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Original Research

Effect of perioperative intravenous lidocaine infusion on postoperative recovery following laparoscopic Cholecystectomy-A randomized controlled trial

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HIGHLIGHTS

- Perioperative intravenous lidocaine is an effective adjunct for pain management after laparoscopic surgery.
- Perioperative intravenous lidociane improves the postoperative recovery profile.
- Perioperative intraveous lidocaine attenuates initiation of the excessive inflammatory response.

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ABSTRACT

Background and objective: Intravenous lidocaine infusion has been shown to facilitate postoperative recovery after major abdominal surgery. The current randomized controlled study was performed to assess the effect of perioperative intravenous lidocaine infusion on pain intensity, bowel function and cytokine response after larparoscopic cholecystectomy.

Methods: Eighty patients undergoing laparoscopic cholecystectomy were randomly allocated to receive intravenous lidocaine (bolus injection of 1.5 mg/kg lidocaine at induction of anesthesia, then a continuous infusion of 2 mg/kg/h until the end of surgery) or an equal volume of saline. Patients, anesthesiologists, and study personnel were blinded, and anesthesia and multimodal perioperative analgesia were standardized. Blood cytokines were measured at scheduled times within 48 h. Pain scores, opioid consumption, time to first flatus and time to first bowel movement were also measured after surgery.

Results: Seventy-one of the 80 patients who were recruited completed the study protocol. Patient demographics were similar in the two groups. Lidocaine significantly reduced pain intensity [visual analogue scale (VAS), 0–10 cm] at 2 h (lidocaine 3.01 ± 0.65 cm vs. placebo 4.27 ± 0.58 cm, $p = 0.01$) and 6 h (lidocaine 3.38 ± 0.42 cm vs. placebo 4.22 ± 0.67 cm, $p = 0.01$) and total fentanyl consumption 24 h after surgery (lidocaine 98.27 ± 16.33 μg vs. placebo 187.49 ± 19.76 μg, $p = 0.005$). Time to first flatus passage (lidocaine 20 ± 11 h vs. placebo 29 ± 10 h, $p = 0.01$) and time to first bowel movement (lidocaine 41 ± 16 h vs. placebo 57 ± 14 h, $p = 0.01$) were also significantly shorter in patients who received lidocaine. Intravenous lidocaine infusion experienced less cytokine release than the control group.

Conclusions: This study indicates that perioperative systemic lidocaine improves postoperative recovery and attenuates the initiation of excessive inflammatory response following laparoscopic cholecystectomy.

1. Introduction

Laparoscopic cholecystectomy (LC) is one of the common ambulatory surgeries. Pain remains a significant factor to delay postoperative recovery and discharge from the day-surgery unit,

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leading to unanticipated hospital admission [1]. Unfortunately, pain is considered to be inadequately treated in one-half of such surgical procedures [2,3].

Opioids remain as the mainstay for postoperative pain management in this patient population. However, opioids administration can exacerbate postoperative ileus and further delay patient recovery. Multimodal approaches and adjunctive therapies are thereby recommended for pain control after abdominal surgery, in order to reduce opioid consumption and opioid-related adverse effects. Intravenous lidocaine has been used perioperatively as an adjuvant to treat pain; it was associated with a significant opioid-sparing effect, earlier return of bowel function, and shorter hospital stay after surgery [4–10]. Our previous meta-analyses [11] and most recent systematic review [12] suggested perioperative systemic lidocaine may promote postoperative recovery after abdominal surgery. It was considered that intravenous lidocaine infusion may attenuate IL-8, IL-6 and IL-1ra production and accelerate the recovery of bowel function following open abdominal surgery [13–18]. However, the beneficial effects of perioperative intravenous lidocaine infusion for postoperative recovery after LC and the role of anti-inflammatory properties of lidocaine needed be further studied. Therefore, we performed the current randomized, double-blinded, placebo-controlled study to assess the effects of intravenous lidocaine infusion on postoperative pain intensity, bowel function and cytokine response.

2. Materials and methods

This randomized, blinded placebo-controlled trial (registered at Clinicaltrials.gov) follows the CONSORT statement for reporting the results of randomized trials. This study was conducted in a tertiary, university affiliated hospital between December 2015 and December 2016. After obtaining written informed consent and ethical committee approval, adult patients of age between 18–65 years, with American Society of Anesthesiologists (ASA) physical status I-III, undergoing LC under general anesthesia were enrolled. Patients with severe underlying cardiovascular disease, impaired kidney or liver function, history of drug or alcohol abuse, history of chronic pain or daily intake of analgesics, uncontrolled medical disease (diabetes mellitus and hypertension), history of intake of non-steroidal anti-inflammatory drugs within 24 h before surgery, and the inability to operate a patient-controlled intravenous analgesia (PCIA) device were excluded from the study.

Using the computer generated codes maintained in sequentially numbered opaque envelopes patients were randomly allocated to either lidocaine infusion (L) or saline placebo control group (C). An independent anesthesiologist, who was not involved in the study, was assigned to open the sealed opaque envelope that contained the patient allocation and instructions for the solution preparation. Then, the preparations for the bolus and continuous infusion were arranged by the anesthesiologist who read the card. Lidocaine or normal saline (placebo) was prepared in a syringe that was only labeled with a case number, in order to keep the anesthesiologist "blind" from the patients assigned in each group. The study participants and all perioperative care staff were blinded to the treatment assignments. Two minutes before tracheal intubation, patients in the lidocaine infusion group received IV bolus injection of lidocaine (1.5 mg/kg slowly over 10 min) 30 min before the skin incisions followed by a continuous IV infusion at the rate of 2 mg/kg/h via infusion pump (B-BRAUN) whereas the patients in the saline group received 0.9% normal saline in equal volume and in the same manner. The infusion was continued throughout the surgery and terminated at the end of surgery. Local anesthetic in any form was not given throughout the surgery.

All anesthetic procedures were performed in a standardized fashion. On arrival in the operation theatre, on the day of surgery, peripheral venous access was secured in all the patients with 16G intravenous cannula on the dorsum of left hand. Patients were connected to the patient monitor for monitoring ECG, pulse rate, noninvasive blood pressure (NIBP), and pulse oximetry. Before induction, all patients received 0.5 mg of atropine and 5 mg of dexamethasone. General anesthesia was intravenously induced using 0.02 mg/kg of midazolam, 2–3 μg/kg of fentanyl, 1.5–2 mg/kg of propofol, and 0.2 mg/kg of *cis*-atracurium. Anesthesia was maintained with sevoflurane and continuous infusion of remifentanil. Sevoflurane concentration was adjusted to keep the Bispectral Index of the encephalogram (BIS) within 40–60. Mean arterial pressure and heart rate were maintained within ±20% of baseline values by adjusting the speed of remifentanil infusion. Mechanical ventilation was controlled using a ventilator (Aestiva/5, Datex-Ohmeda, USA) and respiratory parameters were adjusted to keep end-tidal CO_2 at 35–45 mmHg. All patients were given a single intravenous dose of 4 mg of ondansetron as prophylaxis against postoperative nausea and vomiting. At the end of surgery, residual neuromuscular blockade was antagonized with 0.02 mg/kg of neostigmine and 0.01 mg/kg of atropine. The trachea was extubated once the patient regained consciousness and the patients were transferred to the post-anesthesia care unit (PACU).

Patients in both groups were postoperatively treated with patient-controlled intravenous analgesia (PCIA). One day before the surgery, all patients were instructed on how to use the patient controlled intravenous analgesia (PCIA) pump and rate pain intensity on a 10-cm visual analog scale (VAS), identifying 0 as "no pain" and 10 as "worst imaginable pain." In addition, each patient was requested to record the first appearance of flatus and defecation after surgery. On arrival to the post-anesthesia care unit (PACU), patients from both groups were connected to a fentanyl-PCIA pump. The PCIA mode was set at a bolus of 20 μg of fentanyl with a 10-min lockout interval, without basal infusion (a 100-mL total regimen with saline). The analgesic requirements for the first 24 h after operation were recorded.

Our primary endpoints were pain intensity and total opioid consumption after surgery as well as bowel function. Pain intensities were measured using a VAS at 2, 6 and 24 h after surgery. Opioid demand by PCA was monitored daily. The cumulative postsurgical consumption of opioid was recorded. To determine return of gastrointestinal motility, bowel sounds were auscultated and patients asked twice daily if first flatus and defecation had occurred. Nausea, vomiting, and lidocaine-related complications were recorded. Blood samples for the measurement of inflammatory cells were taken immediately before the induction of anesthesia, at the end of surgery, at 12 h postoperatively. Concentrations of plasma IL-1ra, IL-6 and IL-8 were determined in the culture medium of cells of the patient by bead based multiplex flow cytometry using a specific AimPlex multiplex assay kit, following manufacturer's instructions (QuantoBio, Beijing, China). The assay procedure included a 60-min antigen and capture antibody conjugated bead incubation step, followed by a 30-min biotinylated detection incubation step and a 20-min streptavidin-PE incubation step. Fluorescence signals of the sample beads were acquired using a flow cytometer (BD FACSCalibur), and results were analyzed using FCAP Array 3.0. Intraassay and interassay coefficients of variation were all less than 10% in each measurement. Cross reactivity with other factors was negligible.

3. Statistical analysis

Our sample size was calculated based on total opioid consumption at 24 h after the operation. According to our pilot study, 30 patients needed to be recruited in each group for the results to