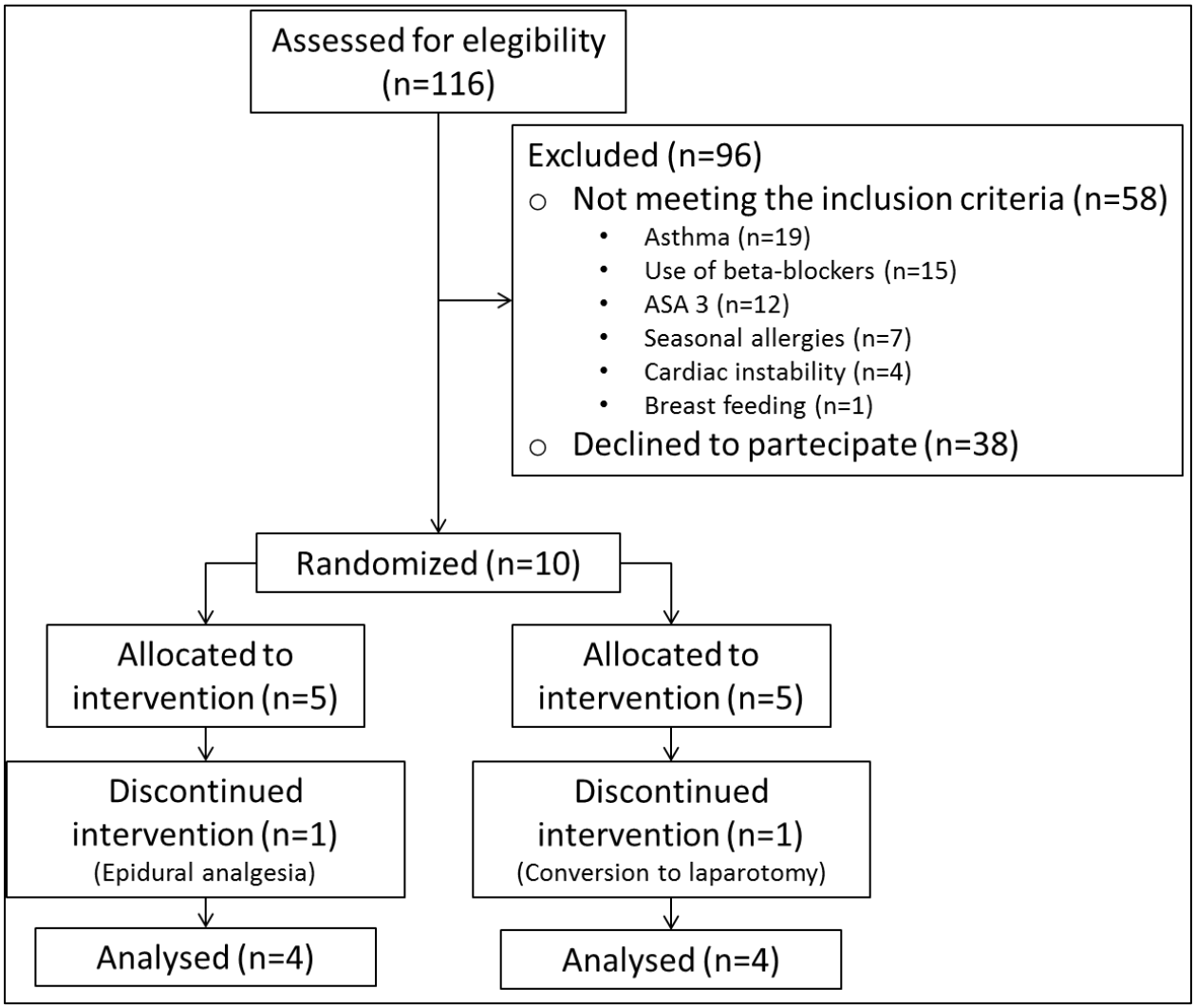

Figure 2. Participants flow diagram according the CONSORT guidelines[84].

Table 3

ID	Rand Log	Sex	Age (years)	BMI (Kg/m^2)	Allergies	Type of surgical procedure
01	Propranolol	male	64	24.8	No	Radical robotic prostatectomy
02	Placebo	Excluded because the patient required epidural analgesia				
03	Propranolol	Excluded because laparoscopic surgery converted to laparotomy				
04	Placebo	female	64	24	No	Robotic total abdominal hysterectomy + BSO
05	Propranolol	female	41	46	No	Robotic total abdominal hysterectomy
06	Propranolol	female	74	26.6	No	Laparoscopic total abdominal hysterectomy + BSO + Omectomy
07	Placebo	male	63	29.4	Yes	Radical robotic prostatectomy
08	Propranolol	female	45	21.9	No	Laparoscopic total abdominal hysterectomy
09	Placebo	female	68	26.6	No	Laparoscopic total abdominal hysterectomy
10	Placebo	female	67	22.5	No	Laparoscopic total abdominal hysterectomy + BSO

Table 3. Demographic characteristic of patients enrolled in the study (BSO= Bilateral Salpingo-Oophorectomy)

Table 4

	Propranolol group (n=4)	Placebo group (n=4)	P-value
Age (yeras)	55 (± 13.7)	65 (±2.4)	0.16
BMI (Kg/m^2)	28.0 (±10.2)	25.8 (±2.9)	0.66
SBP (mmHg)	137 (±9.7)	134 (±21.8)	0.79
DBP (mmHg)	84 (±8.6)	84 (±9.9)	0.93
HR (bpm)	73 (±13.4)	83 (±13.4)	0.29

Table 4. Age and baseline values for systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) in the Propranolol and Placebo group. Values are reported as mean ± standard deviation.

Figure 3

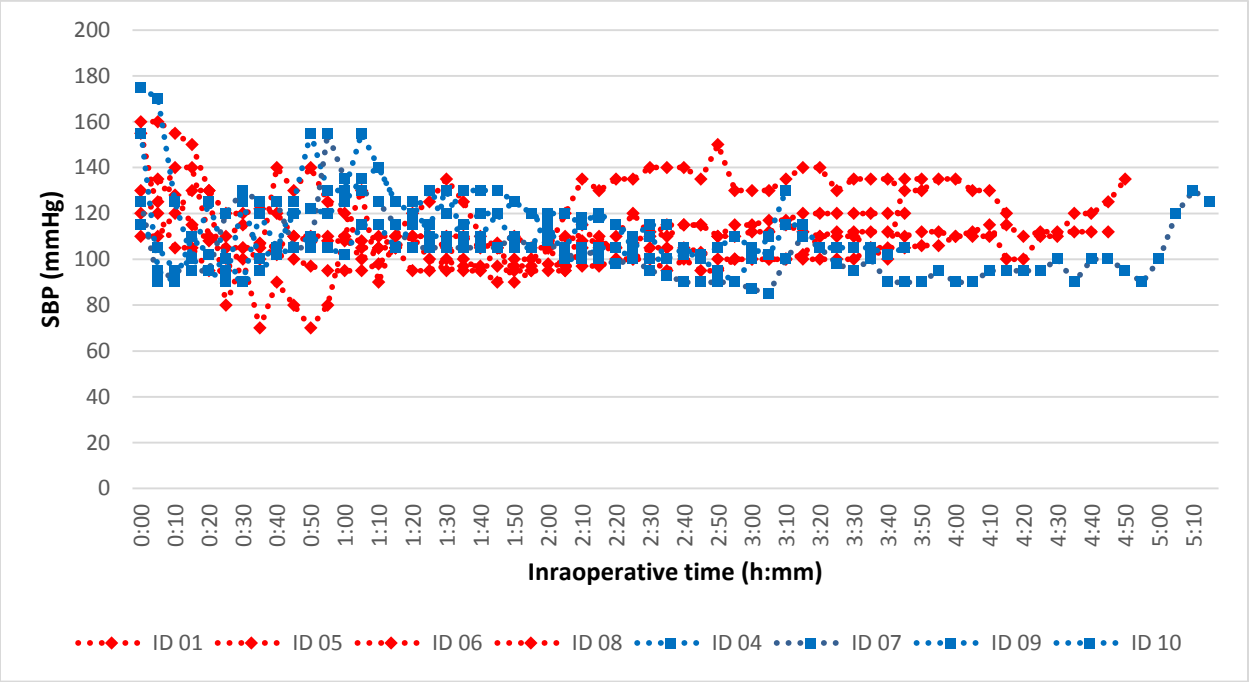

Figure 3. Individual intraoperative systolic blood pressure (SBP) of patients in the Propranolol group (red line) and in patients of the Placebo group (blue line).

Figure 4

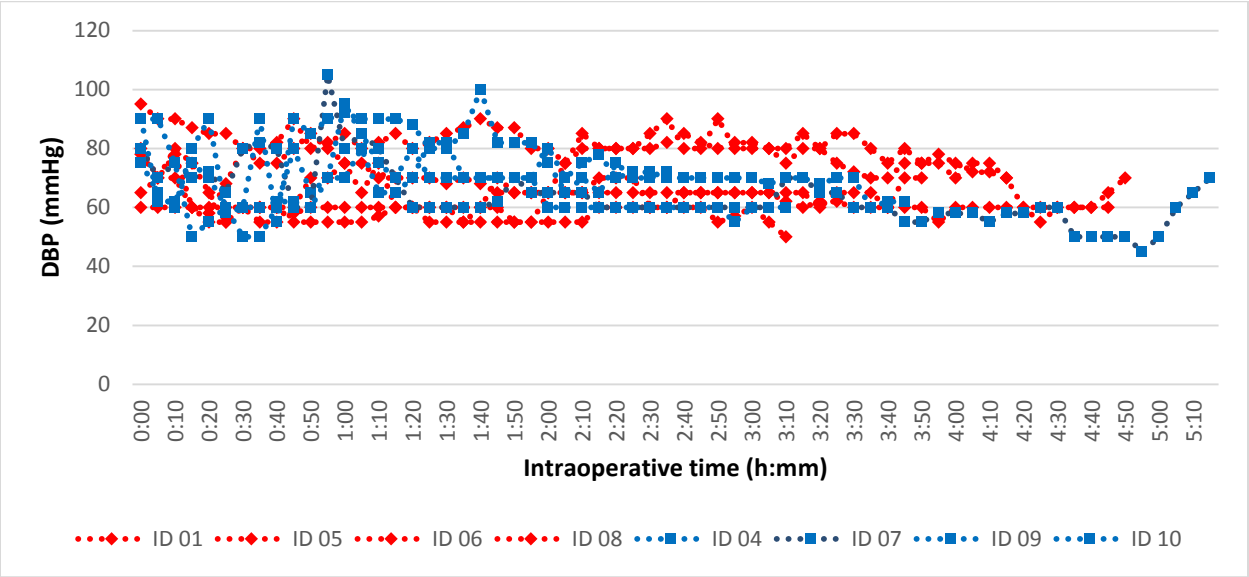

Figure 4. Individual intraoperative diastolic blood pressure (DBP) of patients in the Propranolol group (red line) and of patients in the Placebo group (blue line).

Figure 5

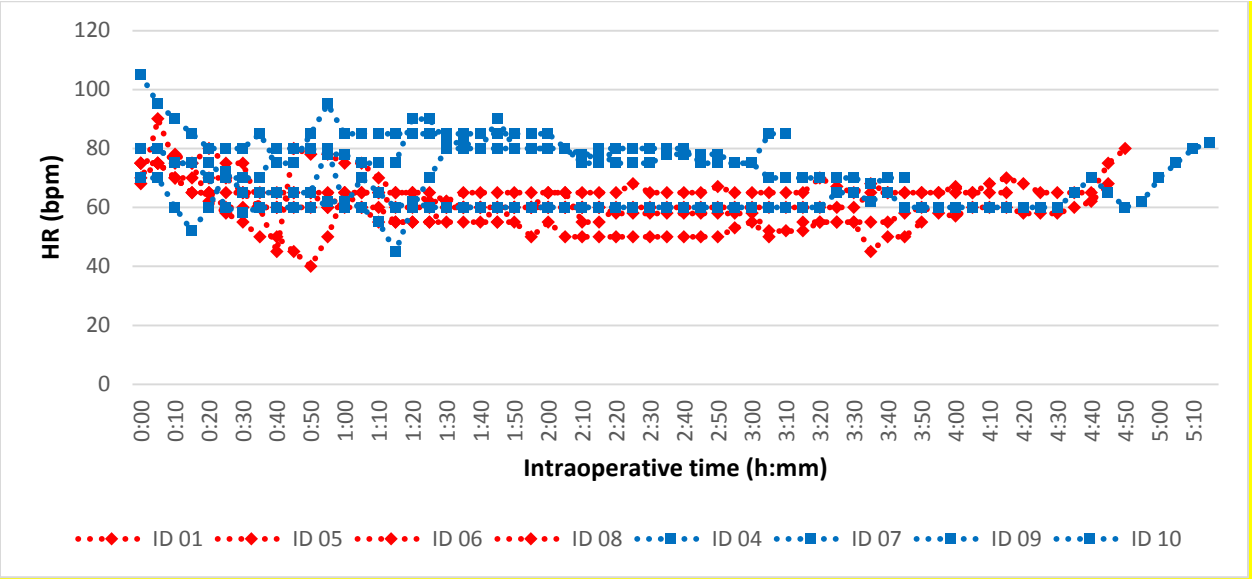

Figure 5. Individual intraoperative heart rate (HR) of patients in the Propranolol group (red line) and of the patients in the Placebo group (blue line).

Table 5

	Propranolol group (n=4)	**Placebo group (n=4)**	**P-value**
SBP induction of anesthesia (mmHg)	121 (±21.5)	110 (±23.7)	0.04*
DBP induction of anesthesia (mmHg)	72 (±11.9)	69 (±11.9)	0.38
HR induction of anesthesia (bpm)	70 (±7.5)	74 (±11.4)	0.11
BP emergence from anesthesia (mmHg)	117 (±12.5)	108 (±10.8)	<0.01*
DBP emergence from anesthesia (mmHg)	65 (±6.5)	62 (±7.6)	0.23
HR emergence from anesthesia (bpm)	61 (±7.4)	74 (±6.5)	< 0.01*
Length of surgery (h:mm)	4:17 (±0:30)	3:41 (±1:08)	0.38

Table 5. Intraoperative hemodynamic variables in the Propranolol group and in the Placebo group. Values are reported as mean ± standard deviation. The α level of significance was set at p = 0.05.

Figure 6

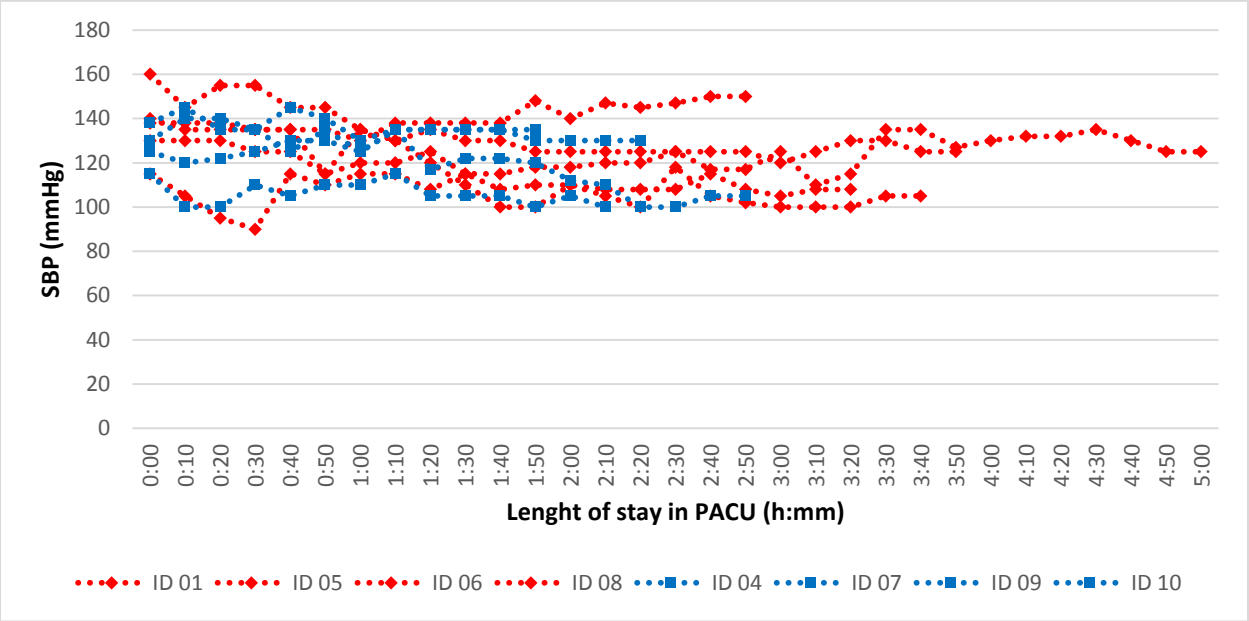

Figure 6. Individual systolic blood pressure (SBP) of patients in the Propranolol group (red line) and of patients in the Placebo group (blue line) during Post Anesthesia Care Unit (PACU) stay.

Figure 7

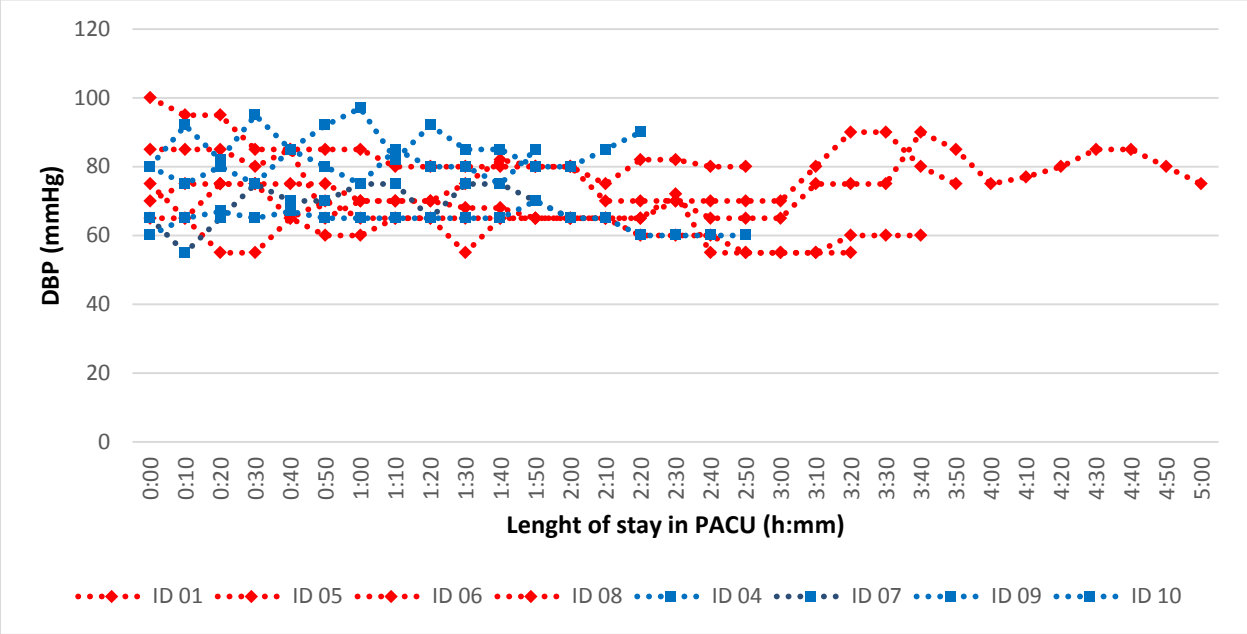

Figure 7. Individual diastolic blood pressure (DBP) of patients in the Propranolol group (red line) and of patients in the Placebo group (blue line) during Post Anesthesia Care Unit (PACU) stay.

Figure 8

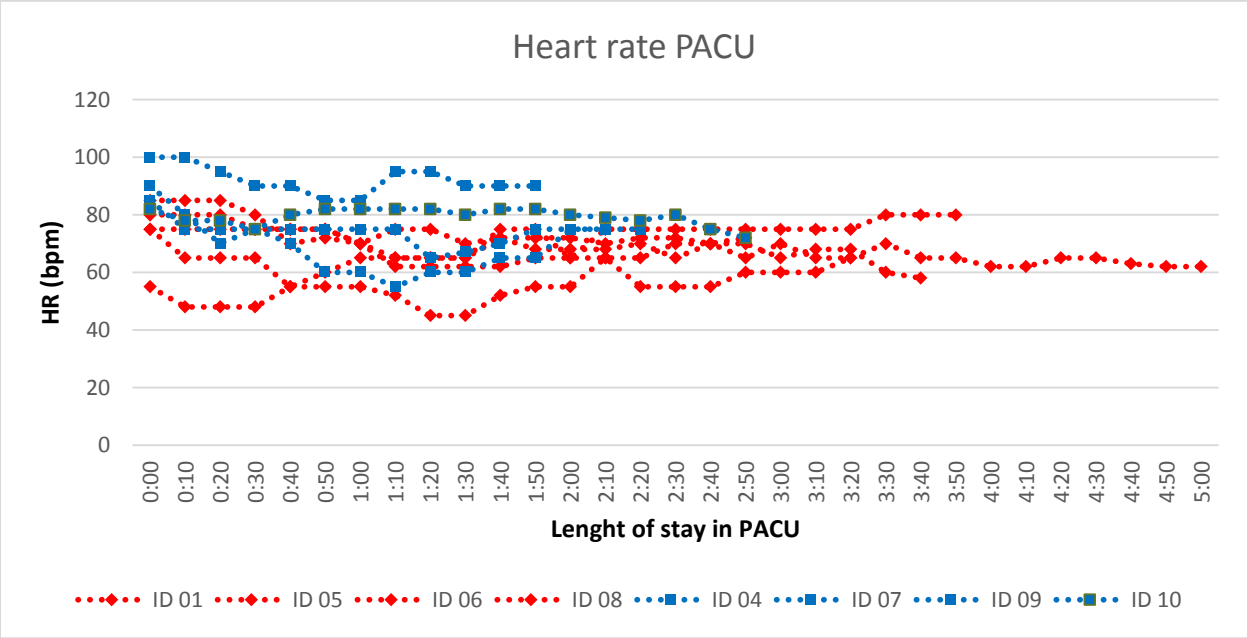

Figure 8. Individual heart rate (HR) of patients of the Propranolol group (red line) and of patients in the Placebo group (blue line) during Post Anesthesia Care Unit (PACU) stay.

Table 6

PACU	Propranolol group (n=4)	Placebo group (n=4)	P-value
SBP (mmHg)	124 (±13)	123 (±14)	0.46
DBP (mmHg)	72 (±7.5)	75 (±10.2)	0.30
HR (bpm)	67 (±7.1)	90 (±21.9)	0.05*
RR (bpm)	14 (±1.7)	13 (±1.1)	0.2
Morphine (mg)	29 (±14.3)	18 (±7.3)	0.23
Pain (NRS)	4.1 (±1.5)	3.8 (±1.4)	0.73
PONV	0	0	-
Sedation, n	2	2	-
LOS in PACU (h:mm)	3:44 (±0:48)	2:17 (±0:25)	0.01*

Table 6. Hemodynamic data, postoperative pain intensity, morphine consumption and sedation during Post Anesthesia Care Unit (PACU) stay in patients of the Propranolol group and in patients of the Placebo Group. Values are reported as mean ± standard deviation. The α level of significance was set at P = 0.05.

Table 7

	Day 0			**Day 1**		
	Propranolol	**Placebo**	**P-value**	**Propranolol**	**Placebo**	**P-value**
SBP (mmHg)	116 (±25.3)	120 (±22.4)	0.39	117 (±11.1)	111 (±10.3)	0.22
DBP (mmHg)	63 (±6.4)	72 (±9.0)	0.07	68 (8±.4)	69 (±2.6)	0.40
HR (bpm)	66 (±6.4)	86 (±12.3)	0.02*	67 (±11.4)	77 (±9.3)	0.10
RR (bpm)	17 (±0.8)	17 (±1.1)	0.29	17 (±0.8)	17 (±1.6)	0.46
Morphine (mg)	6.4 (±7.7)	2.5 (±1.9)	0.32	7.8 (±9.9)	5 (±5.3)	0.61
Pain (NRS)	2.8 (±0.9)	2.3 (±2.2)	0.70	2.3 (±1.0)	1.3 (±1.2)	0.24
PONV	0%	25%	0.31	0%	0%	-
POSS	25%	25%	-	0%	0%	-
OCS	0%	0%	-	0%	0%	-

Table 7. Hemodynamic data, respiratory rate, morphine consumption, postoperative pain intensity, postoperative nausea and vomiting, sedation and Opioid Craving Scale in the Propranolol group and in the Placebo group on surgical wards. Diastolic blood pressure = DBP; OCS= Opioid Craving Scale; SBP = systolic blood pressure; POSS = Pasero Opioid-induced Sedation Scale (POSS); PONV = postoperative nausea and vomiting. Continuous variable were reported as mean ± standard deviation and discrete variable as percentages. The α level of significance was set at P = 0.05.

References:

1. *DAD/HMDB Number of Inpatient Surgical Discharges.* Canadian Insititute for Health Information, CIHI;2014. HAS7.
2. Gan TJ, Habib AS, Miller TE, White W, Apfelbaum JL. Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. *Current medical research and opinion.* 2014;30(1):149-160.
3. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. *Anesthesia and analgesia.* 2003;97(2):534-540, table of contents.
4. *DAD/HMDB Hospitalization Rate, Average Lenght Of Stay, Top 10 High-Volume Inpatient Hospitalization and Surgeries, and Hospital-Based Newborn Rate, 2014-2015.* Canadian Institute for Health Information, CIHI;2016.
5. Information CIfH. Patient Cost Estimator. 2016.
6. Nagda JV, Bajwa ZH. Definitions and Classification of Pain. In: Bajwa ZH, Wootton RJ, Warfield CA, eds. *Principles and Practice of Pain Medicine, 3e*. New York, NY: McGraw-Hill Education; 2016.
7. Lavand'homme P. Perioperative pain. *Current opinion in anaesthesiology.* 2006;19(5):556-561.
8. Brennan TJ. Pathophysiology of postoperative pain. *Pain.* 2011;152(3 Suppl):S33-40.
9. Gandhi K, Heitz JW, Viscusi ER. Challenges in acute pain management. *Anesthesiology clinics.* 2011;29(2):291-309.
10. McQuay HJ, Derry S, Eccleston C, Wiffen PJ, Andrew Moore R. Evidence for analgesic effect in acute pain - 50 years on. *Pain.* 2012;153(7):1364-1367.
11. Pertovaara A. Noradrenergic pain modulation. *Progress in neurobiology.* 2006;80(2):53-83.
12. Deumens R, Steyaert A, Forget P, et al. Prevention of chronic postoperative pain: cellular, molecular, and clinical insights for mechanism-based treatment approaches. *Progress in neurobiology.* 2013;104:1-37.
13. Macrae WA. Chronic post-surgical pain: 10 years on. *British journal of anaesthesia.* 2008;101(1):77-86.
14. Lavand'homme P. The progression from acute to chronic pain. *Current opinion in anaesthesiology.* 2011;24(5):545-550.
15. Campbell JN. APS 1995 Presidential address. *Pain Forum.*5(1):85-88.
16. Upp J, Kent M, Tighe PJ. The evolution and practice of acute pain medicine. *Pain medicine.* 2013;14(1):124-144.
17. Mularski RA, White-Chu F, Overbay D, Miller L, Asch SM, Ganzini L. Measuring pain as the 5th vital sign does not improve quality of pain management. *Journal of general internal medicine.* 2006;21(6):607-612.
18. Solanki A, Akhouri VK. Acute Pain Management in Adults. In: Bajwa ZH, Wootton RJ, Warfield CA, eds. *Principles and Practice of Pain Medicine, 3e*. New York, NY: McGraw-Hill Education; 2016.
19. Helander EM, Menard BL, Harmon CM, et al. Multimodal Analgesia, Current Concepts, and Acute Pain Considerations. *Current pain and headache reports.* 2017;21(1):3.
20. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *The journal of pain : official journal of the American Pain Society.* 2016;17(2):131-157.

21. Jannetto PJ, Bratanow NC. Pain management in the 21st century: utilization of pharmacogenomics and therapeutic drug monitoring. *Expert opinion on drug metabolism & toxicology.* 2011;7(6):745-752.
22. Francis Bonnet HK, Barrie Fischer, Stephan Schug, Girish Joshi, Marc Van de Velde, Philipp Lirk, José De Andrés, Andrew Hill, Narinder Rawal, Patricia Lavand'homme, Helene Beloeil, Johan Raeder, Esther Pogatzki-Zahn. Procedure specific postoperative management [Web page]. 2017; The PROSPECT (PROcedure-SPEcific Postoperative Pain ManagemenT) Working Group (PWG) is an international collaboration of anaesthesiologists and surgeons. Available at: http://www.postoppain.org/. Accessed 11.08.2017, 2017.
23. Khademi H, Kamangar F, Brennan P, Malekzadeh R. Opioid Therapy and its Side Effects: A Review. *Archives of Iranian medicine.* 2016;19(12):870-876.
24. Muller-Lissner S, Bassotti G, Coffin B, et al. Opioid-Induced Constipation and Bowel Dysfunction: A Clinical Guideline. *Pain medicine.* 2016.
25. Radke JB, Owen KP, Sutter ME, Ford JB, Albertson TE. The effects of opioids on the lung. *Clinical reviews in allergy & immunology.* 2014;46(1):54-64.
26. Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *British journal of anaesthesia.* 2014;112(6):991-1004.
27. Eisenberg E, Suzan E, Pud D. Opioid-induced hyperalgesia (OIH): a real clinical problem or just an experimental phenomenon? *Journal of pain and symptom management.* 2015;49(3):632-636.
28. Yu EH, Tran DH, Lam SW, Irwin MG. Remifentanil tolerance and hyperalgesia: short-term gain, long-term pain? *Anaesthesia.* 2016;71(11):1347-1362.
29. Lyons PJ, Rivosecchi RM, Nery JP, Kane-Gill SL. Fentanyl-induced hyperalgesia in acute pain management. *Journal of pain & palliative care pharmacotherapy.* 2015;29(2):153-160.
30. Carullo V, Fitz-James I, Delphin E. Opioid-Induced Hyperalgesia: A Diagnostic Dilemma. *Journal of pain & palliative care pharmacotherapy.* 2015;29(4):378-384.
31. Steyaert A, Lavand'homme P. Postoperative opioids: let us take responsibility for the possible consequences. *European journal of anaesthesiology.* 2013;30(2):50-52.
32. Kessler ER, Shah M, Gruschkus SK, Raju A. Cost and quality implications of opioid-based postsurgical pain control using administrative claims data from a large health system: opioid-related adverse events and their impact on clinical and economic outcomes. *Pharmacotherapy.* 2013;33(4):383-391.
33. Minkowitz HS, Gruschkus SK, Shah M, Raju A. Adverse drug events among patients receiving postsurgical opioids in a large health system: risk factors and outcomes. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists.* 2014;71(18):1556-1565.
34. O'Connor M, Escarpa A, Prys-Roberts C. Ventilatory depression during and after infusion of alfentanil in man. *British journal of anaesthesia.* 1983;55 Suppl 2:217s-222s.
35. Philip BK, Reese PR, Burch SP. The economic impact of opioids on postoperative pain management. *Journal of clinical anesthesia.* 2002;14(5):354-364.
36. Baker DW. History of The Joint Commission's Pain Standards: Lessons for Today's Prescription Opioid Epidemic. *Jama.* 2017.
37. Huxtable CA, Roberts LJ, Somogyi AA, MacIntyre PE. Acute pain management in opioid-tolerant patients: a growing challenge. *Anaesthesia and intensive care.* 2011;39(5):804-823.
38. Fleischmann KE, Beckman JA, Buller CE, et al. 2009 ACCF/AHA focused update on perioperative beta blockade. *Journal of the American College of Cardiology.* 2009;54(22):2102-2128.
39. Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet.* 2008;371(9627):1839-1847.

40. Blessberger H, Kammler J, Domanovits H, et al. Perioperative beta-blockers for preventing surgery-related mortality and morbidity. *The Cochrane database of systematic reviews.* 2014;9:Cd004476.
41. Chia YY, Chan MH, Ko NH, Liu K. Role of beta-blockade in anaesthesia and postoperative pain management after hysterectomy. *British journal of anaesthesia.* 2004;93(6):799-805.
42. Ozturk T, Kaya H, Aran G, Aksun M, Savaci S. Postoperative beneficial effects of esmolol in treated hypertensive patients undergoing laparoscopic cholecystectomy. *British journal of anaesthesia.* 2008;100(2):211-214.
43. Hwang WJ, Moon YE, Cho SJ, Lee J. The effect of a continuous infusion of low-dose esmolol on the requirement for remifentanil during laparoscopic gynecologic surgery. *Journal of clinical anesthesia.* 2013;25(1):36-41.
44. Celebi N, Cizmeci EA, Canbay O. [Intraoperative esmolol infusion reduces postoperative analgesic consumption and anaesthetic use during septorhinoplasty: a randomized trial]. *Revista brasileira de anestesiologia.* 2014;64(5):343-349.
45. B. Teimoori MK, F. Beyrami, N. Sakhavar, Z. Dehbashi, B. Narouie, A. Davarian. Propranolol decrease the post-operative pain and analgesic administration following abdominal hysterectomy. *Life Science Journal* 2012;9(3):1216-1220.
46. Collard V, Mistraletti G, Taqi A, et al. Intraoperative esmolol infusion in the absence of opioids spares postoperative fentanyl in patients undergoing ambulatory laparoscopic cholecystectomy. *Anesthesia and analgesia.* 2007;105(5):1255-1262, table of contents.
47. Kavak Akelma F EJ, Özkan D, Akinci M, Özmen M, Gümüs¸ H. . A comparison of the effects of intraoperative esmolol and lidocaine infusions on postoperative analgesia. *Anestezi Dergisi.* 2014(22):25-31.
48. HAF S-A. The effect of intra-operative esmolol infusion on post-operative opioid consumption and incidence of shivering in patients undergoing ambulatory laparoscopic inguinal hernia repair. *Acta Anaesth Italica.* 2012(60):31-44.
49. Lopez-Alvarez S, Mayo-Moldes M, Zaballos M, Iglesias BG, Blanco-Davila R. Esmolol versus ketamine-remifentanil combination for early postoperative analgesia after laparoscopic cholecystectomy: a randomized controlled trial. *Canadian journal of anaesthesia = Journal canadien d'anesthesie.* 2012;59(5):442-448.
50. Lee MH, Chung MH, Han CS, et al. Comparison of effects of intraoperative esmolol and ketamine infusion on acute postoperative pain after remifentanil-based anesthesia in patients undergoing laparoscopic cholecystectomy. *Korean journal of anesthesiology.* 2014;66(3):222-229.
51. Smith I, Van Hemelrijck J, White PF. Efficacy of esmolol versus alfentanil as a supplement to propofol-nitrous oxide anesthesia. *Anesthesia and analgesia.* 1991;73(5):540-546.
52. Coloma M, Chiu JW, White PF, Armbruster SC. The use of esmolol as an alternative to remifentanil during desflurane anesthesia for fast-track outpatient gynecologic laparoscopic surgery. *Anesthesia and analgesia.* 2001;92(2):352-357.
53. Harkanen L, Halonen J, Selander T, Kokki H. Beta-adrenergic antagonists during general anesthesia reduced postoperative pain: a systematic review and a meta-analysis of randomized controlled trials. *Journal of anesthesia.* 2015;29(6):934-943.
54. Avram MJ, Krejcie TC, Henthorn TK, Niemann CU. Beta-adrenergic blockade affects initial drug distribution due to decreased cardiac output and altered blood flow distribution. *The Journal of pharmacology and experimental therapeutics.* 2004;311(2):617-624.
55. Khasar SG, McCarter G, Levine JD. Epinephrine produces a beta-adrenergic receptor-mediated mechanical hyperalgesia and in vitro sensitization of rat nociceptors. *Journal of neurophysiology.* 1999;81(3):1104-1112.

56. Aley KO, Martin A, McMahon T, Mok J, Levine JD, Messing RO. Nociceptor sensitization by extracellular signal-regulated kinases. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 2001;21(17):6933-6939.
57. Hermans EJ, van Marle HJ, Ossewaarde L, et al. Stress-related noradrenergic activity prompts large-scale neural network reconfiguration. *Science (New York, NY).* 2011;334(6059):1151-1153.
58. Yasui Y, Masaki E, Kato F. Esmolol modulates inhibitory neurotransmission in the substantia gelatinosa of the spinal trigeminal nucleus of the rat. *BMC anesthesiology.* 2011;11:15.
59. Matthews JC, Baker JK. Effects of propranolol and a number of its analogues on sodium channels. *Biochemical pharmacology.* 1982;31(9):1681-1685.
60. Chidlow G, Melena J, Osborne NN. Betaxolol, a β(1)-adrenoceptor antagonist, reduces Na(+) influx into cortical synaptosomes by direct interaction with Na(+) channels: comparison with other β-adrenoceptor antagonists. *British journal of pharmacology.* 2000;130(4):759-766.
61. Chen YW, Chu CC, Chen YC, Hung CH, Wang JJ. Propranolol elicits cutaneous analgesia against skin nociceptive stimuli in rats. *Neuroscience letters.* 2012;524(2):129-132.
62. Chen YW, Chu CC, Chen YC, Hung CH, Wang JJ. Intrathecal propranolol displays long-acting spinal anesthesia with a more sensory-selective action over motor blockade in rats. *European journal of pharmacology.* 2011;667(1-3):208-214.
63. Liang DY, Liao G, Wang J, et al. A genetic analysis of opioid-induced hyperalgesia in mice. *Anesthesiology.* 2006;104(5):1054-1062.
64. Kihara T, Kaneto H. Important role of adrenergic function in the development of analgesic tolerance to morphine in mice. *Japanese journal of pharmacology.* 1986;42(3):419-423.
65. Trang T, Quirion R, Jhamandas K. The spinal basis of opioid tolerance and physical dependence: Involvement of calcitonin gene-related peptide, substance P, and arachidonic acid-derived metabolites. *Peptides.* 2005;26(8):1346-1355.
66. Liang DY, Shi X, Li X, Li J, Clark JD. The beta2 adrenergic receptor regulates morphine tolerance and physical dependence. *Behavioural brain research.* 2007;181(1):118-126.
67. Chu LF, Cun T, Ngai LK, et al. Modulation of remifentanil-induced postinfusion hyperalgesia by the beta-blocker propranolol in humans. *Pain.* 2012;153(5):974-981.
68. Al-Hasani R, Bruchas MR. Molecular mechanisms of opioid receptor-dependent signaling and behavior. *Anesthesiology.* 2011;115(6):1363-1381.
69. Torrecilla M, Marker CL, Cintora SC, Stoffel M, Williams JT, Wickman K. G-protein-gated potassium channels containing Kir3.2 and Kir3.3 subunits mediate the acute inhibitory effects of opioids on locus ceruleus neurons. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 2002;22(11):4328-4334.
70. Zamponi GW, Snutch TP. Modulating modulation: crosstalk between regulatory pathways of presynaptic calcium channels. *Molecular interventions.* 2002;2(8):476-478.
71. Bohn LM, Gainetdinov RR, Lin FT, Lefkowitz RJ, Caron MG. Mu-opioid receptor desensitization by beta-arrestin-2 determines morphine tolerance but not dependence. *Nature.* 2000;408(6813):720-723.
72. Ahlbeck K. Opioids: a two-faced Janus. *Current medical research and opinion.* 2011;27(2):439-448.
73. Civelli O, Birnberg N, Comb M, et al. Regulation of opioid gene expression. *Peptides.* 1983;4(5):651-656.
74. Gris P, Gauthier J, Cheng P, et al. A novel alternatively spliced isoform of the mu-opioid receptor: functional antagonism. *Mol Pain.* 2010;6:33.
75. Wang W, Wang Y, Zhang W, et al. Opioid-induced redistribution of 6TM and 7TM mu opioid receptors: A hypothesized mechanistic facilitator model of opioid-induced hyperalgesia. *Pharmacological reports : PR.* 2016;68(4):686-691.

76. Rios CD, Jordan BA, Gomes I, Devi LA. G-protein-coupled receptor dimerization: modulation of receptor function. *Pharmacology & therapeutics.* 2001;92(2-3):71-87.
77. Prinster SC, Hague C, Hall RA. Heterodimerization of g protein-coupled receptors: specificity and functional significance. *Pharmacological reviews.* 2005;57(3):289-298.
78. Samoshkin A, Convertino M, Viet CT, et al. Structural and functional interactions between six-transmembrane mu-opioid receptors and beta2-adrenoreceptors modulate opioid signaling. *Scientific reports.* 2015;5:18198.
79. Ahlquist R. A study of the adrenotropic receptors. 1948;153:586-600.
80. Tchivileva IE, Lim PF, Smith SB, et al. Effect of catechol-O-methyltransferase polymorphism on response to propranolol therapy in chronic musculoskeletal pain: a randomized, double-blind, placebo-controlled, crossover pilot study. *Pharmacogenetics and genomics.* 2010;20(4):239-248.
81. Interactions LD. Hypotension-Associated Agents / Blood Pressure Lowering Agents. 2017; Blood Pressure Lowering Agents may enhance the hypotensive effect of Hypotension-Associated Agents. Available at: https://www-uptodate-com.proxy3.library.mcgill.ca/drug-interactions/?source=responsive_home#di-document. Accessed 11.08.2017, 2017.
82. Schweinhardt P, Abulhasan YB, Koeva V, et al. Effects of intravenous propranolol on heat pain sensitivity in healthy men. *European journal of pain.* 2013;17(5):704-713.
83. Sinatra R. Causes and consequences of inadequate management of acute pain. *Pain medicine.* 2010;11(12):1859-1871.
84. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ (Clinical research ed).* 2010;340:c869.