Effects of Ketamine and Lidocaine Infusion on Acute Pain after Elective Open Abdominal Surgery, a Randomized, Double-Blinded Study

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Abstract
   Background: Most patients suffer from moderate to severe pain after elective laparotomy. They often require opioids to alleviate their pain. Opiates invariably induce certain side effects and, occasionally, dependence. Intraoperative infusion of lidocaine and low-dose ketamine reduces postoperative pain and analgesic requirements. This study aims to evaluate the effects of simultaneous infusion of lidocaine and ketamine during open abdominal surgery on the postoperative pain severity and analgesic consumption.
   Methods: In this randomized, double-blinded, single-center study that was performed in Iran, 80 patients scheduled for elective open abdominal surgery under general anesthesia were enrolled in two LK and P groups. Group LK (n=40) received lidocaine-ketamine infusion, and group P (n=40) received placebo (normal saline). Both infusions were started thirty minutes after initiation of surgery and were terminated once the surgery was completed. For postoperative pain management, patient-controlled analgesia (PCA), including fentanyl and paracetamol, was administered for both groups. All patients were evaluated for pain visual analogue scale (VAS) and total adjunctive analgesic (diclofenac suppository) consumption within the first 24 hours after the surgery. The data were analyzed using SPSS. *P values* <0.05 were considered significant.
   Results: Intraoperative infusion of Lidocaine and Ketamine resulted in desirable postoperative pain control. Patients of LK group demonstrated a significant reduction in the pain score at 1, 6, 12, 18, and 24 hours after termination of surgery ($p<0.001$). It also resulted in a decreased requirement for postoperative analgesics, as cumulative analgesic consumption was decreased meaningfully in the patients of LK group ($p<0.001$).
   Conclusion: Intravenous infusion of lidocaine and ketamine during elective open abdominal surgery reduces pain intensity and analgesic requirements in the first 24 hours postoperatively, without major additional side effects.

Keywords: Ketamine, Lidocaine, Pain, Laparotomy

Introduction

   Most patients undergoing elective open abdominal surgery experience moderate to severe postoperative pain secondary to tissue damage and the release of inflammatory mediators. Pain results in an early decrease in mobility especially the inability to walk. In part, inability to mobilize imposes serious side effects such as pulmonary atelectasis an d thrombosis, myocardial ischemia, and cardiac arrhythmia (1, 2).

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↑*What is "already known" in this topic:*
Postoperative pain management is one of the most challenging issues for clinicians. Although opioids are the most commonly used for this points, its side effects limit their use in some cases. For this purpose, adjuvant and alternative non-opioid drugs have been studied.

→*What this article adds:*
Ketamine and lidocaine are non-opioid drugs that have some analgesic effects. The combination of these two drugs, without the side effects of opioids, may have appropriate analgesic effects for postoperative pain after abdominal surgeries.

The major aims of postoperative pain control are: (I) provide an adequate level of satisfaction, (II) earlier mobilization, (III) accelerated rehabilitation, and (IV) reduce pain complications and side effects by providing optimal perioperative analgesics (2, 3).

Opioids remain the mainstay of pain reduction because they afford profound analgesic effects. Unfortunately, the price we pay for this efficacy in pain relief is a plethora of unpleasant short-term and long-term side effects, including respiratory depression, hypotension, sedation, nausea and vomiting, urinary retention, and ileus(4-6). Besides aforementioned complications, intraoperative use of opioid analgesics may lead to opioid-induced hyperalgesia, a condition associated with the faster return of severe acute postoperative pain, resulting in a gradually escalating requirement for opioid analgesics (7).

Non-opioid analgesics, such as ketamine and lidocaine, are less effective than opioids in pain reduction but are safer and less prone to abuse (2). Lidocaine has anti-inflammatory effects by blocking the voltage-gated sodium channels, leading to a decrease in pain sensation (3, 8). Ketamine has both analgesic and anti-inflammatory effects achieved by blocking N-methyl-D-aspartate (NMDA) receptors and decreasing IL-6 release respectively, leading to a decrease in pain sensation (9, 10). Ketamine may have some adverse effects such as psychiatric symptoms and cardiovascular problems; however, in some studies, its low dose has been shown to have no significant side effects during the postoperative period (11, 12).

Because of these characteristics, some clinical trial studies demonstrated that intravenous infusion of lidocaine alone or low-dose ketamine alone during surgery has effects on reducing postoperative pain and opioid consumption (13-15). Besides analgesic effects, infusion of Ketamine during surgery as add on to regular anesthesia protocols may also improve hemodynamic stability (16).

In this study, the main purpose is to evaluate the effects of simultaneous intravenous infusion of lidocaine and ketamine during elective open abdominal surgery on postoperative pain and analgesic requirement.

Methods

After obtaining approval from the Institutional Ethics Committee (Ethics code: 105/2891/d), and registration with the Iranian Registry of Clinical Trial (clinical trial registration code: IRCT2017071935187N1), eighty patients were enrolled in this single-center, randomized, placebo-controlled, and double-blinded study.

We used Altman's nomogram for sample size calculation taking consideration of previous studies and power of 80%. After obtaining informed consent, the patients were randomly divided into two groups, LK and P groups using a computer-generated random number table. Group LK (n=40) received lidocaine-ketamine infusion, and group P received placebo (normal saline). For double-blinding, the researchers who were responsible for loading the infusion syringes and recording the data were blinded to the type of groups.

The inclusion criteria were elective open abdominal surgery, general anesthesia, age between 20 and 60 years, ASA I, and II. The exclusion criteria were uncontrolled underlying medical conditions; emergency abdominal surgery; significant renal, hepatic, or psychiatric disease; sensitivity to lidocaine or ketamine; opioid or alcohol abuse; and patient refusal. General anesthesia was performed using identical protocols for all patients in both groups (induction including fentanyl, propofol, and atracurium; and maintenance by isoflurane, atracurium, remifentanil).

In the LK group, 30 minutes after the start of the surgery, patients received an intravenous infusion of lidocaine and ketamine 0.5 mg/kg/hr. The infusion syringe pump contained both lidocaine and ketamine in one 50 ml syringe (including lidocaine and ketamine 1 mg/ml). The infusion was ceased once the surgery was complete. Patients in the P group only received equal volumes of 0.9% saline as in the LK protocol throughout surgery as a placebo. After surgery, the patients were monitored for one hour in the recovery room. For the first 24 hours of postoperative pain management, both groups received intravenous continuous 4 ml/h infusions by patient-controlled analgesia pump including fentanyl and paracetamol (each ml including fentanyl 5 µg and paracetamol 20 mg).

The pain score was recorded at 1, 6, 12, 18, and 24 hours postoperative by means of VAS, consisting of a 10 cm line with zero indicating "no pain" and 10 indicating "the worst pain". In the surgical wards, if VAS was more than three, patients received a diclofenac suppository (50 mg), with the maximum dose of 150 mg/day. Twenty-four hours postoperatively, the PCA pump was removed and the total amount of diclofenac suppository requested by the patient was recorded. In the first twenty-four hours postoperative, we evaluated the patients for the major side effects including hemodynamic (blood pressure and pulse rate) and respiratory changes, dizziness, seizure and hallucination.

Statistical analysis

For statistical analysis, we used Statistical Package for the Social Sciences (SPSS, version 22.0, Chicago, IL, USA). The data were expressed as mean and standard deviation. For intra-group comparisons, we used t-test and Mann-Whitney test for parametric and nonparametric values, respectively. In addition, the Chi-square test and Fisher's exact test were performed when appropriate and $p<0.05$ was considered as statistically significant.

Results

Eighty patients were enrolled in the present study by consideration of the inclusion and exclusion criteria. All the patients finished the study and were followed up to determine if there was any complication. Figure 1 demonstrates the CONSORT flow diagram for the selection of patients and their follow up. In this study 71.25% of the patients were female (n=57), and 28.75% were male (n=23). The mean age was 46.68 (±12.02) and 47.80 (±10.59) years in the patients of LK and P groups, respectively. The mean body mass index (BMI) was 26.38
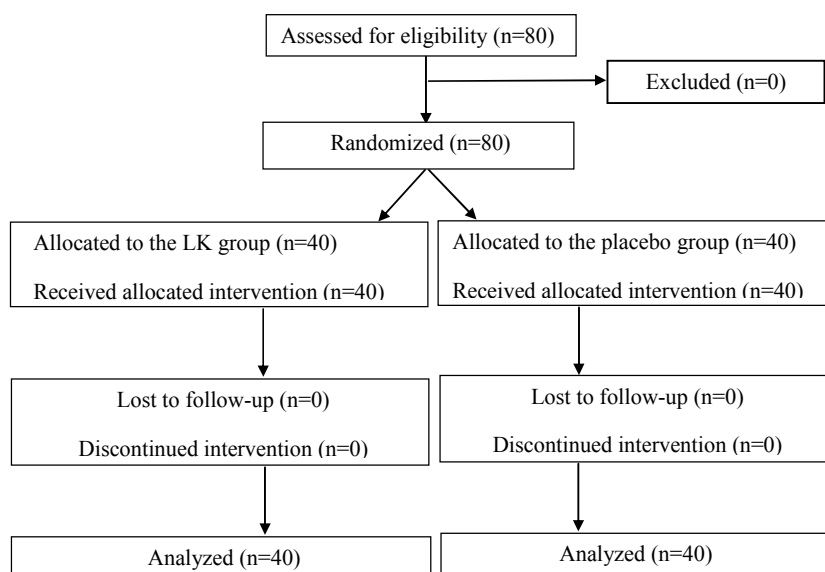
Fig. 1. CONSORT flow diagram

(±2.58) and 25.47 (±2.55) kg/m² in the patients of LK and P groups, respectively. Total abdominal hysterectomy and splenectomy were the most and the least frequently performed types of surgery, respectively. There was no significant difference in age (*p*=0.658), gender (*p*=0.461), BMI (*p*=0.121) and type of surgery (*p*=0.962) between the two groups (Table 1). In the first 24 hours postoperatively, no significant complication was reported by the patients or by evaluations performed by the researchers in either of groups.

Evaluation of VAS pain severity revealed that pain score was decreased significantly one hour (t=1hr) after surgery in the patients of the LK group in comparison with the patients of the P group (*p*<0.001). In addition, at the 6, 12, 18, and 24 hours (t=6, 12, 18 & 24) postoperative,

the difference in pain severity between the two groups was significant (*p*<0.001). Consecutive measurements demonstrated that pain severity decreased gradually in the patients of both groups. In the first postoperative 24 hours, all patients used their PCA pump completely. Some patients in both groups required additional analgesics (diclofenac suppositories). The sum of diclofenac suppository consumption during the first postoperative 24 hours was decreased significantly in the patients of the LK group in comparison with the patients of the P group (*p*<0.001). Table 2 shows pain severity data at the assigned times as well as diclofenac suppository consumption. No psychotomimetic side effects were observed in this study.

Table 1. Distribution of age, BMI, gender, and type of surgery

Variable	LK group (n=40)	P group (n=40)	*p*
Age (mean ± SD)	46.68 ± 12.02	47.80 ± 10.59	0.658
BMI (mean ± SD)	26.38 ± 2.58	25.47 ± 2.55	0.121
Female	30 (75%)	27 (67.5%)	
Male	10 (25%)	13 (32.5%)	0.461
TAH	21 (52.5%)	19 (47.5%)	0.962
Gastrectomy	8 (20%)	7 (17.5%)	
Colectomy	5 (12.5%)	7 (17.5%)	
Cholecystectomy	4 (10%)	5 (12.5%)	
Splenectomy	2 (5%)	2 (5%)	

BMI: Body Mass Index; TAH: Total Abdominal Hysterectomy

Table 2. Postoperative pain score and analgesic consumption

Variable		LK group (mean ± SD)	P group (mean ± SD)	*P*
Pain score (VAS)	1 h	4.88 ± 1.26	7.93 ± 1.18	<0.001
	6 h	4.05 ± 1.26	7.05 ± 0.98	<0.001
	12 h	3.43 ± 0.98	5.85 ± 1.14	<0.001
	18 h	2.78 ± 0.97	5.03 ± 1.14	<0.001
	24 h	2.18 ± 0.90	4.00 ± 0.81	<0.001
Total diclofenac consumption (mg)		35.00 ± 28.19	97.50 ± 25.19	<0.001

VAS: Visual Analogue Scale

Discussion

Great inflammatory provocation after tissue dissection in laparotomy surgeries compels postoperative pain control as a major role on decision about safe discharge of patients after surgery. Due to notorious side effects and dependency of opioid analgesics, it is important to consider non-opioid adjuvants to control the postoperative pain. Postoperative pain control has a tremendous effect on patient's satisfaction, hospital discharge, returning to normal life, and prevention of future dependence on opioid analgesics. On the other hand, effective role of Lidocaine or Ketamine alone on postoperative pain management is controversial. Hence, it is important to research for newer pain control strategies, e.g. simultaneous use of desired dose of analgesic medications. The present study demonstrated that concurrent intravenous infusion of lidocaine and ketamine during elective open abdominal surgery significantly decreases pain score in the first 24 hours postoperatively. Attenuated pain sensation produced by anti-inflammatory effects from receptor blockade or reduced release of inflammatory mediators leads to decrease in analgesic requirement by the patients of the LK group in comparison to the placebo control group.

Having a plan for improving postoperative pain control is important especially for the safety and satisfaction of the patients and for preventing outpatient misuse of opioids, which is progressively becoming a universal concern.

Different routes of analgesic administration, such as oral, regional, epidural, intravenous, and multimodal synergistic non-opioid analgesics need to be considered to relieve pain after medical interventions and surgery and to decrease consumption and dependence on narcotic analgesics (17-21).

Continuous intraoperative infusion and, possibly, a pre-incisional dose of low dose ketamine leads better mood and increased calmness, besides decreasing pain severity after abdominal surgery (22). Diminished postoperative shivering and nystagmus are other features of low dose ketamine infusion, as demonstrated in a study in elective abdominal hysterectomy (23). A review study of thirty-seven trials concluded that, in addition to pain reduction, decreasing nausea, vomiting, and morphine requirements in the first 24 hours postoperatively are some other advantages of perioperative infusion of sub-anesthetic dose of ketamine (24). Despite the beneficial effects of perioperative ketamine administration, our previous study showed that addition of ketamine to the patient controlled analgesia (PCA) pump containing fentanyl and acetaminophen might not have an additional role in relieving pain severity after abdominal surgery (25). Ultrasound-guided transversus abdominis plane (TAP) block after total abdominal hysterectomy also has no additional effect on decreasing postoperative pain (26). These two studies show that pain management in the postoperative period alone may be incompletely effective, i.e. a "closing the barn door after the horse has bolted" effect, and may even be ineffectual in relieving pain as opposed to taking preemptive measures while the surgical trauma is being inflicted.

Intraoperative lidocaine infusion may also diminish pain severity and length of hospital stay (27-29); on the contrary, another study does not verify these findings (30). Tikuisis et al concluded that in patients who need colon surgery, perioperative infusion of lidocaine leads to decrease in postoperative pain as well as time to restoration of normal bowel function (31). The vasodilator feature of lidocaine use also helps to relieve acute ischemic pain and enhance tissue healing. In a case report of abdominal arterial occlusion, the researchers concluded that continuous infusion of lidocaine and nitroglycerine significantly decreases pain intensity for up to 48 hours (32).

Many studies concluded that intraoperative infusion of lidocaine or low-dose ketamine decreases postoperative opioid requirement (14, 15, 33). Other studies have not always verified these findings, e.g. in a study by Grady et al, neither ketamine nor lidocaine reduces postoperative pain, nausea, vomiting and opioid consumption following abdominal hysterectomy (13).

In those receiving regional block to permit surgery, the effects of these medications (lidocaine, ketamine) may be different e.g. in a study on the regional axillary block for upper limb surgery, the researchers concluded that the effects of fentanyl as an adjuvant to lidocaine surpasses ketamine plus lidocaine in decreasing pain and request for analgesics after surgery (21).

Conclusion

In conclusion, the simultaneous infusion of ketamine and lidocaine during elective open abdominal surgery leads to significant reduction of pain severity and analgesic consumption after surgery. Reduction in the pain severity at different postoperative periods is due to the passage of time and positive effect of analgesic; the difference in pain severity between the two groups is attributable solely to the desirable analgesic qualities of intravenous lidocaine and ketamine intraoperatively.

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Conflict of Interests

The authors declare that they have no competing interests.

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