Intravenous lidocaine as sole intraoperative analgesic technique for laparoscopic cholecystectomy

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Abstract

The present project investigates the surgical recovery after laparoscopic cholecystectomy of patients receiving intravenous lidocaine as primary intraoperative analgesic technique, without the use of intraoperative opioids. Specifically, it was hypothesised that intravenous lidocaine provides postoperative analgesia equivalent to intraoperative fentanyl. Different aspects of surgical recovery were also measured the day of surgery and also 24 hr after. In this randomized double blind control trial patients were allocated to receive either intravenous lidocaine until the end of surgery (lidocaine group) or fentanyl (control group). Postoperative opioid consumption, opioid side effects, pain intensity, and length of hospital stay were similar between the two groups. Lidocaine did not blunt the hemodynamic response associated with the beginning of the pneumoperitoneum. The inflammatory and metabolic response was also not attenuated. Surgical recovery was similar 24 hr after hospital discharge. Intravenous lidocaine had the same recovery profile of intraoperative opioids.

Résumé

Le projet actuel évalue l'évolution postopératoire après cholecystectomie laparoscopique chez des patients recevant de la lidocaine intraveineuse comme première modalité analgésique en absence d'opiacés. L'hypothèse spécifique du projet présenté veut vérifier que la lidocaine intraveineuse, administrée seule, apporte une analgésie équivalente au fentanyl. Plusieurs aspects de la période postopératoire sont mesurés le jour de la chirurgie ainsi qu'après 24 heures. Dans cet essai clinique randomisé à double insu, les patients reçoivent soit de la lidocaine (groupe lidocaine), soit du fentanyl (groupe fentanyl) pendant la chirurgie. L'utilisation d'opiacés durant la période postopératoire, l'intensité de la douleur, les effets secondaires causés par les opiacés et la durée d'hospitalisation sont comparable entre les deux groupes. La lidocaine n' empêche pas la poussée hémodynamique associée à la création du pneumopéritoine. La réponse inflammatoire et métabolique est équivalente entre les deux groupes. Le devenir fonctionnel après une période de 24 heures est comparable. La lidocaine intraveineuse periopératoire a un profil identique aux opiacés periopératoires.

Contributions of authors

Dr Gabriele Baldini: literature review, preparation of the study protocol and informed consent, seeking for consent, main and sole anesthesiologist during laparoscopic cholecystectomy, statistical analysis and manuscript preparation.

Professor Liane Feldman: staff surgeon performing laparoscopic cholecystectomy in patients enrolled in the study and revision of the manuscript.

Professor Gerald Fried: Staff surgeon performing laparoscopic cholecystectomy in patients enrolled in the study.

Berson Augustin: postoperative and 24 hr data collection.

Professor Francesco Carli: preparation of the study medications and revision of the manuscript.

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1. Introduction

Advances in surgical and anesthesia techniques have facilitated the recovery following ambulatory surgery and the return to daily activities. Minimal invasive surgical approaches have reduced postoperative morbidity and convalescence by attenuating the surgical stress. Similarly, the discovery of anesthetics with fast pharmacokinetics properties and minimal side effects has shortened the recovery time from anesthesia and improved safety. Despite that, one the major challenges of ambulatory anesthesia still remains the ability to provide effective postoperative analgesia and allow patients to be more rapidly discharged in a safe manner[1]. Postoperative pain after laparoscopic cholecystectomy is complex in nature and includes incisional pain (somatic pain), visceral pain, and shoulder pain (referred visceral pain or diaphragmatic irritation)[2]. This pain presentation would therefore require a multimodal therapy so as to provide better quality of pain relief, spare opioids and therefore facilitate the recovery process.

Systemic opioids are the goal standard to treat surgical pain. However, opioids side effects such as respiratory depression, sedation, nausea and vomiting, ileus, and urinary retention, can worsen surgical recovery and delay hospital discharged[3].

In the last decade, the role of adjuvants such as beta-blockers, local anesthetics, steroids and gabapentinoids has been investigated in different types of surgery, and an opioid-sparing effect has been demonstrated[4]. In particular, intravenous lidocaine, when used as anesthetic adjuvant, has been shown to have analgesic, anti-hyperalgesic and anti-inflammatory properties[5,6], which might have beneficial effects on some aspects of the recovery process. Furthermore, its pleiotropic properties appear to be control many components of pain after laparoscopic cholecystectomy.

However, whether perioperative analgesic interventions might have an impact on the recovery trajectory is still unknown. A theoretical model to study postoperative short and long-term outcomes and their relationship with biological and objective variables measured during the perioperative period has been proposed [7]. One would speculate that an intervention aimed at controlling pain intensity during the intraoperative and immediate postoperative period could influence the metabolic, inflammatory and physiological response, and this in turn would impact on short-term outcome measures such as need of analgesic medications, opioids side effects and quality of surgical recovery.

The surgical model of laparoscopic cholecystectomy will be studied. The aims of this clinical investigation are to determine the effect of intravenous lidocaine, as primary analgesic technique without the use of intraoperative opioids, on postoperative opioid consumption, opioid side effects, and pain intensity, and establish if it can accelerate and improve surgical recovery.

2. Literature review

2.1. Pain after laparoscopic cholecystectomy

Pain after laparoscopic cholecystectomy is one of the major determinant of convalescence after laparoscopic cholecystectomy[1,8]. It is complex in nature, and incisional (somatic), visceral (deep intra-abdominal) and shoulder pain (referred visceral pain) are its main components [2,9]. Somatic pain seems to represents the major source of pain, more than visceral and shoulder pain. Furthermore, pneumoperitoneum induce abdomen distension and activation of parietal nociceptor. The use of pneumoperitoneum pressures pressure higher than 12 mmHg increases abdomen distension, and therefore postoperative pain[8]. The overall pain intensity has a large inter-individual variation and the results from a multivariate analysis in a study investigating predictor factors of surgical pain after laparoscopic cholecystectomy, showed that preoperative neuroticism, sensitivity to preoperative cold pressor-induced pain, age and number of preoperative pain attacks were independent predictors of postoperative pain[2]. However, although these predictors were statistically significant, their correlation with postoperative pain intensity was weak (Sperman's rank correlation coefficients, r_s, ranging from 0.2 to 0.3), indicating that less than 10% of the variability of pain after laparoscopic cholecystectomy can be predicted by these factors. Its intensity is maximal in the first 4-8 hr and after it decreases during the first week[2].

2.2. Postoperative pain control after laparoscopic cholecystectomy

Different classes of medications and analgesic techniques have been used to treat pain after laparoscopic cholecystectomy. Because its complexity, it is suggested that treatment of pain after laparoscopic cholecystectomy should be multimodal, including a preoperative dose of dexamethasone, incisional local anesthetics (at the beginning and/or at the end of surgery), and non-steroidal anti-inflammatory drugs (or cyclo-oxygenase-2 inhibitors) for 3-4 days after the surgery [10]. Perioperative opiods, which are commonly used during the early postoperative period, cause several side effects that prolong the surgical recovery. Their routine is suggested only for intense persistent pain and when the other analgesic techniques fail[10]. Perioperative use of gabapentinoids (pregabalin and gabapentin), have shown to decrease postoperative pain and opioid consumption after laparoscopic cholecystectomy, especially during the first 2 hr postoperatively. However, the risk of oversadation associated with high doses, needs to be considered. A single dose of 150 mg of pregabalin administered 1 hr before the surgery reduced postoperative pain and fentanyl consumption, without increasing side effects[11]. Other preemptive analgesia strategies do not add supplemental analgesic benefits compare to early postoperative analgesia[12].

Evidence-based recommendations to control postoperative pain after laparoscopic cholecystectomy are published by Bisgaard et al[10].

2.3. Systemic effects of intravenous lidocaine and local anesthetics

Lidocaine is an amide local-anesthetic with antiarrhythmic properties. Local anesthetics and antiarrhythmic properties are caused by the interaction of lidocaine with Na^+-channels. As local anesthetic, when injected in proximity of a nerve, lidocaine binds the Na^+-channels and blocks the propagation of the action potentials

induced by the activation of peripheral nociceptive receptors. Through other different mechanisms of action, and at plasma concentrations that are 100-1000 times lower than concentrations needed to block Na^+ channels, intravenous lidocaine has shown to decrease postoperative pain[5], reduce the incidence of hyperalgesia, surgical inflammation, and have anti-thrombotic properties[6]. Furthermore, it improves several clinical outcomes and therefore ought to facilitate surgical recovery[5].

Because of these pleiotropic properties, and because it is easier and safer to use than epidural analgesia, intravenous lidocaine has been extensively used in different clinical settings, especially as alternative to epidural analgesia, either when this is contraindicated or impossible to perform, or when the benefits of this technique are marginal or controversial as in laparoscopic surgeries.

2.3.1. Intravenous lidocaine: pharmacokinetic properties

When injected intravenously, steady state is achieved with a bolus of 1-1.5 mg/kg followed by an infusion of >1.0 mg/kg/hr. Lidocaine is highly bound to plasma proteins (>80%) and it has a plasma half-life of 8 minutes, and an elimination half-life of 120 minutes. It is metabolized 90% by the liver, and excreted by the kidney that eliminates 10% of the lidocaine and its metabolites (monoethylglycinexylidide, MEGX, with an equal potency with lidocaine and a ½ life of 2 hr, and glycinexylidide, GX, with a ½ life 10 hours and 10% convulsive potency compared to lidocaine). Its hepatic metabolism depends on the function of cytochrome P450 1A2 enzyme system. Therefore, some medications such as amiodarone, cimetidine, fluoroquinolones, and fluvoxamine can down-regulate this system and delay the clearance of lidocaine. After 24 hr of continuous infusion, its clearance decreases, and

this effect is probably due to the competitive interaction between the drug and its metabolites that are both metabolized by the same hepatic enzymatic system[13].

2.3.2. Intravenous lidocaine: anesthetic-sparing effects

Reduction of intraoperative anesthetic requirements improves hemodynamic stability, shortens extubation time and decreases postoperative anesthetic-related side effects, such as sedation, postoperative nausea and vomiting and respiratory depression. Infusion of intravenous lidocaine has been shown to reduce intraoperative anesthetic inhalation agents concentrations in animals[14] and humans[15-18]. Reduction of end-tidal concentrations of desflurane or sevoflurane ranged between 11 to 35 %, during colorectal surgery[15,19], laparoscopic prostatectomy[16] and laparoscopic cholecystectomy[18]. Even effect-site concentrations of propofol target-controlled infusion (TCI) during thoracic surgery were reduced in the intravenous lidocaine group[20]. This suggests that intravenous lidocaine might have a central mechanism of action[21] and a synergistic effect with general anesthetics, since indicators of depth of anesthesia were not different in lidocaine and non lidocaine-treated patients. Anesthetic sparing-effect properties of intravenous lidocaine are achieved at plasma concentrations that are the same of analgesic plasma levels observed in other trials[20].

2.3.3. Intravenous lidocaine: systemic analgesia and anti-hyperalgesic properties

Intravenous infusion of lidocaine as adjuvant to systemic opioids, when compared to systemic opioids alone, has been shown to decrease postoperative pain and opioid consumption after different types of surgeries[5,22]. Although different doses and regimes have been used, reduction of postoperative pain and opioid consumption seems to be dose-dependent, and the analgesic effects of intravenous lidocaine seem

to persist up to 72 hr after the infusion is discontinued[17,23-25]. Recently, intravenous infusion of lidocaine has been compared also with thoracic epidural analgesia in patients undergoing colorectal surgery. The results of this study have shown that intravenous lidocaine offers the same advantages of epidural analgesia[26].

Intraoperative opioid requirement: comparison of intraoperative intravenous lidocaine as adjuvant to systemic opioids, with systemic opioids alone: Intravenous lidocaine reduced the amount of intraoperative opioids when used as analgesic adjuvant during general anesthesia during colorectal surgery, abdominal hysterectomy and ambulatory surgery[17,27,28]. However, in five studies in which intravenous lidocaine infusion was used during general anesthesia along with intravenous opioids as needed (to maintain heart rate and blood pressure within baseline values), the amount of intraoperative opioid consumption was not reported [23,29-32]. Rimback et al. did not find any difference in intraoperative fentanyl consumption between patients who received lidocaine and patients who received saline, but fentanyl infusion was maintained constant during the whole surgery[25]. In contrast, sufentanil consumption was not reduced by intravenous lidocaine during total hip arthroplasty (sufentanil was used as continuous infusion and it was adjusted to maintain heart rate within 15% of the preinduction value and systolic arterial blood pressure within 20% of the baseline value, step of ± 0.05 μg/kg/h)[33].

Intraoperative opioid requirements: comparison of intraoperative intravenous lidocaine as adjuvant to systemic opioids with epidural analgesia: there are two randomized control trails comparing intravenous lidocaine with epidural analgesia during the surgery[26]. In the first study, the amount of opioid required during the surgery was 40% less in the epidural group ($p=0.004$)[26] while in the second study, no

differences were found between the epidural and the lidocaine group, but fentanyl requirement was higher in the control group compared the other 2 groups ($p<0.01$)[15].

Postoperative pain intensity: comparison of intravenous lidocaine as adjuvant to systemic opioids, with systemic opioids alone: a meta-analysis by Marret et al. has show that overall pain scores 24 hr after open or laparoscopic abdominal surgery were decreased by the infusion of intravenous lidocaine, [Weighted Mean Difference -5.39 (95% confidence interval, CI -9.63 to 2.23)][5]. Even after thoracic surgery, pain scores were reduced, but only in the first 6 hr from the end of surgery. Moreover, lidocaine attenuated dynamic pain, during mobilization and coughing after abdominal hysterectomy[28], thoracic surgery[20] and laparoscopic colectomy [17]. Also MacKey et al. reported that pain intensity was reduced only in the recovery room but not 24 hr after ambulatory surgery [27]. In contrast, Lauwick et al. showed that, although pain intensity after laparoscopic cholecystectomy was not reduced, fentanyl consumption was less in lidocaine-treated patients ($p =0.018$)[18]. Discrepancies between these results might be explained by different lidocaine doses and infusion time (Table 1). In fact, in the last 2 studies, even if the doses of lidocaine were similar, duration of lidocaine infusion was 1 hr longer in the MacKey et al. 's study. Therefore a shorter duration of infusion used by Lauwick et al. might have attenuated the analgesic effects of lidocaine. Pain scores were also not reduced after total hip arthroplasty[33] and cardiac surgery[34].

Postoperative pain intensity: comparison of intravenous lidocaine as adjuvant to systemic opioids, with epidural analgesia: in the only study that compared intravenous lidocaine with epidural analgesia, median pain scores throughout the length of hospitalization were not statistically different from the epidural group, although higher in the lidocaine group. Median pain scores averaged over 5 days in

the epidural group were 2.2 (interquartile range, 1.6-3.4) and 3.1. (interquartile range, 2.3-4.3) in the lidocaine group (p =0.25)[26].

Postoperative analgesic requirements: comparison of intravenous lidocaine as adjuvant to systemic opioids with systemic opioids alone: postoperative opioid-sparing effect reported in the literature ranges between 33 to 83%[18,20,25,27,29]. After thoracic surgery, the reduced need of opioid observed in the lidocaine group in the first 6 hr did not persist[20]. Reduction of postoperative analgesic requirements was not observed after total hip arthroplasty[33], cardiac surgery[34] and after tonsillectomy[35]. Twenty-four hours after laparoscopic prostatectomy, morphine consumption was not affected by intravenous lidocaine. However, at 48 hr, only 30% of the patients in the lidocaine group required morphine, compared to 70% of the patients in the control group (p=0.011)[16].

Postoperative analgesic requirements: comparison of intravenous lidocaine as adjuvant to systemic opioids, with epidural analgesia: as for postoperative pain, opioid consumption during hospitalization in the lidocaine group (median morphine equivalent, 110 mg) was not statistically different from the epidural group (median morphine equivalent, 75 mg) (p =0.115). However, less patients in the epidural group required morphine during the early postoperative period than the lidocaine group (p > 0.05).

Systemic analgesic properties of intravenous lidocaine are caused by the interaction of lidocaine with different receptors located in the peripheral and central nervous system. Most of the evidence about the mechanisms through which intravenous lidocaine acts, comes from animals and experimental studies. Results from animals studies have shown that at concentrations reached in the clinical setting (5 μg/ml) intravenous lidocaine reduces tonic injury discharge and decreases the excitability of

Aδ and C-fibers in peripheral nerve acutely injured[36], and also ectopic impulse generation of chronically injured peripheral nerves [37]. At central levels, it suppresses neuronal excitability, spinal visceromotor and cardiovascular reflexes induced by visceral pain, and colon distension[38] and inhibits N-methyl-D-aspartate (NMDA) receptors[39-41]. In support of its central mechanism of action, stable concentrations of lidocaine were found in the CSF after an intravenous bolus of 2mg/kg, while peripheral plasma concentration rapidly decrease after the injection[42]. Moreover, in experimental models, intravenous lidocaine has been shown to reduce primary and secondary hyperalgesia after skin incision and intradermal capsaicin injection[43-45]. However, in the clinical setting, lidocaine failed to reduce secondary hyperalgesia after total hip arthroplasty [33]. Since cytokines induce peripheral and central sensitization and increase pain leading to hyperalgesia[46], some of the analgesic effects associated with lidocaine infusion might be due to its anti-inflammatory properties. However, only 2 studies[15,28] out of 4 that reported a reduction of cytokines levels by lidocaine, showed also an improvement of postoperative pain. Finally, intravenous lidocaine has also been used to treat pain syndromes[47] in patients with neuropathic pain[48-52], fibromyalgia[53], cancer pain[54], pain associated with injury of the central nervous system (central pain) [55,56], and pain due to adiposis dolorosa[47].

2.3.4. Opioid side effects

As shown for other class of medications that have an opioid-sparing, such as non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen[57,58], intravenous lidocaine, by decreasing the amount of perioperative opioids, has been associated with a reduction of the most common opioids side effects.

Postoperative nausea and vomiting (PONV): PONV significantly prolongs the length of stay in the recovery room after ambulatory surgery[59]. Its incidence ranges between 30 and 50%[60,61]. Patients' gender, age, co-morbidities, smoking status, choice and amount of anesthetics and analgesics, intraoperative fluids and type of surgery are variables that influence its incidence[62]. Therefore, it is difficult to understand the overall effect of intravenous lidocaine on the incidence of PONV, since lidocaine has been used in different clinical setting and with different anesthetics and analgesic medications. As for other class of medications such as non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen that have an opioid-sparing effect, we might speculate that also intravenous lidocaine decreases the incidence of PONV by reducing the need of opioid requirement. In the literature, the absolute reduction of PONV observed with the use of intravenous lidocaine ranges between 30 and 50%. However, most of these studies failed to show a statistically significant benefit associated with its use [16-18,23,25,29,63]. Only Kuo et al. reported a significant reduction of PONV after colon surgery ($p<0.01$)[15]. Nevertheless, it must be acknowledged that none of these studies were powered to detect a difference in the incidence PONV between the study groups. In a meta-analysis of 5 RCTs (170 patients undergoing abdominal surgery), Marret et al. showed that PONV was significantly reduced by 61% after lidocaine infusion (odds ratio, OR 0.39, 95% confidence interval, CI 0.20-0.76)[5]. After this publication, 3 other studies (2 in abdominal surgery, and 1 in laparoscopic prostatectomy), that reported the incidence of PONV as secondary outcome [16,18,26], failed again to show benefits of intravenous lidocaine in reducing this complication.

In summary, intravenous lidocaine seems to decrease the incidence of PONV, especially after abdominal surgery. However, more studies designed and powered to

detect a significant difference in the incidence of PONV after intravenous lidocaine are warranted.

Ileus: Postoperative ileus after abdominal surgery is one of the major determinants of recovery, it prolongs hospitalizations and increases costs[64]. The pathogenesis of this complication is multifactorial[65]. Abdominal surgery induces an inflammatory reaction in the surgical area and releases inflammatory mediators. Spinal reflexes induced by the surgical insult and pain, enhance sympathetic activity resulting in a inhibition of bowel motility. Furthermore, opioids frequently administered to control postoperative pain contribute to worsen the recovery of bowel function. Since local anesthetic can attenuate systemic and local inflammatory response and sympathetic bowel hyperactivity they have been use to treat and attenuate inflammatory bowel disease symptoms[66]. Patients with ulcerative colitis and proctitis treated rectally with 200 mg of ropivacaine have shown a decrease in mucosal inflammation and an improvement of clinical symptoms[67]. Infusion of intravenous lidocaine has been associated with a faster return of bowel function in patients undergoing radical prostatectomy[30] and colorectal surgery [15,31,32]. First passage of flatus occurred 8-24 h earlier [15,30,31] and first bowel movement occurred 12-28 h earlier[30-32] in patients who received lidocaine compared to patients who received systemic opioids. Also Koppert et al. found that recovery of bowel function occurred 6 h earlier with lidocaine, but the difference was not statistically significant[23]. There are only two studies that compared the effects on bowel function of intravenous lidocaine with epidural analgesia, both in patients undergoing colorectal surgey[15,26]. In. study of Kuo et al, the authors compared the effects of intraoperative lidocaine between three gorups: the intravenous (i.v) lidocaine group received i.v. lidocaine, the thoracic epidural analgesia (TEA) epidural lidocaine, and the control group normal saline throughout the surgery. Time to first

pass of flatus was faster in the TEA group than the lidocaine group ($p<0.01$). In contrast, Swenson et al. who compared intraoperatively and postoperatively the effects of intravenous lidocaine with epidural bupivacaine on bowel function, did not find the same benefits of epidural analgesia in reducing postoperative ilus[26]. These opposite results are difficult to compare since different study designs and different postoperative analgesic techniques were used. In the first study, infusion of lidocaine was discontinued at the end of the surgery and epidural analgesia was used in all three groups for 72 hr after the surgery, while in the second study, the lidocaine group did not receive epidural analgesia postoperatively. Therefore, in Kuo et al.'s study the use of epidural analgesia in all the study groups might have facilitated the return of bowel function in all patients. Although minimal invasive surgery reduces the inflammation response[68,69] and postoperative ileus *per se*, accelerated recovery of bowel motility by intravenous lidocaine has been reported after laparoscopic colectomy[17] but not after laparoscopic prostatectomy[16]. In patients undergoing laparoscopic cholecystectomy time to passage of first flatus and time to first bowel movements were not statistically shortened (although first defection occurred 17 h earlier with lidocaine), but transit of radiopaque markers was faster in the lidocaine group compared to the control group ($P< 0.05$) [24]. As observed for postoperative pain, the anti-inflammatory effects of lidocaine persist after serum levels have decreased[66,70] and this might explain beneficial effects on bowel function observed even 36 h after the infusion was discontinued[25]. The mechanisms, which explain the beneficial effects of intravenous lidocaine on postoperative ileus, are not clearly understood. Intravenous lidocaine might indirectly decrease the length of postoperative ileus by reducing postoperative pain and the amount of opioid used. Furthermore, it might directly block sympathetic inhibitory spinal or paravertebral reflexes[25], elicit stimulatory effects on intestinal

smooth muscle[71], or decrease peritoneal and bowel inflammation associated with surgery[72].

Sedation: intravenous infusion of lidocaine has been shown to induce sedation in animals[73,74] and human[75,76], by acting on the central nervous system. However, plasma concentrations associated with sedation in humans range between 7.5-12.5, significantly higher than plasma levels achieved during clinical studies [75]. Postoperative sedation was reported in only 4 trials [20,23,25,29]. Different scales and methods were used, and sedation was assessed at different intervals. The limited evidence available and the heterogeneity of these studies make these results difficult to compare. Isler et al. showed that as adjuvant to midazolam-fentanyl infusion for postoperative ICU sedation after coronary artery disease, lidocaine significantly reduced sedation scores in the first 4 hours, but not during the whole study period (96 hr). In summary, from the limited evidence available and at doses used in the clinical setting, intravenous lidocaine does not seem to influence the incidence of postoperative sedation. More research needs to be done in this field.

2.3.5. Systemic local anesthetics and the inflammatory response

The inflammatory response associated with surgery is essential for structural and functional repair of injured tissues. However, it is a double-edged sword as excessive production of pro-inflammatory cytokines and release of cellular mediators can aggravate tissues injury and delay the surgical recovery. Furthermore release of pro-inflammatory cytokines can induce peripheral and central sensitization leading to hyperalgesia[46] Local anesthetics, including lidocaine, have shown to modulate the inflammatory response associated with surgery by reducing the excessive release of inflammatory mediators and by attenuating the overactivation of inflammatory cells[6].

However, whether the anti-inflammatory properties of local anesthetics are responsible of the improvement of clinical outcomes reported in the literature, still remains unknown.

Effects on the secretion of inflammatory mediators

In-vitro and animals studies: in-vitro studies have shown that lidocaine inhibits the release of pro-inflammatory mediators from polymorphonuclear granulocytes (PMNs) and monocytes[77]. Leukotriene B_4 (LTB_4) is a potent pro-inflammatory stimulator of PMN activities, and together with prostaglandin E_2 (PGE_2) and histamine, increases vascular permeability and induces edema formation[77]. Lidocaine also inhibits IL-1α release, therefore reducing chemotaxis and degranulation of PMNs induced by this cytokine[77]. In animal models, intravenous lidocaine has shown to attenuate inflammatory response associated with acute lung injury (ALI) induced by endotoxin, by reducing thromboxane B2, IL-1ß and TNF-α concentrations in bronchoalveolar lavage fluid (BALF) of mechanical ventilated rabbits [78,79]. Moreover, hemodynamic changes and plasma concentrations of of TNF-α, IL-1 and IL-8 following systemic injection of *Escherichia Coli* endotoxin in rabbits were attenuated with the infusion of intravenous lidocaine[80].

Clinical studies: clinical studies have confirmed these results. In fact, pro-inflammatory cytokines that are commonly produced during the acute-phase of the inflammatory response to surgery[81], such as IL-6, Il-1ß and IL-1RA, were reduced by the intravenous infusion of lidocaine after total abdominal hysterectomy[28] and colorectal surgery [15,31].

Effect s of local anesthetics on inflammatory cells

Systemic local anesthetics also prevent excessive activation of inflammatory cells, by modulating the response of PMNs and monocytes during early phases of

inflammation. These effects are not due to the inhibition of Na^+-channels, but they are caused by a selective intracellular inhibition of G alpha (q) protein by local anesthetics [6,82,83].

In-vitro and animals studies: systemic local anesthetics have been shown to inhibit endothelium adhesion, PMNs migration, accumulation, priming, extracellular release of reactive oxygen species and intracellular enzymes, and nitric-oxide (NO) generation *i*n *vitro* and *in vivo* studies[6]. In particular, systemic local anesthetics inhibit the expression of CD11b/CD18 a member of integrine family which has a central role in neutrophils adhesion and priming of respiratory burst[6,84], and this effect has been proven also after infusion of ropivacaine in neutrophils from human whole blood [85]. Furthermore, in isolated human neutrophils, and at plasma concentrations observed during clinical studies, they inhibit the extracellular release of reactive oxygen species [83,86]. However, this latter effect has never been proven in human whole blood.

Clinical studies: expression of CD11b was reduced after intravenous infusion of lidocaine in patients undergoing colorectal surgery compared to the control group [31]. In this study reduction of CD11b levels was observed from the end of the surgery till postoperative day 3, despite the infusion of lidocaine was discontinued 4 hours postoperatively.

An excellent and comprehensive review about the anti-inflammatory properties of systemic local anesthetics was published by Hollmann et al. [6].

2.3.6. Systemic local anesthetics and the risk of infection

Because of these anti-inflammatory properties, it was argued that local anesthetic might impair the host defense and increase the risk of infection especially in the setting of bacterial contamination such as bowel surgery. MacGregor at al. showed that 5 of 6 rabbits with peritonitis induced by inoculation of *S. aureus* died after the infusion of intravenous lidocaine. The authors concluded that lidocaine might have adversely affected the animal immune system to respond to an intraperitoneal infection [87]. Leukocyte priming is crucial phase of the cellular inflammatory response. Leukocyte priming is defined as a potentiated response of PMNs after previous exposure to priming agents, such as TNF-α, platelet-activating factor, IL-8, lipopolysaccharide or granulocyte-macrophage colony-stimulating factor, induced by bacterial products [88]. During this process, activation of intracellular pathways leads to the expression of membrane proteins (ex. CD11b) which facilitate endothelial adhesion, activation of intracellular oxidative burst, and extracellular release of oxygen reactive species and enzymes [88]. Activation of phagocytosis and intracellular oxidative bursts during leukocytes priming play a key role for the host defense during bacteria infection. In isolated cell models, clinical concentrations of local anesthetics have been shown to inhibit PMNs extracellular release of oxygen reactive species by inhibiting leukocyte priming[6,83,86,89]. However, neutrophils intracellular oxidative burst of healthy volunteer whole blood is not affected by local anesthetic [90]. This implies that, although never proven, local anesthetics might *in vivo* attenuate PMNs priming and decrease tissue injury induced by extracellular release of oxygen reactive species and enzymes, but they do not impair leukocyte antibacterial function[90]. This theory is supported by clinical studies that have shown that intravenous or infiltration of local anesthetics did not increase the risk of wound infection after laparoscopic

prostatectomy[16], port-access heart surgery[91], reconstructive abdominal procedures[92], and even after abdominal surgery where the risk of bacterial contamination is higher[31]. In fact, neither Herroeder et al. [31], nor Swenson et al. [26] reported any local or systemic infections in 51 patients treated with intravenous lidocaine after colorectal surgery. Only Harvey et al reported 1 wound infection, in 11 patients who received intravenous lidocaine after bowel surgery [32]. Moreover, although a 1000-fold higher concentration than those achieved during clinical studies, *in-vitro* studies have shown that local anesthetics have dose-dependent bactericidal activities[93].

In summary, further studies need to clarify if systemic local anesthetic can attenuate tissue injury by decreasing PMNs extracellular release of oxygen species even in whole blood. However, they seem not to affect neutrophils antibacterial intracellular functions and they do not increase the risk of wound infection.

2.3.7. Systemic local anesthetic: anti-thrombotic properties

Results from *in-vitro* and animals studies have suggested that intravenous local anesthetics at clinical concentrations decreased platelet aggregation[94,95], increase activated coagulation time (ACT) and cause alteration of thromboelastography (TEG)[96]. In 1977 Cook et al. reported that intravenous lidocaine reduces the incidence of deep venous thrombosis after hip arthroplasty. Further investigations have well established that epidural blockade decreases the risk of postoperative venous thrombo-embolism[97-99]. Plasma concentrations of local anesthetics measured during the epidural infusion of local anesthetic, are similar to the concentrations observed during intravenous infusion[100]. Since plasma concentrations of local anesthetic after spinal anesthesia are significantly lower than after epidural anesthesia, and since spinal anesthesia does not affect hemostasis[101], it is hypothesized that the reduction of the

hypercoagulation state induced by the surgery and observed with epidural blockade is mainly due to the systemic absorption of local anesthetics[102]. However, it cannot be excluded that the hemodynamic effects of neuraxial blockade contribute to the reduction of thrombotic events after surgery[99,103].

Inhibition of G alpha (q) protein is the mechanism thorough which local anesthetic inhibit platelet aggregation [104,105 6]. In fact, the G alpha (q) protein plays a key role during platelet activation. This is supported by the results of a study conducted in G alpha (q) knockout mice, where activation of platelets was reduced, and bleeding time increased[106].

2.3.8. Systemic local anesthetics and endocrine-metabolic stress response

Contrasting results regarding the effects of intravenous lidocaine on the endocrine-metabolic stress response to surgery have been reported[17,63,107,108]. Although evidence from *in-vitro* and experimental studies suggests that clinical concentrations of local anesthetics might increase ACTH and cortisol by stimulating IR-CRF[21,109,110], these results have not been confirmed in the clinical setting. In fact, after total abdominal hysterectomy, plasma concentrations of glucose and cortisol were not attenuated by the infusion of intravenous lidocaine [108]. Similar results were found also after laparoscopic colorectal surgery, where concentrations of plasma catecholamines, glucose and cortisol were only slightly reduced by the infusion of intravenous lidocaine[17]. However, in this study, the anti-catabolic effects of laparoscopic surgery might have minimized the metabolic changes induced by intravenous lidocaine, therefore decreasing the possibility to find a statistically significant difference between the two groups. There is only 1 randomized controlled trial that showed a reduction of plasma cortisol concentration by the infusion of lidocaine, 5 minutes after

tracheal intubation and during the postoperative period after cesarean-section, but these results are difficult to interpret and generalize [111]. In fact, the peculiar endocrine, metabolic and hemodynamic changes induced by pregnancy are not commonly observed in the general population.

2.3.9. Intravenous lidocaine: sympathetic response and hemodynamic changes associated with surgery

Sympathetic response to surgery is slightly attenuated by clinical doses of systemic lidocaine. In fact, in rats, only large intramuscular lidocaine doses (15mg/kg, plasma concentrations achieved, 3.6 μg ± 0.4) produced a mild reduction of sympathetic nerve activity of, compared to the significant effects observed after epidural lidocaine and at lower plasma concentrations (< 2.7 μg/ml)[112]. Even experimental studies in humans confirmed these results[113]. Furthermore, only 1 study of patients undergoing abdominal hysterectomy showed a reduction of urinary catecholamines levels after the infusion of lidocaine. However, these results were significant only on postoperative day 2 [63].

The hemodynamic effects induced by intravenous lidocaine are poorly understood. Wallin et al. showed that similarly to the changes observed on the discharge of sympathetic nerves, heart rate and mean blood pressure were only slightly attenuated by large dose of intravenous lidocaine. In contrast, when epidural lidocaine was injected, heart rate and blood pressure significantly dropped. This suggests that the hemodynamic response elicited by the activation of the sympathetic system might not be blunted by plasma concentrations achieved during systemic infusion. However, 2 clinical studies have shown opposite results[63,107]. In the first study[63], heart rate and mean arterial pressure were reduced in the early postoperative period, but not during

tracheal intubation. In the second study, heart rate and mean arterial dropped consistently throughout the whole duration of surgery until 60 min after the end of cesarean-section[107].

2.3.10. Intravenous lidocaine: postoperative fatigue and functional recovery

Fast return to daily activities (functional recovery) is one of the major expectations and requirements of patients scheduled for surgery, especially after ambulatory procedures. The feeling of general well being and the physical capability to sustain routine daily activities are influenced by many factors such as pain, fatigue, medications side effects and health status[7].

Reduction of postoperative fatigue scores by intravenous lidocaine has been reported in only 1 study[17] out of 3[16,18], and it was sustained during the whole hospitalization.

The effect of intravenous lidocaine on functional recovery was measured in two studies [16,33]. In the first study[16], 2 minutes-walking test (2MWT) was used to measure functional walking capacity before and after laparoscopic prostatectomy. On postoperative day 1, the average 2MWT dropped significantly all patients ($p=0.01$). However, the drop was significantly higher in the control group than in the lidocaine group and this effect was not observed on postoperative day 2 and 3. After total hip arthroplasty[33], functional recovery was measured by the hip flexion during the hospitalization and at 3 months. The degree of hip flexion was not affected by the infusion of intravenous lidocaine.

In summary, any conclusions about the effects of intravenous lidocaine on postoperative fatigue and functional recovery cannot be drawn from these results. It can be only hypothesized that the attenuation of postoperative fatigue observed in

Kaba's et al. study was due to a reduction of postoperative pain and opioid consumption by the infusion of intravenous lidocaine. Only new study designs that incorporate specific outcome measures[114] can establish if lidocaine might decrease postoperative fatigue and facilitate the return to daily activities.

2.3.11. Intravenous lidocaine: effects on length of hospitalization (LOS)

Since intravenous lidocaine has been shown accelerate the recovery after surgery by reducing postoperative pain, opiod consumption and side effects it seems logical to expect also a reduction of hospitalization. Reduction of LOS by intravenous lidocaine reported in the literature ranges between 1 to 1.1 days[17,30,31]. In fact, results from a meta-analysis of RCTs in abdominal surgery, showed that intravenous lidocaine shortened the LOS by 0.84 days [weight mean difference, WMD -0.84 (95% confidence interval, CI -1.38-0.31)[5]. Interesting to notice that, the results from the only study that assessed the effects of intravenous lidocaine in a context of an enhanced recovery program, showed that intravenous lidocaine improved many of the outcome previously described (intraoperative anesthetic requirements, postoperative pain and opiod consumption, and bowel function), resulting in a reduction of LOS of 1 day ($p=0.001$)[17]. These findings suggest that when a multidimensional approach is adopted (including revision of surgical and anesthesia practice, minimization of surgical stress, early nutrition and mobilization), benefits of single interventions can be maximized. No difference in LOS was found when lidocaine was compared with epidural analgesia[26] or with systemic opioids after laparoscopic prostatectomy[16] and ambulatory surgery [18,27].

In summary, intravenous lidocaine has been show to shorten the LOS of less than 24 hr. The clinical relevance of this finding seems negligible. However, when used in

a context of a fast-track program, intravenous lidocaine might significantly improve surgical recovery and therefore shorten the length of hospitalization.

2.3.12. Intravenous lidocaine: doses, plasma concentrations and toxicity

Intravenous lidocaine has been used at different doses and in different clinical settings, and its plasma levels have been measured at different intervals. These differences might explain why reported plasma concentrations vary significantly among the studies. Lidocaine plasma concentrations depend also on many other factors, such as the dose and duration of the infusion, plasma levels of binding proteins, and patients' hepatic and renal clearance. Furthermore, compared to the levels measured in non-anesthetized patients, the hemodynamic effects of general anesthetics significantly increase local anesthetic concentrations [115]. A summary of the doses, duration of the infusion, plasma concentrations, and toxicity associated with the infusion of intravenous lidocaine is reported in Table 1.

Lidocaine toxicity occurs at plasma concentrations > 5 μg/ml[116]. Clinical manifestations commonly reported are, light headed, drowsiness, perioral numbness, metal taste, dryness of the mouth, nausea, muscular twitch, tinnitus, visual disturbances and cardiac arrhythmia. These side effects are dose-dependent and central nervous system (CNS) symptoms occur earlier than cardiovascular disturbances. During experimental studies sedation and convulsions have been reported in humans with infusion rates ranging from 7.5 to 12.5 mg/min, substantially higher than those used in the clinical studies [75]. Lidocaine toxicity did not occur in most of the clinical studies (Table 1). In Swenson's et al. study 4 patients had clinical symptoms of lidocaine toxicity[26]. Three patients had perioral numbness/ tingling and 1 had visual hallucinations and was disoriented. Only this patient had plasma lidocaine

concentration higher than 5μg/ml (6.5 μg/ml). In all patients symptoms quickly resolved once lidocaine infusion was discontinued. However 1 patient developed an episode of ventricular tachycardia that required cardioversion 2 days after lidocaine was discontinued. In this study lidocaine was infused until the return of bowel function, defined as return of first flatus. Therefore, in some patients lidocaine was continued until postoperative day 4, while in all the other clinical studies the infusion was continued for maximum 24 hr (Table 1). One patient in MacKey et al.'s study reported dizziness and visual disturbances at the end of the infusion[27].

In summary, in most of the studies, doses of intravenous lidocaine used in different clinical settings did not reach toxic level. Therefore, its use at these doses and regimens is considered safe. However the optimal dosage and regimen associated with the maximum improvement of postoperative outcomes, but with minimal side effects, still needs to be established. Moreover, obese patients (BMI > 35), American Society of Anesthesiology (ASA) physical status III-IV, patients with chronic renal failure, or hepatic failure were excluded in all the clinical trial published. Adjusted doses of intravenous lidocaine in patients with these conditions have not been extensively studied[117]. Finally, analgesic properties of intravenous lidocaine seem to dose-dependent. However, continuous infusion for more than 48 hr might lead to plasma concentrations above the toxic threshold and might cause serious adverse events.

2.4. Intraoperative and postoperative assessment

2.4.1. Depth of anesthesia

The main purpose of monitoring the depth of anesthesia is to prevent awareness. Furthermore, recent studies have shown that the depth of anesthesia might influence surgical recovery and also have an impact on long-term outcomes such as mortality[118,119]. Depth of anesthesia is commonly measured by interpreting hemodynamic signs and by titrating anesthetics administration based either on end-tidal concentrations of inhalation agents or on plasma effect-site concentrations of intravenous anesthetics. In the last decade, the use intraoperative devices that measure the depth of anesthesia by analyzing cerebral activity during general anesthesia, has become more common. Among different monitors, the Bispectral Index monitor (BIS) is the most used, and it has also become the gold standard towards which the efficacy of new technologies that measure the depth of anesthesia has been investigated[118,120]. The BIS index ranges between 0 and 100. Higher the index, lighter is the anesthetic level, and higher is the probability of awareness (above 60). The estimated incidence of intraoperative awareness is 0.2%[121]. Whether or not BIS monitor reduces its incidence is still controversial[121,122]. In fact, Myles et al. showed that in high-risk patients the incidence of awareness was reduced by the use of BIS monitor, while the recent B-unaware did not report the same findings[122]. Intraoperative analgesic doses of systemic opioids weakly affect the BIS index. Whether or not intravenous lidocaine can influence this value it remains uncertain. As many of the studies that monitored the depth of anesthesia during the infusion of intravenous lidocaine titrated anesthetics to maintain the BIS index within a specific range[16,18,20], it is difficult to determine the effects of lidocaine on this parameter. However, in the only study where sevoflurane

was titrated to hemodynamic endpoints, BIS scores were not reduced by intravenous lidocaine[17].

2.4.2. Postoperative acute pain in adults.

Postoperative pain is one of the major determinants of surgical recovery[123]. Therefore, its assessment and treatment is a fundamental step to facilitate surgical recovery and particularly after ambulatory surgery. In fact, underestimation and poor treatment of pain not only aggravates patient discomfort, decreases mobilization and increases postoperative complications, but it also can lead to unplanned hospital admission. On the other hand, overestimation might induce caregivers to overtreat pain, and therefore increasing the risk of opioid side effects and delaying hospital discharge. Pain is an individual and subjective experience modulated by physiological, psychological and environmental factors such as previous events, culture, prognosis, coping strategies, fear and anxiety[124]. Most measures of pain are self-reported, and most of the pain scales used can be influenced by sedation, medications and mood states. Unfortunately, objective measurements of pain intensity do not exist. However, hemodynamic and respiratory changes (tachycardia, hypertension and tachypnea), autonomic reflexes (sudoration), quantification of the stress response associated with surgery and analgesics requirement can be interpreted as indirect signs of pain.

2.4.2.1. Analgesic requirements

Postoperative analgesic requirements are commonly used as objective indicators of postoperative pain. Furthermore, statistical methods to analyze pain measurements and quantification of the efficacy of an analgesic treatment are easier to assess than scores obtained from pain scales[125]. For this research, when opioids other than

fentanyl were administered, total analgesic requirements in the recovery room was calculated by converting opioids doses to fentanyl equivalents (μg), by using the Internal McGill University Health Centre opioids guidelines (Table 2)[126].

2.4.2.2. Postoperative pain intensity

Several scales have been used to measure postoperative pain intensity. Although not frequently used, the severity of postoperative pain can also be measure by quantify the degree of pain relief following the administration of an analgesic treatment (pain relief scales). In contrast to scales that measure intensity, this approach does not require baseline pain assessment, since all patients have the same baseline score (0)[127,128]. Pain intensity is commonly measured at rest (static pain) and on coughing, moving and ambulating (dynamic pain). Whereas the former provides information about the severity of discomfort experienced by the patient, the latter is more important to estimate functional recovery. Furthermore, low dynamic pain scores correlates with less postoperative complications[127].

Pain intensity scales can be categorical or numerical. Categorical scales quantify pain by using words such as severe, moderate, mild or absence of pain. Then, numerical ranges can be associated with different terms and facilitate the quantification of postoperative pain[128]. These scales (*verbal descriptor scales*, VDS) are simple and quick to administer, especially in a context where other confounding factor (such as sedation, confusion etc…) might affect the accuracy of the measurement. On the other hand, they are not optimal to differentiate the analgesic efficacy of 2 analgesic treatments, since the limited choices that they offer cannot properly rank pain intensity[129].

Two different types of numerical scales exist: the *verbal rating scale* (VRS) and the *visual analogue scale* (VAS). The verbal rating scale consists in asking the

patients to rate their pain intensity on a scale from 0 to 10 (VRS 0-10, where 0 is no pain and 10 the worst excruciating pain). The visual analogue scale is 100 mm horizontal line, with two anchors signs at its the extremities. The anchor placed at the left end is labeled as "no pain" and the anchor at the right end as "worst pain". Patients are asked to mark this line, according to the pain experienced at that moment, and the distance measured (mm) from the left anchor represents their pain intensity. VRS and VAS are equally sensitive to measure postoperative pain, but superior to VDS[127]. VRS scales are commonly used since they are quick and simple and they have shown a good correlation with VAS scores[127,129,130].

In this study, in order to minimize inter-scales variability between VRS and VAS [32,131], postoperative pain was measured by VRS scale and the obtained results were compared with VRS scores of a previous trial, conducted in this institution and using a similar research protocol[18].

Finally, the short-form McGill Pain Questionnaire (SFMPQ)[132], mainly used for research purposes, has also been used in the clinical practice to measure acute postoperative pain[133]. However, in this context, its correlation with pain intensity is weak , and its administration time is longer than the VRS and VAS scales [131] .

2.4.3. Recovery after ambulatory surgery

Surgical recovery is an ongoing process that begins from the end of intraoperative care until the patient return to his/her preoperative physiological state[134]. It can be divided in three phases: *early recovery*, from the discontinuation of anesthetic agents until recovery of protective reflexes and motor function; *intermediate recovery*, when the patient achieves criteria for discharge; and *late recovery*, when the patient returns to his/her preoperative physiological state. Medical and surgical complications,

anesthetics and analgesics side effects, fatigue, psychological elements, and organizational aspects of patients care can delay this process. Even if the assessment of surgical recovery should include a variety of specific outcome measures to represent all its different aspects, it is commonly based only on the evaluation of clinical and surgical parameters and on the achievement of discharge criteria. Different scores have been used to discharge patients either from the PACU to the step-down unit (or ambulatory surgery unit, ASU), or from the ASU to home[135] (Table 3) and, if patients fulfill specific discharge criteria, they can directly be fast-tracked from the operating room to the ASU[136]. Although fast-track pathways shorten length of hospital stay, they do not reduce nurse workload and hospital costs after ambulatory surgery[137].

The Aldrete score, and the followed modified version[138], was the first scoring system to measure surgical recovery and it was designed to facilitate physicians and nurses to decide when discharge patients from the PACU to the ASU[139]. It includes clinical parameters (motor functions, respiration, circulations, level of consciousness, and oxygenation), and a score ranging from 0 to 2 is assigned to each variable. When patients reach a total score ≥ 9 are considered fit to be discharged to the ASU.

The White-Song scoring system is used to by-pass the PACU and transfer patients directly from the operating room to the ASU, and in comparison with the Aldrete score, it offers the advantage to assess postoperative pain and PONV [136]. Seven clinical parameters (level of consciousness, motor function, respiration, oxygenation, mean arterial blood pressure, pain and PONV) are evaluated and a score ranging from 0 to 2 is assigned to each parameter. A total score ≥ 12 is required to fast-track patients directly to the ASU.

Readiness to be discharged home is commonly measured by the postanesthetic discharge scoring system (PADS), or by the outcome-based discharge criteria. The PADS includes the assessment of vital signs, motor function, PONV, pain intensity and surgical bleeding. It assigns as score ranging from 0 to 2 to each variable and a score ≥9 is required to discharge patients home. Alternatively, outcome-based discharge criteria, adapted to specific hospital needs and policies, can be used. However, scoring systems, in comparison with the achievement of discharge criteria, offer a more objective and uniform method to decide when patients can be discharged.

2.4.4. Postoperative fatigue (POF)

Fatigue is a clinical symptom commonly present after surgery and it can significantly prolong postoperative recovery especially after major abdominal surgery[140,141]. Its etiology is multifactorial, and physiological, biological and social factors contribute to the development of POF. It has also been shown that POF correlates with several postoperative outcomes, such as reduction of cardiovascular fitness and muscular strength, and changes in body composition and biomarkers.[142]

There is not a "gold standard" to measure postoperative fatigue, and most of the scales used in the surgical setting were validated for patients with chronic conditions such as multiple sclerosis or sarcoidosis [142,143]. These scales range from single items scales to multidimensional scales. The most used scale in the surgical setting is the Christensen's Visual Analogue Scales (VAS), scoring POF from 1-10 (1 fit, 10 fatigued) [141] .Since the etiology of POF is multifactorial, this unidimensional scale can't discriminate which factors might have facilitated the development of fatigue. On the other hand, the Identity-Consequence-Fatigue Scale is 28-items multidimensional

scale, that measures the mental and physical components of fatigue and to which extent these factors interfere with social activities feeling[144].

2.4.5. Quality of surgical recovery

Common end-points chosen to measure surgical recovery are mortality, morbidity and length of hospital stay. In the last two decades new aspect of surgical recovery, such as measurement of Quality of life and of health status, have been investigated and reported in many clinical trials [145,146]. Even if from a scientific point of view the incidence of perioperative complications might appear a better outcome measure to assess surgical recovery or establish the efficacy of a new intervention, from patients' point of view quality of recovery becomes very important, especially after ambulatory procedures. Recovery of preoperative physiologic conditions, life style and health status are difficult to quantify, but many outcome measures have been used[147]. In a systematic review of postoperative recovery outcomes measurements after ambulatory surgery the Quality of recovery score 40-items (QoR-40) [148] was the only instrument considered appropriate to measure the quality of recovery [147]. This questionnaire includes 40 items that can be grouped in 5 categories that summarized the quality of recovery: emotional state, physical comfort, physiological support, and pain. However, it was initially validated for the general surgical population, and only few studies have used after ambulatory surgery. The original questionnaire was validated in a shorter form, including 9 items (QoR-9)[149]: had the feeling of general well-being, have support from others (especially doctors and nurses), been able to understand instructions and advice, been able to look after personal toilet and hygiene unaided, been able to pass urine and having no trouble with bowel function, be able to breath easily, been free from headache, backache or muscular pain, been free from nausea

dry-retching or vomiting, been free from experiencing severe pain or constant moderate pain. Based on the frequency with which these conditions and symptoms occur ("not all the time", "some of the time" and "most of the time"), a score ranging from 0 to 2 is assigned to each item (0= not all the time, 2= most of the time). A maximum score of 18 can be achieved, reflecting an optimal recovery. As for the QoR-40, the QoR-9 is mainly designed to measure the quality of recovery in in-patients, and although simpler than the QoR-40, some of the questions included are not appropriate for outpatients.

2.4.6. Length of Hospital stay (LOS)

LOS is the most common outcome measure reported to establish the efficacy of a clinical, surgical or pharmacological intervention. However, it does not completely reflect readiness to discharge. In fact, in a study evaluating the appropriateness of enhanced recovery after colorectal surgery, 90% of the patients remained in the hospital, despite they already fullfilled the discharged criteria[150]. This might imply that time to achieve single discharge criteria could be a more appropriate outcome measure than the entire duration of hospitalization. Until when new outcome measures to assess the readiness of discharge are available, length of hospital stay remains the most used tool to measure surgical recovery.

2.4.7. Stress response: inflammatory and metabolic biomarkers

The endocrine-metabolic and the inflammatory response to surgery are 2 embraced processes induced by the surgical insult.

Inflammatory response: the inflammatory response is represented by the activation of the inflammatory cells and by the local and systemic release of inflammatory mediators, such as the cytokines and acute-phase proteins.

The interaction between cytokines and the acute-phase proteins is a complex network that regulates the host response during an acute trauma or infection. Furthermore, beside their immunological functions, cytokines modulate metabolic pathways (with the aim to supply energetic substrates), the coagulation cascade and pain transmission[81]. Several circulating cytokines and acute-phase proteins have been considered inflammatory biomarkers associated with surgery. IL-1, IL-6, IL-10, TNFα and C-reactive protein (CPR) are the most commonly reported [81]. During surgery, circulating plasma levels of TNFα are the earliest to rise, followed by IL-6 and IL-10. IL-1 plasma half-life of is too short (8 min) to measure its levels during surgery. The magnitude of the inflammatory response is proportional to the intensity of surgical trauma[69,151] and among these cytokines, IL-6 reaches the highest plasma concentrations [31,151]. Although other cytokines are involved, IL-6 produced by activated macrophages, fibroblasts and endothelial cells, and promoted by TNFα and IL-1, appears to be the major regulator of this response[152,153]. Furthermore, its increase well correlates with the degree of injury and pick plasma concentrations of IL-6 occur 4 hr after laparoscopic cholecystectomy[68]. C-reactive protein, even if is a positive marker of inflammation (peak concentrations 48 hr after laparoscopic cholecystectomy), poorly correlates with the degree of the surgical insult[154].

The inflammatory cellular response is commonly measured by the activation of leukocytes. Flow cytometry is commonly used to quantify the expression of membrane proteins such as CD11b/CD18 on leukocytes, usually over-expressed during the early phase of inflammation[31,85,155].

Endocrine-metabolic response: peripheral impulses originated from the site of the injury activate the pituitary-adrenal axis and the sympathetic system. Many stress hormones are secreted but the most common biomarkers reported are plasma concentrations of corticotrophin (ACTH), cortisol and catecholamines. Hyperglycemia, as results of cortisol and glucagon release, also correlates with the magnitude of the surgical stress [156]. Cortisol can reach maximum concentrations of 1500 nmol/L, depending on the magnitude of the surgical insult. After laparoscopic cholecystectomy, peak plasma levels of cortisol are observed at the end of the surgery and 12 hr after they return to baseline values[68].

3. Manuscript

Intravenous lidocaine as sole intraoperative analgesic technique for laparoscopic cholecystectomy

3.1. Abstract

Background: This study evaluates the analgesic properties of intravenous lidocaine and its effects on postoperative recovery when used as primary and sole analgesic technique, in patients undergoing ambulatory laparoscopic cholecystectomy surgery.

Methods: The clinicaltrial.gov registration number is NGT01062906. Ninety-two patients were enrolled in this randomized double-blinded study. Following induction of anesthesia with propofol and rocuronium, the control group (C) (n=46) received fentanyl (3μg/kg) followed by a continuous infusion of normal saline, while the lidocaine group (L) (n=44) received a bolus of lidocaine (1.5 mg/kg) followed by a continuous infusion of lidocaine (2mg/kg/h) until the end of the surgery. Desflurane was titrated to keep BIS between 30 and 50 in both groups. No supplemental opioids were given during surgery in group C. Opioids consumption, postoperative pain intensity, side effects, and quality of recovery were recorded in the PACU and 24 hr after the surgery. Intraoperative hemodynamic data, cortisol and IL-6 levels were also measured.

Result: Consumption of fentanyl in the PACU was similar in both groups (87.5 [50-150] μg in group C, and 112.5 [75-150] μg in group L, p= 0.17). Total fentanyl consumption (intraoperative and postoperative) was significantly lower in group L ($p < 0.0001$). Postoperative pain, opioids side effects and readiness to discharge, were also similar. Heart rate following the induction of pneumoperitoneum was higher in group L ($p < 0.001$). Plasma concentrations of cortisol and IL-6 were not attenuated by the infusion of intravenous lidocaine.

Conclusion: Intravenous lidocaine showed the same postoperative analgesic efficacy and recovery profile of fentanyl, but did not blunt the hemodynamic changes

associated with the pneumoperitoneum, and it did not reduce the stress and inflammatory response induced by the surgery.

3.2. Introduction

The introduction of minimally invasive surgery, especially laparoscopic cholecystectomy, has significantly reduced postoperative morbidity by decreasing surgical stress, postoperative pain and inflammation, and by accelerating recovery after surgery[157]. Since 1987, when the first laparoscopic cholecystectomy was performed in Germany[158], the number of laparoscopic cholecystectomies per year has increased[159] and today in most institutions laparoscopic cholecystectomy is an established and safe ambulatory surgical procedure.

Perioperative use of opioids remains the gold-standard analgesic treatment to control surgical pain following laparoscopic cholecystectomy. However, opioids side effects and postoperative pain still remain the main causes of overnight unplanned admission[160] and prolonged convalescence[2] . It is well documented that systemic opioids cause dose-dependent side effects such as nausea and vomiting (PONV), constipation, pruritus, urinary retention, dizziness and respiratory depression [161]. Zhao et al showed that in patients undergoing laparoscopic cholecystectomy, after 10.6 mg of morphine equivalent administered, additional opioids side effects were reported for each additional 3-4 mg administered[161].

In the quest to minimize the side effects and reduce opioids consumption, there has been great interest to investigate the clinical efficacy of non-opioid analgesic techniques in the context of minimally invasive surgery [3]. This is particularly true in ambulatory surgery where the use of these techniques could significantly improve the quality of postoperative analgesia and accelerate recovery after surgery, and in patients for whom the use of opioids is relatively contraindicated, such as obese, with COPD, elderly and those with obstructive sleep apnea.

Intravenous infusion of lidocaine has been shown to have analgesic and anti-inflammatory properties and to reduce the incidence of postoperative hyperalgesia [6]. A recent meta-analysis including clinical trials of patients undergoing different types of surgery, has summarized its clinical effects[5]. In patients undergoing laparoscopic surgery, intravenous lidocaine reduces the intraoperative requirement of anesthetics, provides adequate postoperative analgesia with less opioid consumption, facilitates the return of bowel function and shortens the length of hospital stay. Recently, Lauwick et al. compared the effect of intraoperative intravenous lidocaine with a small dose of fentanyl (1.5 μg/kg) vs fentanyl 3 μg/kg on postoperative analgesia, and found a 36% decrease in postoperative opioid consumption in the lidocaine group [18].

3.3 Aims of the study

While all published studies on the use of intravenous lidocaine as an adjuvant to perioperative opioids have shown favourable postoperative analgesic effects, there are no controlled trials comparing the analgesic efficacy of intraoperative intravenous lidocaine, as sole and primary analgesic treatment, with the efficacy of intraoperative opioids.

The aims of this prospective, randomized double-blind trial were:

1) to evaluate the effect of intravenous lidocaine as sole intraoperative analgesic technique on postoperative opioid consumption and pain intensity;
2) to evaluate if lidocaine could decrease the incidence of opioid side effects and accelerate the surgical recovery

in patients undergoing laparoscopic cholecystectomy.

3.4 Study Hypothesis:

It was hypothesized that in the recovery room fentanyl consumption of patients who receive intraoperative intravenous lidocaine would be similar to the consumption of patients receiving intraoperative opioids

3.5 Methods

Patients

This double-blind randomized controlled trial (GEN#06-021) was approved by the McGill University Health Centre Ethics Board and was conducted between August 2008 and April 2010 in patients who required elective ambulatory laparoscopic cholecystectomy with the diagnosis of cholelythiasis. The study was registered on clinicaltrial.gov (NGT01062906). Exclusion criteria were: age <18 yr or > 85 yr, ASA physical status 3 and greater, history of hepatic, renal or cardiac failure, organ transplant, diabetes, morbid obesity (BMI > 40), chronic use of opioids, allergy to local anesthetics, or inability to comprehend pain assessment. Before surgery patients were instructed in the use of Verbal Rating Scale (VRS, 0-10) to assess postoperative pain (0 = no pain, 10 = excruciating pain) and fatigue (0 = no fatigue, 10 = worst fatigue imagined). They were also informed that they would receive a call 24 hours after surgery and would be asked their VRS scores at that time as well as the amounts of medications used and potential opioids side effects .

On the day of surgery and before induction of anesthesia patients who consented to participate in the study were randomly assigned, using a computer-generated randomization schedule, to two equal groups of 46 patients each. The control group (C) received iv fentanyl and the lidocaine group (L) iv lidocaine. Allocation concealment was achieved by placing the randomization sequence for each subject in

sequentially numbered sealed brown envelopes. The study medications were prepared by one investigator (FC), who was not involved in the anesthesia care and postoperative data collection.

Anesthesia, analgesia and surgical care

On arrival to the operating room, baseline heart rate, arterial blood pressure, oxygen saturation and bispectral index (BIS) were measured. The anesthesia technique was standardized and the anesthesiologist (GB), the same for all patients, and blinded to the study medication, followed the study protocol. Patients were premedicated with iv midazolan 0.03 mg/kg. At the induction of anesthesia, group C received iv fentanyl 3.0 μg/kg followed by a continuous infusion of normal saline, while group L received a bolus of iv lidocaine 1.5 mg/kg followed by a continuous infusion of lidocaine 2 mg/kg/h. The volumes of the syringes used for both groups were similar to avoid potential bias. General anesthesia was achieved with propofol 2.5 mg/kg and endotracheal intubation was facilitated with rocuronium 0.8 mg/kg. Anesthesia was maintained with desflurane at an end-tidal concentration adjusted to maintain BIS between 30 and 50, and the heart rate and systolic blood pressure ± 20% the respective baseline values. In group C, no supplemental fentanyl was given during maintenance of anesthesia. Patient's lungs were mechanically ventilated with a mixture of air in oxygen (FiO_2 40%) to maintain normocapnia. Neuromuscular blockade was maintained with rocuronium following assessment of neuromuscular function with train-of-four monitoring. Intravenous normal saline (0.9% NaCl) was administered during surgery at a rate of 6 ml/kg/h. A nasopharyngeal probe was placed to measure body temperature throughout the surgery and intraoperative normothermia was maintained with forced air warming blankets positioned over the exposed parts of the body. Soon after induction of anesthesia acetaminophen 1.3 g

was administered per rectum, and dexamethasone 8 mg was given iv to all patients. Intraoperative hypotension (mean arterial blood pressure lower than 60 mmHg), and bradycardia (heart rate less than 40 beats per minute), if occurred, were treated in all groups with fixed dose of intermittent phenylephrine 40 μg (or ephedrine 5mg) or atropine 0.4 mg respectively. Intraoperative persistent hypertension (systolic blood pressure >20% the baseline and not controlled by titrating desflurane concentration) and tachycardia (HR > 120 bpm), were treated with fixed dose of either labetalol 5 mg or propranolol 0.5 mg respectively. Desflurane, together with the continuous infusion of the study medication used (either normal saline or intravenous lidocaine) were discontinued at the end of surgery after the last skin suture. In all patients, residual neuromuscular block was antagonized with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg. Ketorolac 30 mg and droperidol 0.625mg were also given i.v. Patients were then transferred to the PACU.

All patients were operated by two surgeons highly experienced in laparoscopic cholecystectomy (LF, GF). After infiltration of lidocaine 2% in the infraumbilical skin, open insertion of a blunt-tipped 12 mm trocar was used to access the peritoneal cavity. Pneumoperitoneum was achieved with carbon dioxide, and intra-abdominal pressure was maintained below 12 mmHg throughout surgery. Three additional 5-mm ports were introduced after infiltration of lidocaine 2%. Patients at risk of deep venous thrombosis received a single dose of 5000 Units of subcutaneous heparin and wore antiembolic stockings. Patients were positioned in 30^{o} reverse-Trendelenburg position and rotated toward the left side to facilitate exposure of the gallbladder. At the end of surgery, patients were returned to a supine position and the carbon dioxide left in the peritoneal cavity was expelled by abdominal compression. A total of 10 ml of bupivacaine 0.25% with epinephrine was injected into the surgical incisions.

Postoperative care and evaluations

At the end of surgery patients were transferred to PACU, where nurses, unaware of the study hypothesis, monitored the arterial blood pressure, heart rate, respiration and temperature every 5 minutes. The nursing staff did not have access to the anesthesia record and did not interact with the anesthesiologist who administered anesthesia. A standardized prescription for the nursing staff included administration of fentanyl 25 μg iv for postoperative pain relief up to a maximum of 200 μg/h if the VRS for pain was more than 3 at rest. If at the time of hospital discharge VRS on ambulation was > 3, oxycodone 5 mg was administered. Ondansetron 4 mg iv was prescribed for persistent nausea (lasting >5 minutes) or vomiting, and it could be repeated up to 4 times over a 3-h period if necessary. Recovery status was evaluated on arrival in the recovery room every 30 min for the first 2 h by a research assistant (BA) who was unaware of the group assignment and study hypothesis, and had not interaction with PACU nurses. The White-Song scoring system, previously validated for bypassing the PACU and transfer of patients directly from the operating room to the step-down unit, was used to assess the recovery profile. It includes the following variables: level of consciousness, physical activity, hemodynamic stability, respiratory stability, oxygen saturation status, postoperative pain assessment and postoperative emetic symptoms[136]. A minimal score of 12 of 14 points would be required for an outpatient to be fast-tracked after general anesthesia. In our institution, no step-down unit is available and patients are discharged home directly from PACU. The time to achieve the White-Song score of 12 of 14 points was used as a tool to assess the speed of recovery.

Patients were discharged home by the nursing staff according to the following institutional standardized criteria used for all outpatient surgery: awake and oriented,

stable cardiovascular hemodynamics, stable oxygen saturation >95% on room air, minimal pain (VRS < 4 on ambulation), absence of PONV, ability to tolerate oral fluids and to void, and to walk unaccompanied. At time of hospital discharge, patients were given detailed instructions by the surgeon in consultation with the anesthesiologist responsible for the study (GB) in the use of analgesics to take home. Patients were instructed to take regularly acetaminophen 1000 mg every 6 h and naproxen 500 mg every 12 h, and, if pain persisted, oxycodone 5mg every 6 hr. Dimenhydrinate 50 mg was prescribed every 6 hr for nausea or/and vomiting.

Study outcomes

The primary outcome was the amount of fentanyl administered in the PACU for pain relief to maintain VRS <3. Secondary outcomes were quality of analgesia in the PACU, incidence of PONV, the White-Song score and the time spent in the hospital before being discharged home. Intermediate outcomes included intraoperative changes in systolic and diastolic arterial blood pressure, and heart rate, end-tidal desflurane concentrations, BIS values, and plasma cortisol and IL-6 concentrations. A summary of the intraoperative and postoperative outcomes measured is reported in Table 4.

Data collection

The following perioperative data were collected: demographic characteristics of the patients studied, ASA score, number of pain attacks and worst pain score (VRS) in the month prior to surgery, Apfel score[162], history of motion sickness, duration of surgery, laparoscopic time and amount of fentanyl used during surgery. Furthermore, non-invasive systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), patient temperature (T°), end-tidal desflurane concentrations and BIS values were reported at the arrival in the operating block (T_0), at the beginning of pneumoperitoneum (T_p) and every 15 minutes throughout the surgery. In the PACU,

the amount of fentanyl and ondansetron used, VRS for pain, incidence of PONV, pruritus, urinary retention, White-Song score and length of hospital stay (defined as time spent in PACU until discharge home) were also recorded. All patients were phoned at home 24 h after discharge from hospital to assess pain intensity (VRS), shoulder pain (VRS) presence of PONV and urinary retention, fatigue (VRS), and the amount of analgesics used in the first postoperative 24 hours.

Biochemical assay

Plasma cortisol and IL-6 concentrations were measured before the induction of anesthesia (T_0), at the end of surgery (skin closure, T_1), and when patients met the criteria to be discharged home (T_2).

Plasma human-cortisol was measured by the Access Cortisol assay (Access ® Immunoassay systems, Beckman Coulter ®) that is a paramagnetic particle, chemilluminescent immunoassay for the quantitative determination of cortisol levels in human serum, plasma (heparin, EDTA) and urine using the Access Immunoassay Systems[163]. The Access Cortisol assay is a competitive binding immunoenzymatic assay. A sample is added to a reaction vessel with rabbit antibody to cortisol, cortisol-alkaline phosphatase conjugate, and paramagnetic particles coated with goat anti-rabbit capture antibody[163]. After unbound particle are removed by washing, a chemilluminisscent substrate, Lumi-Phosp 530, is added to produce light directly proportional to the amount of analyte in the sample as determined from a stored calibration curve[164].

Plasma human IL-6 cytokines were measured by suspension bead array immunoassay using a Luminex 200 X-map instrument (Luminex Corp, Austin, TX, USA). The cytokine was measured using a Milliplex human cytokine kit following manufacturer's specifications (MPXHCYTO-60k, Millipore Corp, Bilerica, MA,

USA). All samples were measured in duplicate and the kit had a sensitivity of 0.4 pg/ml. Serial dilutions were made of a reconstituted human cytokine standard to produce a standard curve from 3.2 to 10,000 pg/ml. The standards were mixed 1:1 with 25µl of serum matrix and added to the micotiter plate. The serum samples were mixed 1:1 with 25µl of assay buffer and transferred to the appropriate wells of the plate. After sonication, 25µl of diluted antibody coated beads were added to all standard, blank or sample wells. The plate was sealed and agitated on a titer plate shaker (Barnstead Int, Dubuque, IO, USA) for one hour at room temperature. Fluid was removed by vacuum filtration and then the plate was washed two times with 200µl of wash buffer. Following the wash, 25µl of detection antibody was added to all wells. The plate was again sealed and agitated at room temperature for 30 minutes. Finally, 25µl of Streptavidin-Phycoerythrin was added and then incubated for an additional 30 minutes with agitation. The fluid was then removed by vacuum filtration and the plate was washed two more times with wash buffer. The beads were resuspended in sheath fluid and agitated for 5 minutes. The cytokines were analyzed on the Luminex instrument using MasterPlex CT 1.2 software (MiraiBio Inc, Alameda, CA, USA). Mean fluorescence intensity was obtained from a minimum of 50 beads per sample. Concentrations were calculated from the standard curve generated by the MasterPlex QT 4.0 analysis software (MiraiBio Inc, Alameda, CA, USA).

Statistical analysis

Comparisons for each demographic and clinical variable between groups were performed. Student's *t*-test was used to compare numeric normally distributed variables. Pearson $\chi 2$ test or Fisher's exact test were used to compare categorical nominal variables, while Mann-Whitney-U test was used for not normally distributed

variables and categorical ordinal variables such as VRS and White-Song scores. Data are presented as means ± standard deviation (median) if normally distributed, median if not, and as absolute numbers, percentages or proportions. The level of significance was set at $P < 0.05$ for all analysis. Statistical analyses were performed with SPSS Statistic 18.0 package (© 2010 SPSS, Inc. IBM Company, Chicago, Illinois, USA) and GraphPad Software 4.0 (Inc. La Jolla, California, USA).

Determination of sample size requirement was based on mean postoperative fentanyl consumption in PACU (150 μg) reported in a previous study of patients undergoing laparoscopic cholecystectomy, following the same anesthetic protocol, and receiving intraoperative opioids [18]. A power analysis indicated that 46 patients in each of the two groups studied were needed to show similar postoperative fentanyl consumption, between the patients who received intraoperative lidocaine and the patients who received intraoperative fentanyl, with a type-1 error of 0.05 and a power of 95%.

3.6. Results

Patients

Of the 202 patients scheduled to undergo elective cholecystectomy, 94 did not meet the protocol inclusion criteria, 16 patients refused to participate, leaving 92 patients who agreed and signed the consent form. Of these, 46 were randomly assigned to group C, and 46 to group L. Two patients in the group L were subsequently excluded from the analysis for conversion to laparotomy, for intraoperative bleeding and for re-exploratory surgery to control bleeding (Figure 1, consort diagram).

Demographic and preoperative clinical data.

Demographic characteristics, preoperative clinical data and surgical and laparoscopic times are shown in table 5. There were no statistically significant differences between the two groups.

Postoperative clinical data: day 0.

Postoperative and total fentanyl consumption, incidence of PONV and length of hospital stay are reported in table 6 and White-Song scores in table 7. The distribution of fentanyl consumption in the two groups is presented in figure 2, with 3 outliers in group C, and 4 in group L who used more than 200 μg of fentanyl. One outlier in group L required 2 mg PO of hydromorphone. The decision to use this cut-off to define outliers values was based on the average postoperative fentanyl consumption of patients who underwent laparoscopic cholecystectomy in this institution[18]. Statistical analysis of fentanyl consumption excluding outliers' values did not show significant difference between the two groups. The incidence of PONV and the need of ondansetron were similar in both groups. Length of hospital stay was also not different (*p=0.30*) (Table 2). At the arrival in the recovery room there were more patients in group C (n= 16) than in group L (n=6) who had a White-Song score > 12 (*p=0.03*). However, median values of White Song-scores did not differ between the groups during the length of stay in the recovery room. When the scoring of the individual components of the White-Song questionnaire was compared between the two groups, patients in groups C and L recovered to the same extent. At arrival in the PACU more patients in group L had oxygen saturation greater than 90% on room air than patients in group C (*p=0.03)* (Table 7).

VRS for pain at rest and on coughing were similar in the first 30 minutes and at 90 minutes from the arrival in the recovery room (Table 8). No clinical signs of toxicity

associated with the use of intravenous lidocaine were observed in all patients who received lidocaine

Postoperative clinical data: day 1.

VRS scores for pain, at rest, on coughing and on walking, shoulder pain, VRS scores for fatigue and the incidence of postoperative nausea and vomiting were not different between the two groups 24 hours after hospital discharge (Table 8). Analgesic consumption at home is shown in table 9. There was no difference in the consumption of acetaminophen and naproxen between the two groups. Only 23.9 % of patients in group C and 22.7 % of patients in group L followed the recommendations given on how to take postoperative analgesic medications (acetaminophen and naproxen). More patients in group L took oxycodone (n=30) vs group C (n=23) (p= 0.09). However, if patients followed analgesic prescriptions, the number of patients who required also oxycodone did not differ in the two groups (p= 1.00).

Quality of surgical recovery was similar in both groups (table 10). Median QoR scores were 16 in group C, (interquartile range, 14.5-17) and 17 in group L, (interquartile range, 15-17.5) (p =0.09).

Intraoperative hemodynamic data, end-tidal desflurane concentrations, BIS values and need of beta-blockers or vasopressors.

Median and interquartile range of systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), end-tidal desflurane and BIS values were recorded at different intervals: at arrival in the operating room (T_0), beginning of pneumoperitoneum (T_p) and every 15 minutes for a total of 60 min throughout the surgery (Figure 3). There were no significant differences in SBP and DBP at any time point between the two groups (Figure 3). In contrast HR was significantly higher in group L compared to group C at T_p (L = 95 bpm [83-108.5], C = 78 bpm [68-91], p =

0.0001) and at T_1 (L = 85 bpm, [74-91] C = 80 [66-88.5], p = 0.04) (Figure 3). Furthermore, HR in group L increased significantly at T_p compared to T_0 (*p <0.0001*) (Figure 3). End-tidal desflurane concentrations (%) were similar in both groups, while BIS values in group L were significantly lower at T_p, T_1, and T_4 (L = 35.5 [32-41], C = 43 [37.5-47], p = 0.0018; L= 35 [31.5-41], C= 41 [35.5-45], p= 0.02; L = 35 [30.5-44.5], C = 40 [36-45] p =0.02 respectively) compared to the group C (figure 4). Hemodynamic data, end-tidal desflurane concentrations (%) and BIS values are reported in Table 11. Beta-blockers were required to treat tachycardia during the first 15 min from the beginning of pneumoperitoneum in 3 patients (6.5%) in the group C and in 8 patients (17%) in group (p = 0.11). Demographic and clinical data of patients who required beta-blockers are reported in Table 12 and 13. Hypotension which required the use of ephedrine 5 mg iv, occurred in two patients in each group after the induction of pneumoperitoneum and patient positioning. Intraoperative body temperatures were maintained between 35.5 and 37.2 C°, with no difference between groups.

Plasma cortisol and IL-6 and concentrations.

Plasma cortisol and IL-6 and concentrations were measured in a series of 26 patients (13 in group C and in 13 in group L). At the end of the surgery (T_2), cortisol plasma concentrations were significantly higher in group L than group C (median 808 nmol/L interquartile range [723-1005], and median 747 interquartile range [619-797.5] respectively, *p=0.04*). IL-6 plasma concentrations were similar between the two groups, although baseline median IL-6 concentrations (T_1) in group L were higher than group C (*p=0.59*) (Figure 5).

Postoperative complications

Two patients in group C were admitted overnight for postoperative bleeding. An abdominal drain was inserted in only 1 of them and kept until discharge. Both patients were discharged on postoperative day 1. One patient in group C was admitted for Endoscopic Retrograde Cholangiopancreatography (ERCP) to remove a stone in the common bile duct. Abnormal ECG showing negative T waves were observed in a 74 y old man, with no past medical history of coronary artery disease and completely asymptomatic in the PACU. Following cardiology consultation, the patient was discharged the same day 4 h after the surgery. No postoperative complications were reported in group L.

3.7. Discussion

The results of this study show that in patients undergoing elective laparoscopic cholecystectomy the sole use of intraoperative intravenous lidocaine as a primary analgesic technique and without the administration of intraoperative opioids has the same postoperative analgesic efficacy of intraoperative fentanyl. Postoperative consumption of opioids, side effects and readiness to discharge were similar.

Several clinical trials have shown that systemic administration of lidocaine, as adjuvant to perioperative opioids, decreases postoperative pain and opioid consumption. The anti-inflammatory properties of lidocaine are well established in many surgical models [6]. Similarly, lidocaine reduces secondary hyperalgesia as shown in experimental models in which systemic administration of lidocaine (2mg/kg) followed by a continuous infusion of 2mg/kg/hr for 50 minutes) reduced the area of pin-prick hyperalgesia after intradermal injection of capsaicin [47]. These analgesic properties are mediated through different pharmacological mechanisms of action by

blocking the nociceptive activity at the level of the dorsal roots of the spinal cord and at the level of peripheral Aδ and C-fibers. Sodium channels blockade [6], inhibition of G protein-coupled receptors[6,149] and N-methyl-D-aspartate receptors[40,147] have been reported as principal pharmacological mechanisms through which intravenous lidocaine decreases pain intensity.

This is the first study in which intravenous lidocaine was used as primary analgesic medication without supplemental opioids during the surgery. The use of intravenous lidocaine showed to have the same analgesic efficacy of intraoperative fentanyl. In fact, in the immediate postoperative period, postoperative fentanyl consumption and postoperative pain intensity were similar in the lidocaine and in the group C (Table 6 and 8). Although fentanyl consumption was slightly higher in group C, this difference was not statistically and clinically significant. The analysis was repeated excluding patients who received more than 200 μg of fentanyl, and normalizing the values by body weight, and the opioid consumption in the PACU did not differ between the two groups. It is interesting to notice that postoperative fentanyl consumption in the present study was similar to that reported previously using the same surgical model where patients received intravenous lidocaine as adjuvant to an intraoperative smaller dose of fentanyl[18]. Even the incidence of PONV was similar in the two groups (20.4% compared to 19.5%[18]. This could be explained by the PONV prophylaxis with preoperative dexamethasone (8 mg) and iv droperidol (0.625 mg) 30 minutes before the end of the surgery, and this may have minimized the incidence of PONV in both groups, and therefore reduced the probability to detect a significant difference between the two groups. In the control group of Lauwick's study the incidence of PONV and the postoperative consumption of fentanyl were respectively 40.9% and 47 % higher than in the control group of the present study. These results would therefore

confirm previous findings[27,161] and show that, despite a strict pharmacological PONV prophylaxis, the incidence of PONV in patients who have the same risk factors to develop PONV (same gender, Apfel scores and type of surgeries), is dose-opioid dependent.

In the present study heart rate increased in both groups at the beginning of the pneumoperitoneum and 15 minutes after, but it was significantly higher in group L. More patients in group L had tachycardia, but the use of beta-blockers was similar between the two groups (Table 12 and 13). Small doses of beta-blockers were used successfully and heart rate returned to normal values for the rest of surgery. These findings are in contrast with other results that have shown an attenuation of the sympathetic response by intravenous lidocaine during caesarean section and after abdominal surgery [107]. However, in this trial several factors beside pain could have contributed to this effect. First, it is well demonstrated that insufflation of carbon-dioxide in the abdominal cavity increases heart rate and systemic vascular resistance[165,166], even in patients receiving large doses of intraoperative opioids. Second, positioning the patient in reverse-Trendelemburg, in combination with the pneumoperitoneum has been associated with an increase of heart rate [148]. Third, administration of desflurane in healthy volunteers without systemic opioids can increase sympathetic tone and cause tachycardia and hypertension, especially when increased rapidly and at a concentration greater then 1 MAC[167]. Finally systemic opioids have a sympatholitic effect, which may have contributed to reduce the increase of heart rate in group C. In fact, desflurane-induced tachycardia is only partially attenuated by intravenous fentanyl administration[168]. While heart rate increased, arterial blood pressure did not increase to the same extent in-group L. It might be possible that the effect of reverse-Trendelenburg and positive abdominal

pressure on venous return counteracted the increase in blood pressure during the peritoneal insufflation. In all patients, hemodynamic changes were easily controlled by increasing desflurane concentrations. The upper limit of heart rate to be treated with beta-blockers was set up at 120 bpm, although some others practitioners might have chosen a lower heart-rate threshold to administered beta-blockers. In addition, in group L baseline HR (T_0) was slightly higher than HR in group C [median 80 bpm, interquartile range (70-87), and 75 bpm, interquartile range (65-85), respectively, p =0.35)]. This is another reason that might explained why more patients in group L received intraoperative beta-blockers (Table 11-13).

End-tidal desflurane concentrations were similar in both groups, while BIS values were significantly lower in the group L (Figure 5). Other studies have found that intravenous lidocaine decreases volatile anesthetic concentrations but not BIS values [17,18] [16]or auditory evoked potentials [15]. These findings, would suggest that intravenous lidocaine *per se* may either have general anesthetic properties or produce a hypnotic synergistic effect together with general anesthetic inhalation agents.

We attempted to measure recovery after surgery by using the White-Song scores and readiness to discharge, and these measures were similar in both groups. Although more patients in group C had a White-Song more than 12 at the arrival in the PACU (p =0.03), recovery assessed by comparing the individual components of the White-Song score was similar between the two groups. More patients in group L were able to maintain oxygen saturation more than 90% on room air at the arrival in the PACU (Table 7). Overall, high White-Song scores were reported soon after the surgery in both groups (median 12 in group C and 11.5 in group L) and they improved in a similar manner during the recovery period. This would demonstrate the limitation of the White-Song scoring system in detecting significant difference in the quality and

readiness of recovery between the two groups [136]. Although the White-Song scoring system was here used to compare our results with the previous data obtained in this institution[18], there is a need for more extensive and validated scores to assess recovery after ambulatory surgery.

Twenty-four hours after surgery hospital discharge, pain intensity, consumption of analgesics and opioids and incidence of opioids side effects were similar in both groups. The same findings were also described in other studies[18,24]. Although an attempt was made before leaving the hospital to standardize postoperative analgesia by providing detailed information and schedule on analgesic dosage, only 23.9% of patients in group C and 22.7 % in group L followed these recommendations. In these patients the use of oxycodone did not differ between the two groups, and this finding is in agreement with the well established opioids-sparing effect of non-steroidal anti-inflammatory medications [5](Table 9). Although QoR-9 score is not validated in outpatients, quality of surgical recovery was the same between the two groups (Table 10). New questionnaires assessing surgical recovery in out-patients are warranted.

Finally, the results from this series of patients showed that at the end of the surgery plasma cortisol concentrations were higher in group L than in group C ($p = 0.04$). However, when patients with plasma cortisol concentrations higher than 1000 nmol/L were excluded from the analysis (n=3), this difference was not statistically significant ($p = 0.09$). In these patients the laparoscopic time was particularly short (< 25 minutes) and the measurement of cortisol at the end of the surgery might have coincided with the pick of plasma cortisol. Plasma IL-6 concentrations were similar in the two groups, although baseline levels were higher in group L ($p = 0.59$). Although the anti-inflammatory effects of intravenous lidocaine previously reported in other trials were not observed in this study, the use of dexamethasone and the short duration

of the infusion might have dumped the anti-inflammatory properties of lidocaine. In fact, plasma IL-6 concentrations found in this study were 10 times lower than plasma IL-6 levels found after laparoscopic cholecystectomy but without the administration of dexamethasone [68].

Some limitations to this study must be acknowledged. First, the external validity of the study was limited. Exclusion criteria used for this study were very strict and these results may not be generalizable to the entire population. Secondly, a criticism could be made to the study design. In fact, the analgesic properties of fentanyl last approximately 30-45 minutes, while the median duration of surgery in group C was 65 minutes. Therefore, one would raise the contention that the fentanyl required in PACU in group C might overestimate the real opioids consumption of these patients. However, a subgroup analysis showed that in 21 patients (45.6%) of group C the laparoscopic time lasted less then 45 minutes, and the median fentanyl consumption was 125 μg, surprisingly higher then the median fentanyl consumption of the entire group C (87.5 μg).

In conclusions, the results of this study showed that, postoperative fentanyl consumption in patients receiving intravenous lidocaine, as primary analgesic technique without the use of intraoperative opioids, is similar to the consumption of patients receiving intraoperative opioids. Postoperative pain scores, opioids side effects and length of hospital stay were also similar. However, the hemodynamic changes induced by the pneumoperitoneum, were not blunt by intravenous lidocaine and plasma concentrations of cortisol and IL-6 were not attenuated by the infusion of intravenous lidocaine. Even if these results do not support the intraoperative use of lidocaine in this selected group of patients, patients who require general anesthesia and for whom opioids might be contraindicated, such as those with obstructive sleep

apnea, COPD, obese, or elderly, may benefit from the use of this non-opioid analgesic technique, but further validation is warranted.

4. Final conclusions and summary

The main goals of this study clinical investigation were to establish the effect of intravenous lidocaine, as primary analgesic technique without the use of intraoperative opioids, on postoperative opioid consumption, opioid side effects, pain intensity and on surgical recovery. It was found that postoperative opioid consumption and pain scores were similar between the patients who received intraoperative lidocaine and the patients who received intraoperative fentanyl. Opioid side effects, length of hospital stay and quality of surgical recovery were also similar. However, the sympathetic response observed at the beginning of pneumoperitoneum was not blunted by lidocaine. Plasma concentrations of cortisol and IL-6 were not attenuated by the infusion of intravenous lidocaine.

In conclusion, these findings suggest that by replacing opioids with intravenous lidocaine does not offer any postoperative advantages in this selected group of relatively healthy patients. On the other hand, this study unveiled for the first time a new anesthetic tool that could be potentially beneficial in patients at high-risk to develop opioids-related complications and/or side effects such as morbidity obese patients, patients with OSA, elderly patients or patients with COPD. However, further studies should evaluate the analgesic efficacy and the recovery profile of intravenous lidocaine, specifically in these populations. Then, it might be possible that the use of non-opioid analgesic techniques, such as intravenous lidocaine, might reduce postoperative morbidity and improve surgical recovery.

Tables (1-13).

Study	Type of Surgery	Doses (bolus + c.i)	Duration of continuous infusion	Plasma levels (µl/ml)	Toxicity
Wallin et al[63]	Cholecystectomy	100 mg† + 2mg/min	Until 24 hr from the end of surgery	Not measured	Drowsiness
Cassuto et al. [29]	Cholecystectomy	100 mg† + 2mg/min	Until the end of surgery	1.52- 1.75 *	Not observed
Rimback et al. [25]	Cholecystectomy	No bolus + 3mg/min †	Until the end of surgery	Not measured	Not reported
Isler et al. [34]	CABG	1.5 mg/kg + 30µg/kg min	Until 48 hr from the end of surgery	Not measured	Not measured
Groundin et al. [30]	Radical prostatectomy	1.5 mg/kg + 2-3 mg/min ♣	Until 60 min after skin closure	1.3-3.7 (average)	Not observed
Koppert et al. [23]	Major abdominal surgery	1.5 mg/kg +1.5mg/kg/hr	Until 60 min after skin closure	1.9 ± 0.7 (average)	Not observed
Kuo et al.[15]	Colorectal surgery	2 mg/kg† +3mg/kg//hr	Until the end of surgery	Not measured	Not measured
Herroeder et al [31]	Colorectal surgery	1.5 mg/kg + 2mg/min	Until 4 hr from skin closure	1.1-4.2 (range)	Not observed
Harvey et al [32]	Bowel surgery	No bolus + 1mg/min ⅄	Until 24 hr from the end of surgery	Not measured	Not observed
Yardeney et al [28]	Hysterectomy	1.5 mg/kg + 2mg/kg/hr	Until the end of surgery	Not measured	Not measured
Swenson et al [26]	Colorectal surgery	1.5 mg/kg + 1-3 mg/min	Day after return of bowel function ††	Not reported ††	CNS toxicity
Cui et al. [20]	Thoracic surgery	No bolus + 0.33µg/kg/min ⅄ ⅄	Until skin closure	2.24-0.12	Not reported
Tahan et al.[107]	C-section	1.5 mg/kg + 1.5 mg/kg/hr	Until 1 hr after surgery	2.05 ± 0.42 (average)†††	Not reported
Martine [33]	Total hip arthroplasty	1.5 mg/kg + 1.5 mg/kg	Until 60 min after skin closure	2,1 ± 0,4 (average)◆◆◆	Not reported

Table 1. Intravenous lidocaine: doses, plasma concentrations and toxicity.

Study	Type of Surgery	Doses (bolus + c.i)	Duration of continuous infusion	Plasma levels (µl/ml)	Toxicity
Wu et al [24]	Lap. Cholecystectomy	No bolus + 3mg/kg/hr †	Until the end of surgery	Not reported	Not reported
Kaba et al [19]	Lap. Colectomy	1.5 mg/kg + 2-1.3 mg/Kg/hr **	Until 24 hr from the end of surgery	2.7 ± 1.1 (average) ◆◆	Not reported
Lauwick et al [18]	Lap. Cholecystectomy	1.5 mg/kg + 2mg/kg/hr	Until skin closure	Not measured	Not reported
Lauwick et al [16]	Lap. Prostatectomy	1.5 mg/kg + 2-1 mg/kg/hr **	Until 24 hr from the end of surgery	Not measured	Not reported
McKay et al[27]	Ambulatory surgery	1.5 mg/kg + 2mg/kg/hr	Until 60 min after skin closure	Not measured	CNS toxicity✢

Table 1 (continuing)**.** Intravenous lidocaine: doses, plasma concentrations and toxicity.

Table 1. Intravenous lidocaine: doses, plasma concentrations and toxicity. Boluses, when not specified were given at the induction of anesthesia, and they were followed by a continuous infusion (c.i). † = bolus given, or c.i. started, 30 min before skin incision; ♣ = 2 mg/min if weight was < 70 kg, 3mg/min if weight was > 3 mg/min; ⅄ = started at the end of surgery; ⅄⅄ = started 20 min before induction of anesthesia; * = Average plasma lidocaine concentrations, at 8 and 20 hr, respectively; ** = 2mg/min = intraoperatively, 1 or 1.3 mg/min= for 24 hr after the end of surgery; ◆◆ = average at the end of the infusion; †† See text for details; ††† = 1 hr after delivery; ◆◆◆ = at the end of the infusion. ✢ = 1 patient experienced drowsiness and visual disturbance at the end of the infusion (lidocaine plasma concentrations 2μg/ml) CABG = coronary artery by-pass graft. CNS= Central Nervous System; Lap = laparoscopic. CABG = coronary artery by-pass graft.

DRUG	Equianalgesic dose	
	PO	IV
Morphine	10 mg	5 mg
Hydromorphone	2 mg	1 mg
Fentanyl	N/A	50 μg
Codeine (IV/IM, not recommended)	100 mg	N/A
Oxycodone	7.5 mg	N/A

Table 2. Opioids comparative table. Internal McGill University Health Centre opioids guidelines.

Phase	Scoring system and	Total scores required to pass to the following phase
Phase I	Aldrete score White-Song score*	≥9 ≥ 12
Phase II	PADS Outcome-based discharge criteria	≥9
Phase III	-	-

Table 3. Phases of surgical recovery and scoring systems after ambulatory surgery. Phase I: from the post-anesthesia care unit (PACU) the step-down unit. Phase II: from the step-down unit to home. Phase III: return to preoperative physiological status. Postanesthetic discharge scoring system (PADS). * To bypass PACU and patients can be directly transferred.

Outcomes	Measurements
Primary	
Analgesic requirements in PACU	Amount of fentanyl equivalents in PACU (μg)
Secondary	
Intraoperative:	
hemodynamics	HR (bpm), SBP, DBP, (mmHg)
depth of anesthesia	Et Desflurane concentrations (%)
PACU	
Postoperative pain	Verbal Rating Scale (0-10)
Postoperative recovery	White-Song score
Opioids side effects	
PONV	Y/N, requirement of ondansentron
POUR	Bladder scan > 600 ml
Stress response	Cortisol (nmol/L)
Inflammatory response	IL-6 (pg/ml)
POD 1 *	
Postoperative pain	Verbal Rating Scale (0-10)
Analgesic requirements	Acetaminophen (mg)
	Naproxen equivalents (mg)
	Oxycodone (mg)
PONV	Y/N
Need of Dimenhydrinate	Dimenhydrinate (Y/N, mg)
Quality of surgical recovery	QoR Score

Table 4. Intraoperative and postoperative outcomes measures.

Table 4. Intraoperative and postoperative outcomes measures. HR=heart rate, SBP = systolic blood pressure; DBP = diastolic blood pressure; Et = end-tidal concentrations. QoR = Quality of Recovery.

	Control (n = 46)	**Lidocaine** (n = 44)	**p**
Male / Female	11/ 35	11/ 32	0.81
Age (years)	43.6 ± 14.6 (44)	48.4 ± 13.3 (47)	0.13
Weight (kg)	71.3 ± 15.8 (69.5)	73.2 ± 13.4 (71.9)	0.54
Body mass index (kg/m^2)	25.2 ± 4.9 (24.5)	26.3 ± 3.7 (25.8)	0.26
ASA 1/2/3	21/24/1	19/22/3	0.56
Active Co-morbidities: n (%)			
Arterial hypertension	5 (10.9)	5 (11.3)	1
Hypercholesterolemia	3 (6.5)	1 (2.3)	0.61
Hypothyroidism	3 (6.5)	2 (4.5)	1
Asthma	3 (6.5)	3 (6.8)	1
GERD	4 (8.7)	5 (11.3)	0.73
Medications n (%)			
Calcium-antagonists	2 (4.3)	-	0.49
Diuretics	2 (4.3)	-	0.49
ACE-inhibitors	1 (2.3)	3(6.8)	0.35
Hydralazine	-	2(4.5)	0.23
Statins	3 (6.5)	1(2.3)	0.61
Levothyroxine	3 (6.5)	2(4.5)	1
Salbutamol	2 (4.3)	3(6.8)	0.67
PPIs	1 (2.2)	5 (11.3)	0.10
Pain colic attacks in the last month (n)	1 [1-3.5]	1 [1-4]	0.99
VRS of the worst pain colic attack in the last month	7 [5-9]	8 [5.5-9.5]	0.39
Apfel score 0/1/2/3/4	0/2/22/15/7	0/2/19/17/6	0.94
Motion sickness n (%)	6 (13)	8 (18.2)	0.57
History of previous PONV: n (%)	5 (10.9)	6 (13.7)	0.75
Duration of surgery (min)	65 [57.5 – 90]	68 [55– 85.5]	0.92
Laparoscopic time (min)	47.5 [40-73.5]	45 [37 – 64]	0.35
Amount of intraoperative fentanyl (mcg)	213.6 ± 47.4 (208.5)	-	-
Amount of intraoperative lidocaine (mg)	-	290.2 ± 89.3 (263.8)	-
Converted to open: y/n	0/ 44	01/ 45	-
Second surgery: y/n	0/44	01/45	-

Table 5. Demographic and clinical data.

Table 5. Demographic and clinical data. Values are presented as absolute numbers (percentage), mean ± standard deviation (median), or median [interquartile range].

P values are calculated with Pearson c^2 or Fisher's exact test for categorical variables, Student's T test for parametric normally distributed variables and Mann-Whitney-U test for parametric not-normally distributed variables and VRS scores. ASA = American Society of Anesthesiologists; VRS = Verbal Rating Scale; PONV = postoperative nausea and vomiting. GERD = Gastric Esophageal Reflux Disease. PPI = Proton Pump Inhibitors.

	Control n = 46	**Lidocaine** n = 44	**p**
Amount of fentanyl used in the PACU (μg)			
with outlier values	87.5 [50-150]	112.5 [75-150]	0.17
without outlier values	75 [50-125]	100 [75-137.5]	0.25
Amount of fentanyl /Kg used in the PACU (μg)	1.2 [0.6-2.2]	1.5 [1-2.1]	0.28
Oxycodone 5 mg PO (VRS > 4) (n)	34	33	1
Nausea or vomiting in the PACU: n (%)	9 (19.5)	9 (20.4)	1.00
No. of patients requiring ondansetron: 4 /8 mg	7/0	6/1	1.00
Time from arrival to PACU to discharge home (min)	197.8 ± 61.6 (193.5) [95% CI, 179.5-216.1]	185.3 ± 48.9 (180) [95% CI, 170.5-200.2]	0.30

Table 6. Fentanyl consumption, postoperative nausea and vomiting in PACU and length of hospital stay. Values are presented as median [interquartile range], mean ± standard deviation (median) and absolute numbers. P values are calculated with Pearson χ^2 or Fisher's exact test for categorical variables, Student's t-test for parametric normally distributed variables and Mann-Whitney-U test for parametric not-normally distributed variables. CI = confidence interval. PACU = Post Anesthesia Care Unit.

White-Song score (0-14)			
	C	**L**	**p**
White-Song score 1 min	12 [11 – 13]	11.5 [11 – 12]	0.21
White-Song score 30 min	12 [12 – 13]	12 [12– 13]	0.86
White-Song score 60 min	13 [12 – 13]	13 [12 – 13]	0.84
White-Song score 90 min	13 [13 – 13]	13 [13 – 14]	0.20
No. of patients with White-Song score > 12 at: 1^{st}/ 30^{th} / 60^{th}/90^{th} min / never in 90 min	16*/5/10/6/9	6*/14/8/8/8	*0.05

White-Song score				
	T_1 n of patients	**T_{30} n of patients**	**T_{60} n of patients**	**T_{90} n of patients**
Level of consciousness				
0/1/2 **(C)**	5/33/8	1/29/16	0/21/25	0/19/27
0/1/2 **(L)**	7/33/4	2/28/14	1/19/24	0/11/33
Physical activity				
0/1/2 **(C)**	0/3/43	0/1/45	0/1/45	0/1/45
0/1/2 **(L)**	1/1/42	0/2/42	0/1/43	0/0/44
Hemodynamic				
0/1/2 **(C)**	2/19/25	0/19/27	0/20/26	0/18/28
0/1/2 **(L)**	2/17/25	0/17/27	0/18/26	0/17/27
Respiration				
0/1/2 **(C)**	2/1/43	2/0/44	1/0/45	1/0/45
0/1/2 **(L)**	0/1/43	0/0/44	0/0/44	0/0/44
Oxygenation				
0/1/2 **(C)**	1/5/40▲	0/4/42	0/1/45	0/1/45
0/1/2 **(L)**	0/0/44	0/0/44	0/0/44	0/0/44
Pain				
0/1/2 **(C)**	8/13/25	5/16/25	1/12/33	0/10/36
0/1/2 **(L)**	9/19/16	6/15/23	1/17/26	0/9/35
PONV				
0/1/2 **(C)**	0/1/45	0/2/44	0/0/46	0/1/45
0/1/2 **(L)**	1/2/42	0/1/43	0/0/44	0/0/44

Table 7. Surgical recovery assessed by the White Song score. Values are presented as median (interquartile range) and as absolute number (proportions). P values are calculated with Pearson χ^2 or Fisher's exact test . ▲ p =0.03.

Postoperative Day 0			
	Control n = 46	**Lidocaine** n = 44	**p**
VRS at rest			
VRS 1 min	4.5 [2.5– 7]	5.5 [2.5– 8.5]	0.20
VRS 30 min	3 [2 – 5]	3.5 [2 – 5]	0.60
VRS 60 min	2 [1 – 5]	3 [2 – 5]	0.11
VRS 90 min	2 [0.5 – 3]	2 [1– 3.5]	0.32
VRS on coughing			
VRS 1 min	4.5 [3– 7.5]	5.5 [2.5– 8.5]	0.24
VRS 30 min	4 [2.5 – 7]	5 [3 – 6.5]	0.55
VRS 60 min	3 [2 – 5]	4 [3 – 6]	0.07
VRS 90 min	3 [1 – 4]	3.5 [2-5]	0.24
Postoperative Day 1			
	Control n = 46	**Lidocaine** n = 44	**p**
VRS at rest	2 [1-4]	2 [1-4]	0.28
VRS on coughing	4 [2-5]	4 [3-7]	0.42
VRS walking	3 [1-5]	2 [1-4.5]	0.29
VRS shoulder pain	0 [0-3]	0 [0-1.5]	0.45
VRS fatigue	5 [2.5-6]	4 [2-7]	0.68
PONV: n (%)	10 (21.7)	5 (11.3)	0.26

Table 8. Postoperative clinical data on day 0 and 1. VRS= verbal rating scale for pain. Values are presented as median [interquartile range] or absolute numbers (percentages). P values for VRS scores are calculated with Minn-Whitney-U test and with Fisher's exact test for PONV.

	Control n = 46	**Lidocaine** n = 44	**p**
Analgesic consumption 24 h after the surgery			
Acetaminophen taken by the patient (mg)	2750 [1000-4000]	2000 [250-4000]	0.33
Acetaminophen as prescribed, 1000 mg every 6 h: n (%)	13 (28.2)	12 (27.3)	1.00
Naproxen taken by the patient (mg)	1000 [500-1000]	1000 [500-1000]	0.88
Naproxen as prescribed, 500 mg every 12 h: n (%)	30 (65.2)	32 (72.7)	0.50
Oxycodone taken by the patient (mg)	2.5 [0-10]	8.7 [0-15]	0.06
Oxycodone as prescribed, 5 mg every q 6 hr if needed: n (%)	23 (50)	30 (68.1)	0.09
Compliance to postoperative analgesia prescriptions			
Acetaminophene and Naproxene as prescribed n (%)	11 (23.9)	10 (22.7)	1.00
Acetaminophene, Naproxene and Oxycodone as prescribed n (%)	8 (17.4)	7 (15.9)	1.00
Dimenhydrinate 0-75/ 100-150 mg (n)	42/4	42/2	0.67

Table 9. Postoperative day 1: analgesic and dimenhydrinate consumption 24 hr after hospital discharge. n= number of patients. Values are presented as absolute number (percentages) or median [interquartile range]. P values are calculated with Mann-Whitney-U test for parametric not-normally distributed variables and χ^2 Square test or Fisher's exact test for categorical variables.

QoR-9 score (0-18)	0	1	2
Had the feeling of general well-being			
C n (%)	1 (2.2)	17 (36.9)	28 (60.9)
L n (%)	0 (0)	11 (25)	33 (75)
Had support from others			
C n (%)	3 (6.5)	3 (6.5)	40 (87)
L n (%)	1 (2.3)	2 (4.5)	41 (93.2)
Been able to understand instructions and advice. No being confused.			
C n (%)	1 (2.2)	1 (2.2)	44 (95.6)
L n (%)	1 (2.3)	1 (2.3)	42 (95.4)
Be able to look after personal toilet and hygiene unaided.			
C n (%)	1 (2.2)	1 (2.2)	44 (95.6)
L n (%)	0 (0)	2 (4.5)	42 (95.4)
Been able to pass urine (waterworks) and having no troubles with bowel function			
C n (%)	0 (0)	31(67.4)	15 (32.6)
L n (%)	0 (0)	24 (54.5)	20 (45.5)
Been able to breath easily			
C n (%)	1 (2.2)	6 (13)	39 (41.3)
L n (%)	0 (0)	2 (4.5)	42 (95.4)
Been free from headache or muscle pains			
C n (%)	1 (2.2)	12 (26.1)	33 (71.7)
L n (%)	0 (0)	9 (20.4)	35 (79.6)
Been free from nausea, dry-retching or vomiting			
C n (%)	2 (4.3)	5 (10.9)	39 (84.8)
L n (%)	0 (0)	4 (9.1)	40 (90.9)
Been free from experiencing severe pain or constant moderate pain			
C n (%)	0 (0)	12 (26.1)	34 (73.9)
L n (%)	2 (4.5)	11 (25)	31 (70.5)

Table 10. Quality of recovery score (QoR-9) 24 hr from hospital discharge. Values are presented as absolute number (proportions). P values are calculated with Pearson χ^2 or Fisher's exact test.

	T_0	T_p	T_1	T_2	T_3	T_4
SBP (mmHg)						
C	123.5 [118-137]	115 [95-135]	129.5 [117.5-144]	126 [117.5-140]	125 [115-133]	125.5 [110-140]
L	123.5[120-133.5]	123 [110-133.5]	122.5 [112-137]	125 [109-140.5]	126[110-133]	125 [110-139]
DBP (mmHg)						
C	79.5 [70-88]	72.5 [65-85]	82 [73-90]	80 [72-87]	76[69-85]	74 [66-86.5]
L	79 [72.5-83]	81.5 [67.2-90.5]	84.5 [74.7-93]	80 [70-94]	80 [69-89]	80 [74-91.5]
HR (mmHg)						
C	75 [65-85]	78 [68-91]	80 [66-88.5]	76.5[67-86]	78 [68-89]	72.5 [65.5-83]
L	80 [70-87] $^{\Delta}$	95 [83-108.5]*	85 [74-91]**	80 [70-89]	77 [70-87]	82 [72-86]
ET Desf (%)						
C	0	4.6 [4.2-5.2]	5.0 [4.5-5.9]	5.3 [4.8-5.8]	5.4 [4.7-6.2]	5.5 [4.4-5.9]
L	0	5.1 [4.4-5.7]	5.2 [4.3-6]	5.0 [4.2-5.8]	4.9 [4.1-5.5]	5 [4.1-5.9]
BIS						
C	100	41 [37-47]	40.5 [35.2-45]	39.5 [33.2-4.5]	37 [32.5-43]	40 [36-45]
L	100	36 [32.5-41] †	35 [32-42] ††	37 [32.2-45]	35 [33.5-44.7]	35 [31-44.5] $^{\blacktriangle}$

Table 11. Intraoperative hemodynamic data, desflurane concentrations and BIS value.

Table 11. Intraoperative hemodynamic data, desflurane concentrations and BIS values. Systolic blood pressure (SBP); diastolic blood pressure (DBP); heart tae (HR); end-tidal desflurane concentrations (ET Desf); Bispectral index (BIS). C = control group; L = lidocaine group. (T_0) arrival in the operating block; (T_p) beginning of the pneumoperitoneum; 15 min after the beginning of the pneumoperitoneum (T_1), 30 min after the beginning of the pneumoperitoneum (T_2), 45 min after the beginning of the pneumoperitoneum (T_3), 60 min after the beginning of the pneumoperitoneum (T_1). * group L compared to group C, $p < 0.0001$; ** group L compared to group C, $p = 0.04$; $^{\Delta}$ in group L, T_0 compared to T_p, $p < 0.0001$. † group L compared to group C, $p = 0.0018$; †† group L compared to group C, $p = 0.018$; $^{\blacktriangle}$ group L compared to group C, $p = 0.02$. Values are presented as median [interquartile range]. *P* values are calculated with Mann-Whitney-U test.

n (%)	Age	Sex (F/M)	ASA	BMI kg/m^2	N attacks/ last month	VRS	Baseline HR(bpm)	Beta-blocker (mg)	Fentanyl in PACU (μg)	Fentanyl/kg in PACU (μg)
C: 3 (6.5)										
1	50	M	2	19.5	4	7	80	Propranolol (0.5)	125	2.1
2	38	F	1	23.4	25	10	87	Labetalol (5)	175	2.5
3	43	F	2	38.3	2	5	72	Propranolol (1) Labetalol (30)	25	0.2
HR (T_0)							**79.7 ± 7.5**			
L: 8 (18.2)										
1	42	F	1	25.6	4	4	92	Propranolol (1)	50	0.8
2	59	F	2	23.8	3	5	70	Propranolol (1)	125	2
3	45	F	1	23	4	3	85	Labetalol (5)	75	1.2
4	28	M	2	22.8	0	0	95	Propranolol (0.5)	75	0.8
5	18	F	2	29.4	6	10	68	Propranolol (0.5)	100	1.2
6	47	F	1	22.2	0	0	106	Propranolol (0.5)	150	2.5
7	41	M	2	29.9	4	10	95	Labetalol (10)	50	0.5
8	63	F	2	24.9	4	10	74	Labetalol (5)	175	3.1
HR (T_0)							**85.7 ± 13.7**			

Table 12. Descriptive table of patients who required iv beta-blockers to maintain HR and BP ± 20 % of baseline value.

Table 12. Descriptive table of patients who required iv beta-blockers to maintain HR and BP ± 20 % of baseline value. Values are presented as absolute numbers (percenteges), median [interquartile range] or mean ± standard deviation. P values are calculated with Pearson χ^2 test to compare the number of patients who received beta-blockers and with Mann-Whitney-U test to compare fentanyl consumption in the PACU. ASA =American Society of Anesthesiologists; BMI = Body mass index; VRS = Verbal Rating Scale; N attacks = number of pain colic attacks in the last month.

	Fentanyl in PACU (μg)	P
Median Fentanyl consumption in PACU (μg)		
group C + L (n= 90)	100 [50-100]	p =0.56
group C + L, patients who received beta-blockers (n =11)	75 [50-125]	
Median Fentanyl consumption in PACU (μg)		
group L (n= 44)	112.5 [75-150]	p = 0.23
group L, patients who received beta-blockers (n =8)	75 [62.5112]	

Table 13. Median fentanyl consumption in PACU, of patients who required iv beta-blockers. to maintain HR and BP ± 20 % of baseline value. Values are presented median [interquartile range]. P values are calculated with Mann-Whitney-U test to compare fentanyl consumption in the PACU.

Figures (1-5)

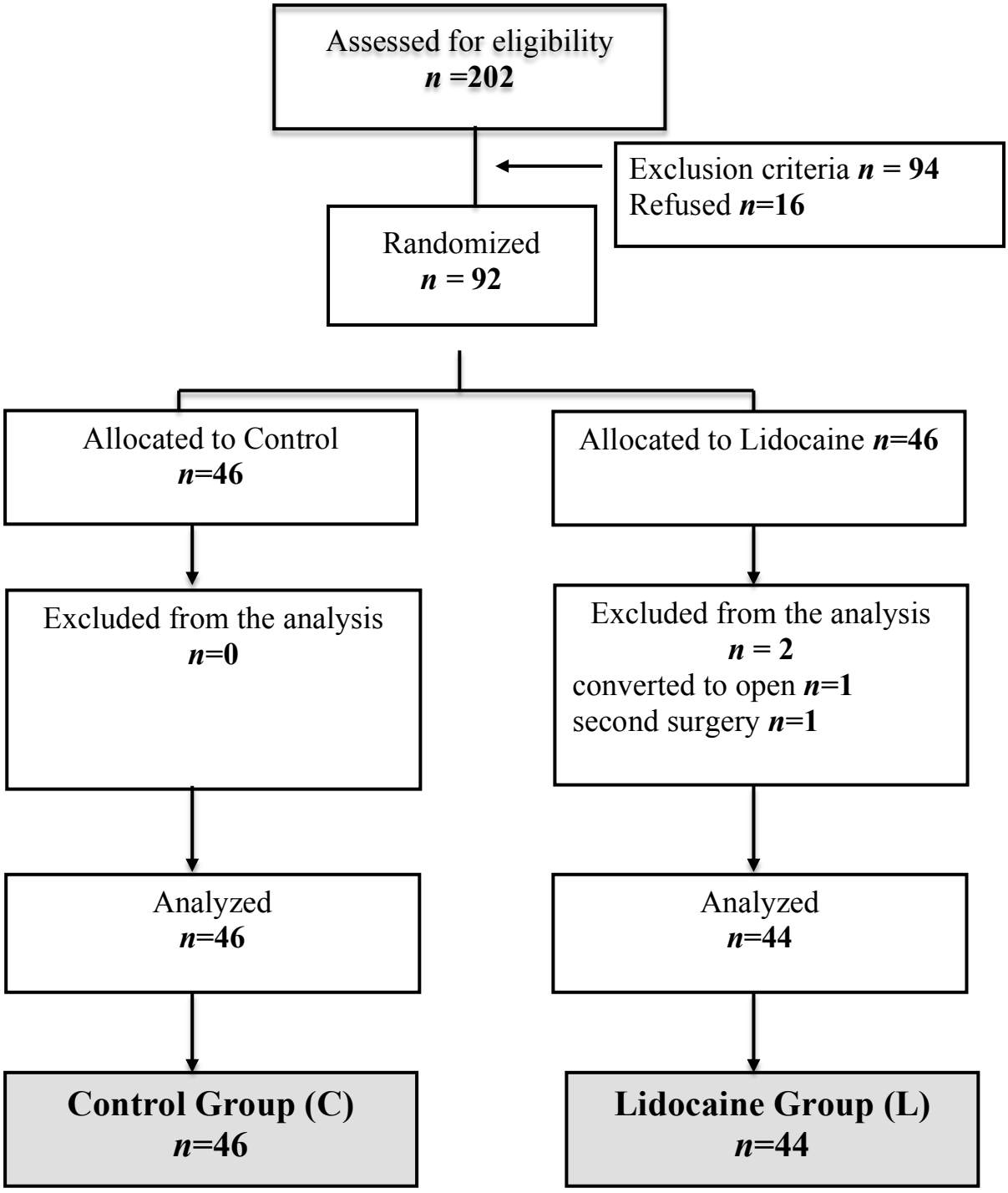

Figure 1. Consort diagram.

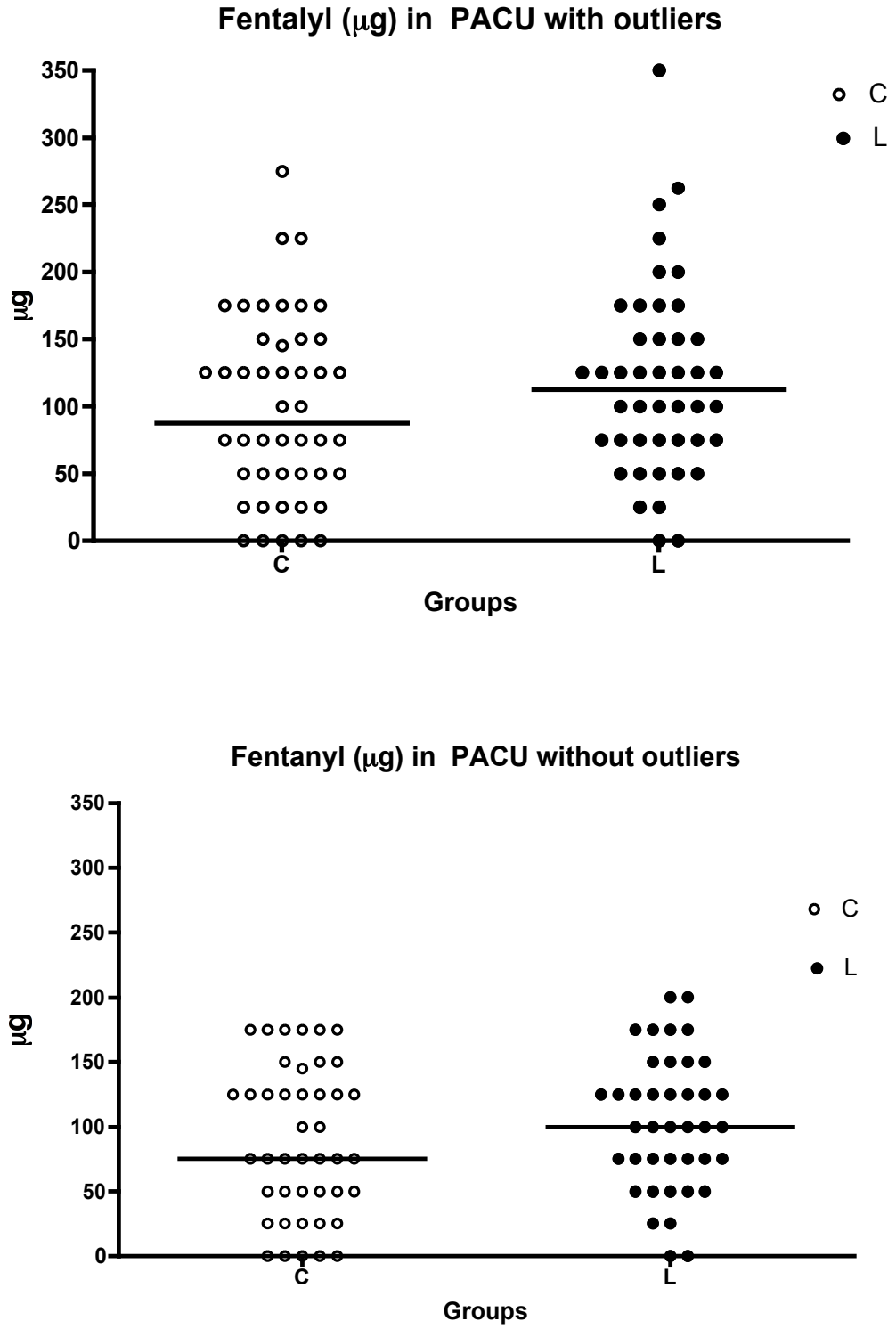

Figure 2. Fentanyl consumption in post-anesthesia care unit (PACU) with and without outliers' values (n = 3 in the group C, n=4 in the Group L). Bars represent median values. P values are calculated Minn-Whitney-U test.

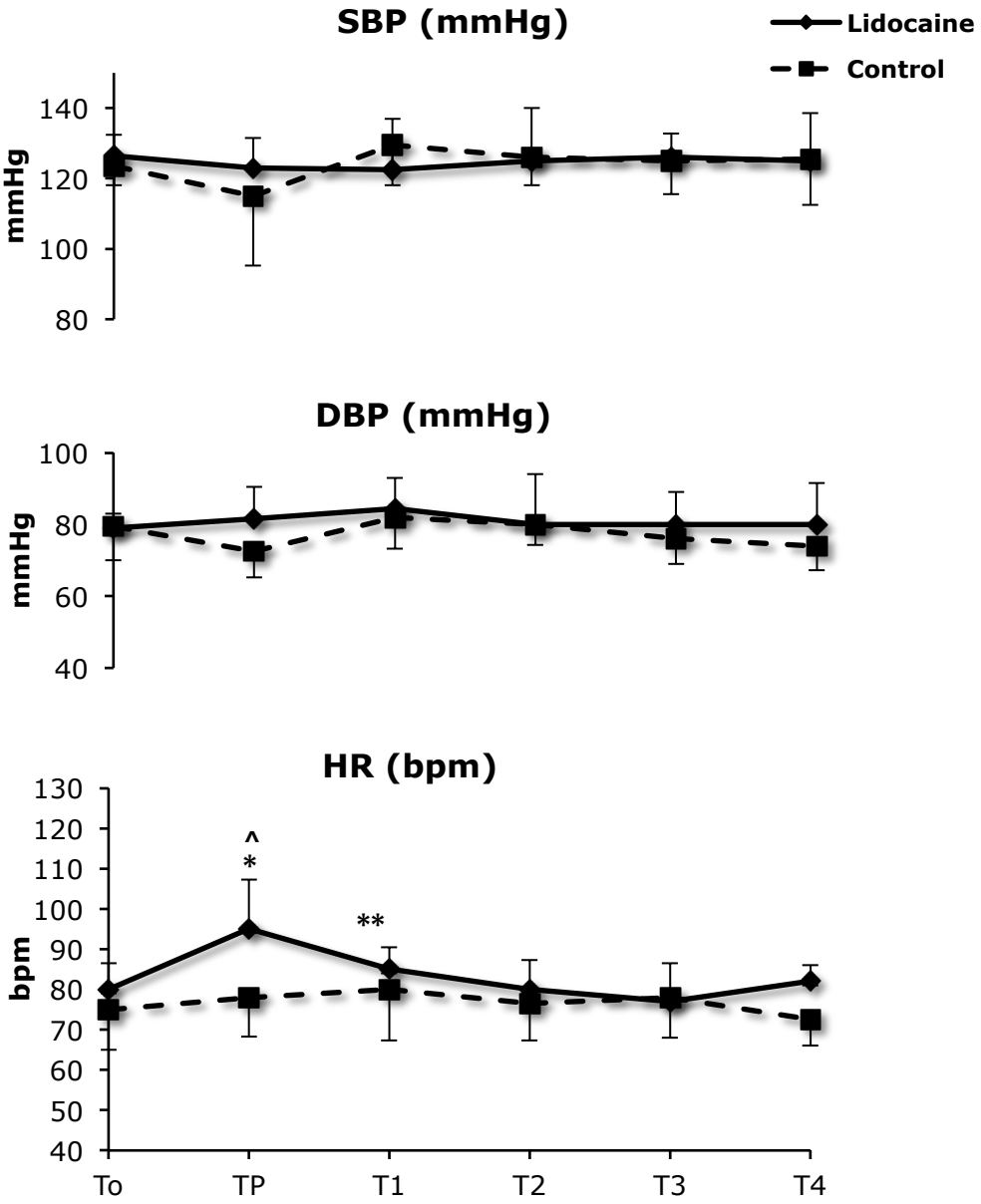

Figure 3. Systolic blood pressure (SBP) (mmHg), diastolic blood pressure (DBP) and heart rate (HR) in the control and in the lidocaine group during the surgery. T_0 = baseline; T_p = beginning of the pneumoperitoneum; T_1 = 15 minutes from the beginning of the pneumoperitoneum; T_2 = 30 from the beginning of pneumoperitoneum; T_3 = 45 from the beginning of pneumoperitoneum; T_4 = 60 minutes from the beginning of Pneumoperitoneum. * $p < 0.0001$, T_p control compared to T_p lidocaine; ** $p = 0.04$, T_1 control compared to to T_1 lidocaine; ^ $p < 0.0001$ T_P lidocaine compared to T_0 lidocaine.

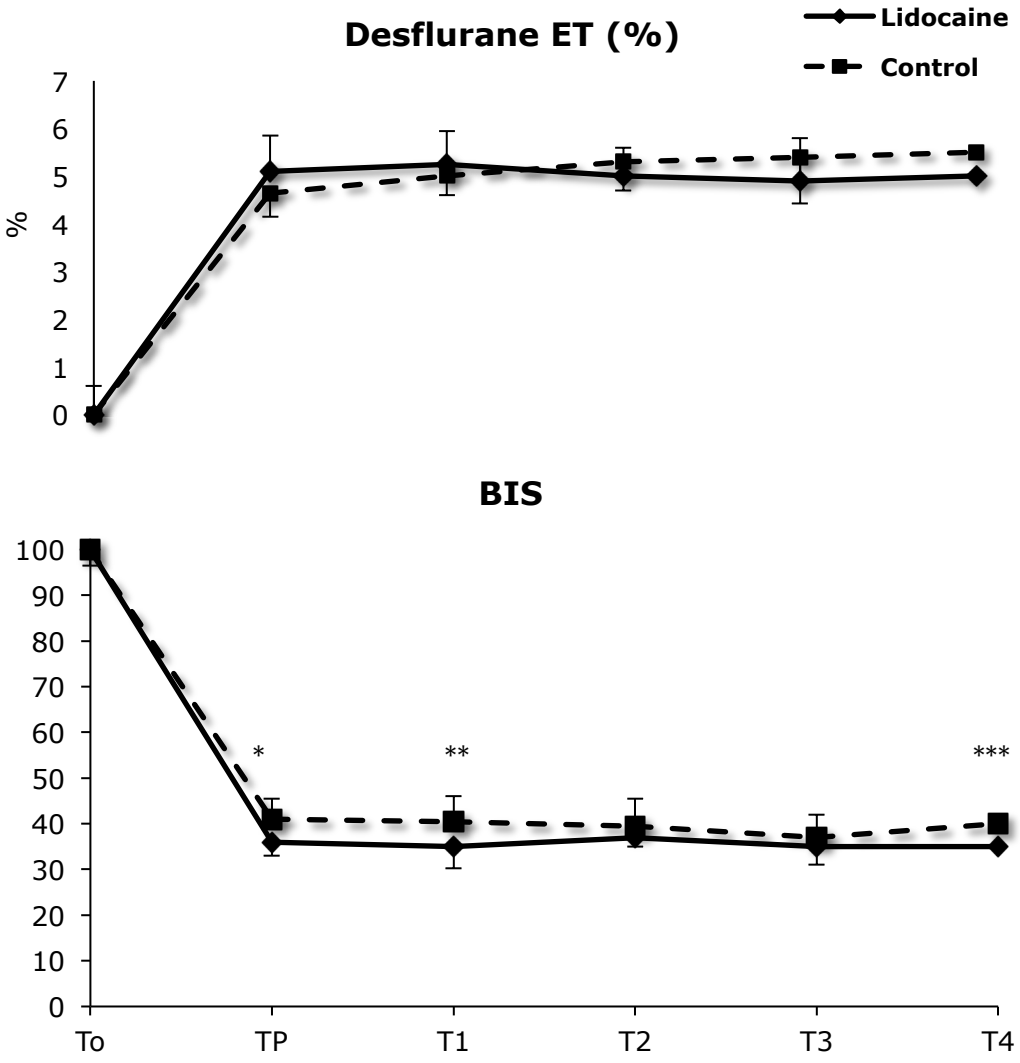

Figure 4. End Tidal desflurane concentration (Desflurane ET) (%) and BIS values in in the control and in the lidocaine group during the surgery. T_0 = baseline; T_p = beginning of the pneumoperitoneum; T_1 = 15 minutes from the beginning of the pneumoperitoneum; T_2 = 30 from the beginning of pneumoperitoneum; T_3 = 45 from the beginning of pneumoperitoneum; T_4 = 60 minutes from the beginning of pneumoperitoneum. * p = 0.0018, T_p control compared to compared to T_p lidocaine; ** p =0.0018, T_1 control compared to to T_1 lidocaine; *** p =0.02 T_4 control compared to T_4 lidocaine.

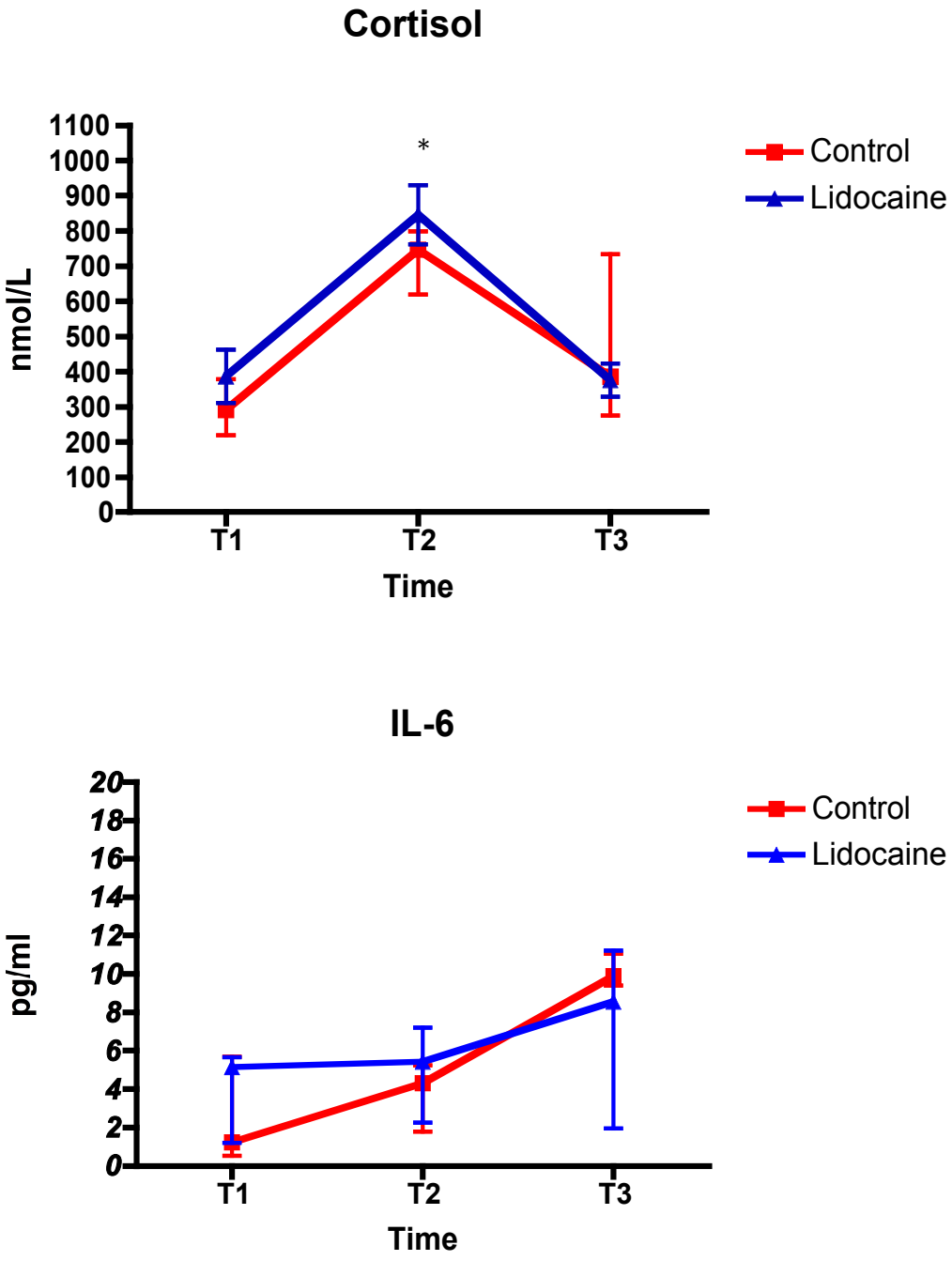

Figure 5. Plasma cortisol and IL-6 concentrations. T_1 = arrival in the operating room; T_2= end of the surgery (skin closure); T_3 = hospital discharge. * *p =0.04.*

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