Original Article

A comparison between intravenous lidocaine and ketamine on acute and chronic pain after open nephrectomy: A prospective, double-blind, randomized, placebo-controlled study

ABSTRACT

Background: Recently, there has been increasing interest in the use of analgesic adjuncts such as intravenous (IV) ketamine and lidocaine.

Objectives: To compare the effects of perioperative IV lidocaine and ketamine on morphine requirements, pain scores, quality of recovery, and chronic pain after open nephrectomy.

Study Design: A prospective, randomized, placebo-controlled, double-blind trial.

Settings: The study was conducted in Charles Nicolle University Hospital of Tunis.

Methods: Sixty patients were randomly allocated to receive IV lidocaine: bolus of 1.5 mg/kg at the induction of anesthesia followed by infusion of 1 mg/kg/h intraoperatively and for 24 h postoperatively or ketamine: bolus of 0.15 mg/kg followed by infusion of 0.1 mg/kg/h intraoperatively and for 24 h postoperatively or an equal volume of saline (control group [CG]).

Measurements: Morphine consumption, visual analog scale pain scores, time to the first passage of flatus and feces, postoperative nausea and vomiting (PONV), 6-min walk distance (6MWD) at discharge, and the incidence of chronic neuropathic pain using the "Neuropathic Pain Questionnaire" at 3 months.

Results: Ketamine and lidocaine reduced significantly morphine consumption (by about 33% and 42%, respectively) and pain scores compared with the CG ($P < 0.001$). Lidocaine and ketamine also significantly improved bowel function in comparison to the CG ($P < 0.001$). Ketamine failed to reduce the incidence of PONV. The 6 MWD increased significantly from a mean ± standard deviation of 27 ± 16.2 m in the CG to 82.3 ± 28 m in the lidocaine group ($P < 0.001$). Lidocaine, but not ketamine, reduced significantly the development of neuropathic pain at 3 months ($P < 0.05$).

Conclusion: Ketamine and lidocaine are safe and effective adjuvants to decrease opioid consumption and control early pain. We also suggest that lidocaine infusion serves as an interesting alternative to improve the functional walking capacity and prevent chronic neuropathic pain at 3 months after open nephrectomy.

Key words: Analgesia; chronic pain; ketamine; lidocaine; nephrectomy; recovery

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Introduction

Nephrectomy is one of the most common surgical procedures in urologic practice. Pain after surgery remains a significant clinical problem as it impairs rehabilitation and may lead to the development of chronic pain syndromes.[1] The open approach represents a major physical trauma including postoperative pain and discomfort in the convalescence period.[2]

Adequate control of postoperative pain facilitates earlier mobilization and rehabilitation.[3,4] In addition, effective postoperative analgesia is an important measure for the prevention of chronic surgical pain.[5]

Multimodal analgesia is an important concept to improve analgesia and reduce the incidence of opioid-related adverse events.[6]

Recently, there has been increasing interest in the use of analgesic adjuncts such as N-methyl-D-aspartate (NMDA) receptor antagonists (e.g., ketamine)[7] and systemic infusion of lidocaine.[8]

The aim of the present study was to evaluate and compare the effects of perioperative intravenous (IV) lidocaine and ketamine on postoperative morphine requirement, pain scores, quality of postoperative recovery, and chronic pain after elective open nephrectomy.

Methods

After approval of the Local Ethics Committee and written informed consent, 63 patients undergoing elective open nephrectomy were enrolled in this prospective, randomized, double-blind study. The trial was registered at ClinicalTrials.gov (NCT 02653651). Inclusion criteria were age ≥18 years and the American Society of Anesthesiologists (ASA) physical Class I or II. Exclusion criteria were known allergy to any of the study medications, an inability to understand the use of patient-controlled analgesia (PCA), renal (serum creatinine >2 mg/dl) or hepatic (alanine aminotransferase or aspartate aminotransferase >2 times normal) dysfunction, a severe cardiovascular disorder (ejection fraction <30%), ASA physical status ≥3, history of chronic pain, epilepsy, psychiatric disorders, chronic use of opioids or alcohol, and drug abuse.

Management protocol

The day before surgery, all participants received instructions on the use of the PCA device and the visual analog scale (VAS; ranging from 0 cm = no pain to 10 cm = worst possible pain).

All patients were premedicated with hydroxyzine 1 mg/kg orally, the night before surgery and 2 h before surgery. No prophylactic antiemetic was given.

General anesthesia was induced with propofol 2–3 mg/kg, fentanyl 3 μg/kg, cisatracurium 0.15 mg/kg and maintained by boluses of fentanyl 1 μg/kg every 30 min and inhaled sevoflurane 1 minimum alveolar concentration in 50% oxygen/air. Isotonic saline was infused at 5 ml/kg/h. Normothermia was maintained with a forced-air cover.

Patients were monitored using pulse oximetry, continuous electrocardiography, noninvasive blood pressure, end-tidal carbon dioxide (CO_2) and end-tidal sevoflurane concentration. Ventilation was adjusted to maintain the end-tidal CO_2 level at 35–40 mmHg.

The patients were randomly assigned to one of the three treatment groups using the sealed envelope method. A "blinded" nurse prepared the study solutions. None of the other investigators involved in patient management or data collection were aware of the group assignment. Lidocaine group (LG) received an IV lidocaine bolus of 1.5 mg/kg (0.075 ml/kg of lidocaine 2%) at the induction of anesthesia, followed by a continuous infusion of 1 mg/kg/h intraoperatively and for 24 h postoperatively. Ketamine group (KG) received an IV ketamine bolus of 0.15 mg/kg (0.075 ml/kg of solution of ketamine diluted to a concentration of 2 mg/ml in normal saline) at the induction of anesthesia, followed by infusion of 0.1 mg/kg/h intraoperatively and for 24 h postoperatively. The control group (CG) received an equal volume of normal saline 0.9%. The rate of infusion was similar for the three groups according to the patient's weight.

All patients received 1 g of IV paracetamol and 20 mg of IV nefopam 30 min before the end of the surgical procedure. After completion of the surgery, neuromuscular blockade was reversed with atropine 0.02 mg/kg and neostigmine 0.04 mg/kg, and patients were extubated when adequate spontaneous ventilation was established and were transferred to postanesthesia care unit (PACU).

In the PACU, pain was controlled by titration of IV morphine by a nurse (2 mg boluses every 5 min), if permitted according to the respiration rate (>10 bpm) and sedation score (score <1), until a VAS <3/10 cm had been achieved. The sedation score was as follows: 0 = no sedation; 1 = intermittent drowsiness; 2 = patient drowsy but

could be aroused verbally; 3 = impossible to arouse the patient verbally). Thereafter, patients were connected to a PCA device set to deliver 1 mg morphine as an IV bolus with a 7 min lockout interval. There was no basal infusion. The PCA regimen was continued for 24 h. In the surgical ward, additional postoperative analgesia was provided in three groups by the combination of the paracetamol (Perfalgan®, Bristol-Myers Squibb, Rueil-Malmaison, France) (1 g every 6 h) and nefopam IV (Acupan®, Biocodex, Gentilly, France) (20 mg every 8 h). IV ondansetron 4 mg was given on demand if patients complained of nausea or vomiting.

Primary outcome measures

The primary outcome of the study was the cumulative morphine consumption over 24 h PO. Consumption of morphine was recorded respectively, in the periods of 0–1 h (T1), 0–6 h (T2), 0–12 h (T3), 0–18 h (T4), and 0–24 h after operation (T5).

Secondary outcome measures

Predefined secondary outcomes were: number of patients requiring morphine titration in the PACU and dose of morphine administered; pain scores (0–10 cm) at rest and during coughing during 48 h; occurrence of opioid-induced side effects (sedation, nausea vomiting, and itching); hallucinatory effects of ketamine or signs of systemic toxicity of lidocaine such as perioral numbness and metallic taste. The recovery of bowel function was assessed by the time to first passage of flatus and feces and oral intake of clear fluids. Functional walking capacity was measured by the 6-min walk distance (6MWD) in the fourth postoperative morning.[9] For patients with length of stay <4 days, the 6 MWT was performed at discharge.

The duration of hospital stay was also recorded. At 3 months, patients were contacted by telephone and were questioned for chronic postoperative pain using the neuropathic pain 4 questionnaires. The Douleur Neuropathique 4 (DN4) questionnaire indicated neuropathic pain for patients with a score ≥4.[10]

Statistical analysis

Calculation of the sample size indicated that a minimum of 54 patients (18 per group) would be required to detect a 30% difference in morphine consumption between the interventional group (lidocaine or ketamine) and the CG for an α risk of 0.05 and a power of 80%, assuming a mean morphine consumption of 48 mg ± 16 in the CG based on a preliminary evaluation.

Statistical analysis was performed with SPSS for Windows version 15.0 (SPSS, Chicago, IL, USA). Data are expressed as a mean (standard deviation [SD]). The Chi-square test was used to assess differences between groups for categorical variables. Between-group comparisons were performed with ANOVA for parametric values or the Kruskal–Wallis test otherwise. $P < 0.05$ was considered to be statistically significant.

Results

A total of 63 patients were enrolled. Three patients were excluded: One patient because significant hemorrhage with hemodynamic instability (KG) and two cases (one in the CG and one in the LG) because of technical problems with the PCA device. Thus, 60 patients ($n = 20$ in each group) were included in the final analysis [Figure 1].

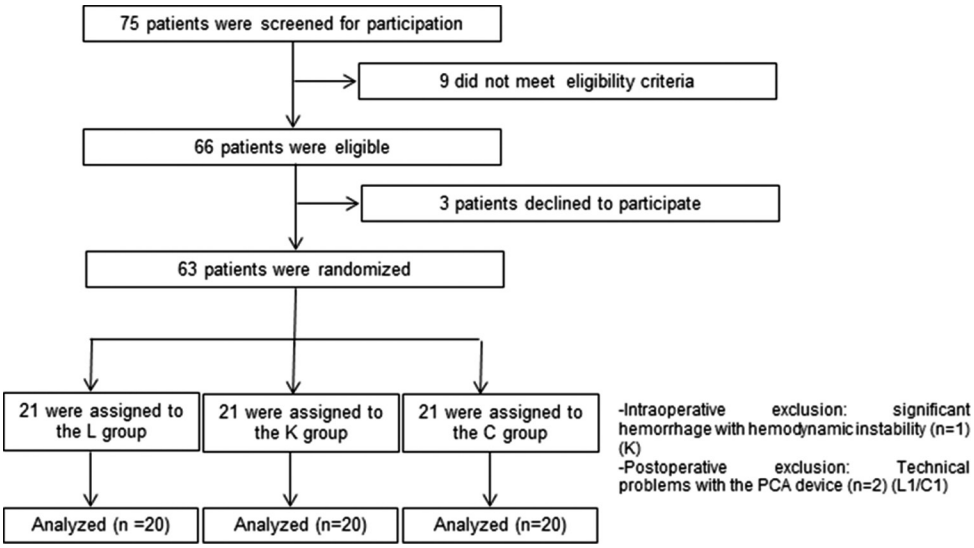

Figure 1: Trial flow chart. L: Lidocaine group, K: Ketamine group, C: Control group

The three groups were comparable with respect to age, height, body mass index, ASA physical status, and duration of surgery. Intraoperative fentanyl requirements were also comparable among groups [Table 1].

Morphine consumption and pain scores

The mean titrated dose of IV morphine in the PACU was significantly greater in the CG ($P < 0.001$). The mean ± SD cumulative morphine consumption for the 24 h after surgery was significantly decreased with lidocaine 27.8 ± 5.51 mg and ketamine 32 ± 6.99 mg compared with the CG 47.6 ± 4.98 mg [Figure 2]. During the first 48 h after surgery, the VAS pain scores at rest and during coughing and movement in LG and KG were significantly lower than CG [Figure 2].

Opioid-induced side effects

Sedation scores were similar among groups, and no patient had a score more than 1. No urinary retention was noted in three groups at bladder catheter removal. Compared to CG, IV lidocaine infusion significantly reduced the incidence of postoperative nausea and vomiting (PONV) (no patients experienced PONV in LG (0/20) in comparison to 15 patients in CG (75%); $P < 0.001$), whereas, no significant difference was found between KG (13/20) and CG.

Table 1: Demographic and intraoperative data

Variables	Control ($n=20$)	Lidocaine ($n=20$)	Ketamine ($n=20$)	*P*
Age (years)	48.3±13.5	47.6±12.5	55.8±13.5	0.174
Sex (male/female)	9/11	9/11	11/9	0.775
Height (cm)	165±0.09	169±0.07	167±0.06	0.253
BMI (kg/m^2)	26.09±4.5	25.7±3.8	26.1±4	0.935
ASA physical Status I/II (*n*)	15/5	14/6	12/8	0.590
Indication (*n*)				
Renal tumor	4	6	6	0.092
Urolithiasis	7	7	12	
Donor nephrectomy	9	7	2	
Duration surgery (min)	146±43	135±52	119±11.4	0.230
Intraoperative fentanyl requirement (mcg/kg/h)	2.6±0.99	2.6±1.12	2.57±0.63	0.975
Intraoperative fluids (ml)	3025±638	2700±784	2775±525	0.271

Values are expressed as mean±SD or *n* (%). BMI: Body mass index; SD: Standard deviation; ASA: American Society of Anesthesiologists

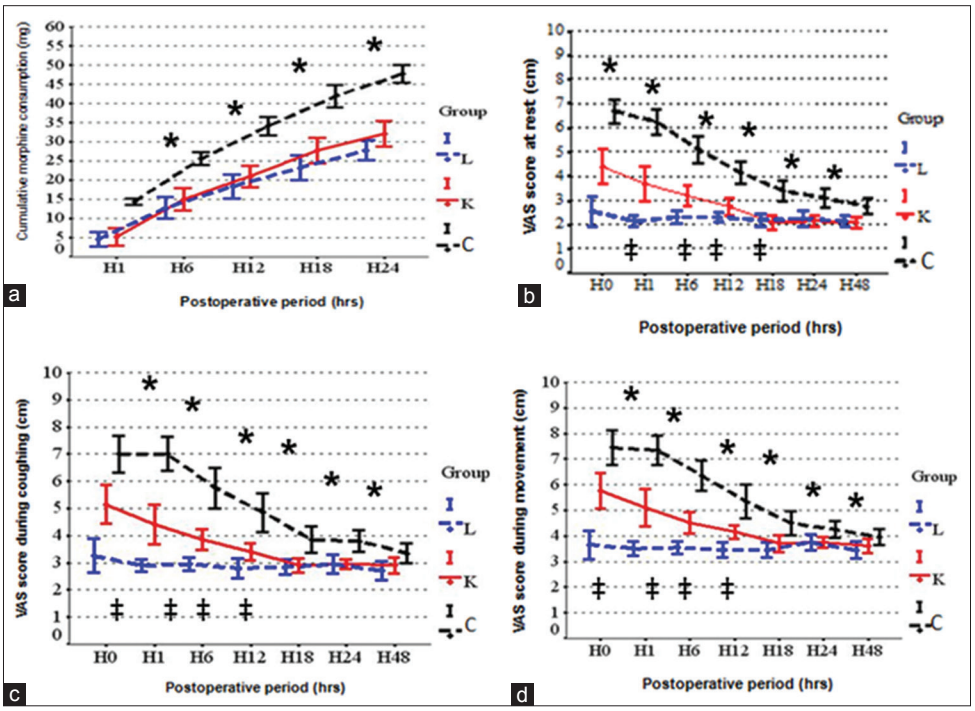

Figure 2: (a) Postoperative morphine consumption during the first 24 h after open nephrectomy.(b) Pain intensity at rest assessed using a visual analog scale. (c) Pain intensity during coughing assessed using a visual analog scale.(d) Pain intensity during movement assessed using a visual analog scale. *$P < 0.05$, control group compared with treatment groups (ketamine and lidocaine); ‡$P < 0.05$, lidocaine group compared with ketamine group

Recovery parameters

Mean time to the first flatus and to the first meal was significantly shorter in LG and KG than in CG. First defecation, mobilization time, and length of hospital stay were statistically shorter in LG and KG compared with CG [$P < 0.05$, Table 2].

The distance covered during 6-min walking test increased significantly from a mean ± SD of 27 ± 16.2 m in the CG to 82.3 ± 28 m in the LG ($P < 0.001$). There was no significant difference between KG and CG patients in terms of the distance walked.

The improvement of recovery parameters (bowel function and walking capacity) was significantly better with lidocaine than ketamine [$P < 0.05$, Table 2].

Chronic neuropathic pain

Concerning chronic neuropathic pain, the DN4 score was calculated for all patients; it was positive (≥4) in 17 patients. In the CG, 9 patients had a DN4 score ≥4 while in the LG, only one patient had a score of 5 ($P = 0.006$). Seven patients had a DN4 score ≥4 in the KG [Table 2]. Lidocaine, but not ketamine, reduced significantly the development of chronic neuropathic pain after open nephrectomy.

Adverse and toxic effects of analgesic adjuncts

There were not notable lidocaine-related adverse effects. No patients complained of hallucinations or dysphoria.

Discussion

This study demonstrated that perioperative IV infusion of lidocaine or ketamine during 24 h associated with morphine PCA improved postoperative analgesia and reduced total cumulative morphine consumption over a 24-h period in patients undergoing open nephrectomy. In addition, total PCA morphine requirement was decreased by about 33% and 42% in the ketamine and LGs, respectively, compared with the CG ($P < 0.001$).

Both ketamine and lidocaine significantly reduced mean VAS pain scores versus placebo ($P < 0.05$) at rest and during cough or movement for up to 48 h postoperatively. The VAS pain scores were significantly lower in the LG compared with the KG in the first 12 h postoperatively ($P < 0.05$).

IV lidocaine has analgesic, antihyperalgesic,[11,12] and anti-inflammatory effects[13] mediated by a variety of mechanisms including voltage-gated sodium channel blockade, G-protein-coupled receptor signaling,[14] NMDA antagonism,[15] suppression of central sensitization and inhibition of visceromotor reflexes.

The anti-inflammatory effects of lidocaine[13-17] can probably be explained by the lower neutrophil accumulation at the site of injury[18] and reduced release of inflammatory mediators. These actions justify its use in a multimodal approach to postoperative analgesia.

The studies showed a reduction in 24-h opioid consumption by about 50% in outpatients undergoing laparoscopic surgery,[19] cholecystectomy,[20] and laparoscopic colectomy.[21] Another recent study in patients who underwent laparoscopic nephrectomy, Tauzin-Fin *et al*.[22] found that IV lidocaine reduced the overall postoperative morphine consumption by about 66% as well as pain score at rest and during coughing during the first 2 postoperative days. A more recent Cochrane review[8] analyzed 45 studies (2802 patients) and showed that pain immediately after surgery and until 24 h was reduced by lidocaine infusion when compared to placebo or usual care.

Ketamine acts mainly as an NMDA receptor antagonist. It attenuates central sensitization induced by tissue injury and decreases the development of opioid tolerance.[23-25] Our study showed that a 24-h low-dose continuous IV infusion of ketamine combined with morphine PCA reduced morphine consumption by 33% compared to CG without any increase of side effects such as sedation or psychiatric disorders due to ketamine.

Table 2: Postoperative recovery parameters and chronic neuropathic pain in the three groups

Parameters	Control C ($n=20$)	Lidocaine L ($n=20$)	Ketamine K ($n=20$)	P (C vs. L)	P (C vs. K)	P (L vs. K)
Bowel function						
Time to first bowel movement (h)	39.15±10.5	15.2±6.17	31.4±17.5	<0.001	0.16	<0.001
Time to first flatus (h)	67.7±13	29.5±11	52.7±21	<0.001	0.013	<0.001
Time to first meal (h)	53.1±15.2	27.6±8.7	40.8±19.2	<0.001	0.037	0.01
First defecation time (h)	139±30	68.4±14	114±17.1	<0.001	0.002	<0.001
Mobilization (h)	55±15.7	24±2	34±14	<0.001	<0.001	<0.001
6MWD (m)	27±16.2	82.3±28	42.5±21.4	<0.001	0.102	<0.001
Duration of hospital stay (days)	7.7±2.1	3.7±1.12	5.5±0.7	<0.001	<0.001	<0.001
DN4 questionnaire						
DN4 score ≥4, *n* (%)	9/20 (45)	1/20 (5)	7/20 (35)	0.006	NS	<0.001

Values are expressed as mean±SD. 6MWD: 6-min walking distance; DN4: Neuropathic pain questionnaire in 4 questions; SD: Standard deviation; NS: Not significant

In a meta-analysis of studies of more than 2000 patients, the authors found that perioperative subanesthetic doses of ketamine reduced 24 h PCA morphine consumption. Adverse effects were mild or absent.[26] A more recent narrative review[7] concluded that ketamine was effective in controlling postoperative pain, but there is no consensus about the best ketamine administration method. Ketamine was administered using a variety of regimens, but the majority involved a preincisional loading dose of 0.15–1.00 mg/kg, with additional intraoperative infusion. Further randomized controlled trials are to determine which subgroups benefit and the optimum dose and duration of therapy.

Our results showed that systemic lidocaine and ketamine also significantly improved postoperative bowel function and reduced the duration of hospitalization in comparison to the CG. The recovery was significantly better with lidocaine than ketamine. The mean time to the first flatus and bowel movement was significantly shortened by 23 h and duration of hospital stay was reduced by an average of 1.8 days in the lidocaine-treated patients in comparison to the KG.

Several factors may contribute to the postoperative ileus such as opioid use, sympathetic hyperactivity, and the release of inflammatory mediators.[27-29]

The positive effects of IV lidocaine on bowel function could be explained by three mechanisms: the opioid sparing effect, the anti-inflammatory effect, and the blockade of inhibitory sympathetic reflexes involved in postoperative ileus. Our data are in accordance with those of Kaba *et al*.[21] and Tauzin-Fin *et al*.[22] A recent Cochrane review[8] confirms the benefits of lidocaine infusion on recovery of bowel function allowing for earlier rehabilitation and shorter duration of hospital stay.

However, the benefits of lidocaine in terms of recovery and reducing the length of hospital stay were not demonstrated in patients undergoing total hip arthroplasty or coronary artery bypass surgery.[30,31]

The anti-inflammatory effect of ketamine was documented in several studies.[32,33] The effect of ketamine on perioperative inflammatory responses has been studied in patients undergoing total hip arthroplasty,[34] hysterectomy,[35] thoracotomy,[36] and cardiac[37] and spine surgery.[38] The role of ketamine as a component of perioperative recovery process remains unclear.

Functional walking capacity as measured by 6MWT distance increased significantly in lidocaine-treated patients. Similar findings were reported by the previous studies evaluating the functional walking capacity after laparoscopic prostatectomy[39] and laparoscopic nephrectomy.[22]

Our data showed that perioperative lidocaine infusion reduced significantly PONV. This is in agreement with the Vigneault *et al*. meta-analysis.[40] However, the opioid sparing effect of ketamine did not lead to a subsequent reduction in the incidence of PONV. This finding disagree with a Cochrane review analyzing 37 studies (2240 patients) indicating that subanesthetic perioperative ketamine was effective in reducing the incidence of PONV.[26] On the other hand, several studies confirm our data showing no significant reduction in PONV with ketamine infusion.[41,42] Furthermore, ketamine exacerbated PONV in patients at high risk of PONV undergoing lumbar spinal surgery.[43]

In contrast to the LG, ketamine failed to improve the functional walking capacity. Our results are in line with a previous study in which ketamine failed to improve 6MWT on the 2nd postoperative day after open hysterectomy. Ketamine was given as a bolus 0.35 mg/kg, followed by ketamine infusion of 0.2 mg/kg/h for the first 2 h and then 0.12 mg/kg/h for 24 postoperative h.[35]

Chronic postsurgical pain (CPSP) is defined as pain that persists for longer than 3 months.[44] Inadequate pain management after surgery elevates the risk of postoperative complications and it is one of the major risk factors associated with CPSP, which adversely affects the quality of life and delays rehabilitation and return to usual activities.

CPSP is a largely unrecognized problem that may occur in 10%–65% of postoperative patients depending on the type of surgery, with 2%–10% of these patients experiencing severe CPSP. Little is known about the progress of persistent pain after nephrectomy.[1,45] One month after nephrectomy, pain has been reported in 58% and 78% of patients into two different studies.[46,47] The incidence of CPSP after open nephrectomy ranges from 4% to 27%.[48]

Our results further indicated that chronic neuropathic pain was found to be significantly lower in the LG compared with the ketamine and CGs. More recent studies have also demonstrated the effectiveness of lidocaine infusion in decreasing chronic pain.[49-51]

In agreement with our data, recent studies reported that perioperative ketamine improved early recovery but lacked the effect on chronic postoperative pain.[52,53]

In contrast, a recent meta-analysis performed in 2013 suggested the modest but statistically significant reduction in the incidence of chronic pain after surgery following treatment with ketamine. Unfortunately, most of the included studies were small which could lead to the overestimation of treatment effect.[54]

Regarding adverse events, no lidocaine-related systemic toxicity signs were reported. Perioperative low-dose ketamine infusion was not associated with significant side effects, which is similar to the previous reports. Low-dose ketamine has been defined as a bolus of <1 mg/kg IV and an infusion rate <1.2 mg/kg/h.[55]

Our study is one of the very few head-to-head randomized clinical trials comparing ketamine versus lidocaine.

The limitations of this study include its single-center design, which limits generalization of the findings. Another limitation concerns the absence of physical examination of the patients with persistent pain and the use of simple questionnaire to confirm neuropathic pain. The choice of DN4 was based on its simplicity.

Conclusion

In summary, our findings confirmed beneficial effects of IV infusion of lidocaine or ketamine during the first 24 h postoperatively in combination with morphine PCA to reduce postoperative opioid consumption and improve postoperative recovery after elective open radical nephrectomy.

We could suggest that lidocaine infusion serves as an interesting alternative to improve the functional walking capacity and prevent chronic neuropathic pain at 3 months after open nephrectomy. However, our results do not support the use of ketamine for improving the 6MWT, the 4th postoperative day after open nephrectomy. Ketamine could not reduce the incidence of PONV and it failed also to prevent neuropathic pain. Nevertheless, further studies are needed to determine the best perioperative lidocaine and/or ketamine regimen for postoperative pain control and prevention of postoperative chronic pain syndrome after open nephrectomy.

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Conflicts of interest
There are no conflicts of interest.

References

1. Alper I, Yüksel E. Comparison of acute and chronic pain after open nephrectomy versus laparoscopic nephrectomy: A prospective clinical trial. Medicine (Baltimore) 2016;95:e3433.
2. Aminsharifi A, Salehipoor M, Arasteh H. Systemic immunologic and inflammatory response after laparoscopic versus open nephrectomy: A prospective cohort trial. J Endourol 2012;26:1231-6.
3. Kehlet H, Holte K. Effect of postoperative analgesia on surgical outcome. Br J Anaesth 2001;87:62-72.
4. Joshi GP. Multimodal analgesia techniques and postoperative rehabilitation. Anesthesiol Clin North America 2005;23:185-202.
5. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet 2006;367:1618-25.
6. Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg 1993;77:1048-56.
7. Radvansky BM, Shah K, Parikh A, Sifonios AN, Le V, Eloy JD. Role of ketamine in acute postoperative pain management: A narrative review. Biomed Res Int 2015;2015:749837.
8. Kranke P, Jokinen J, Pace NL, Schnabel A, Hollmann MW, Hahnenkamp K, *et al*. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery. Cochrane Database Syst Rev 2015;(7):CD009642.
9. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-7.
10. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, *et al*. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 2005;114:29-36.
11. Koppert W, Zeck S, Sittl R, Likar R, Knoll R, Schmelz M. Low-dose lidocaine suppresses experimentally induced hyperalgesia in humans. Anesthesiology 1998;89:1345-53.
12. Dirks J, Fabricius P, Petersen KL, Rowbotham MC, Dahl JB. The effect of systemic lidocaine on pain and secondary hyperalgesia associated with the heat/capsaicin sensitization model in healthy volunteers. Anesth Analg 2000;91:967-72.
13. Hollmann MW, Durieux ME. Local anesthetics and the inflammatory response: A new therapeutic indication? Anesthesiology 2000;93:858-75.
14. Hollmann MW, Herroeder S, Kurz KS, Hoenemann CW, Struemper D, Hahnenkamp K, *et al*. Time-dependent inhibition of G protein-coupled receptor signaling by local anesthetics. Anesthesiology 2004;100:852-60.
15. Nagy I, Woolf CJ. Lignocaine selectively reduces C fibre-evoked neuronal activity in rat spinal cord *in vitro* by decreasing N-methyl-D-aspartate and neurokinin receptor-mediated post-synaptic depolarizations; implications for the development of novel centrally acting analgesics. Pain 1996;64:59-70.
16. Beloeil H, Mazoit JX. Effect of local anesthetics on the postoperative inflammatory response. Ann Fr Anesth Reanim 2009;28:231-7.
17. Mathew JP, Mackensen GB, Phillips-Bute B, Grocott HP, Glower DD, Laskowitz DT, *et al*. Randomized, double-blinded, placebo controlled study of neuroprotection with lidocaine in cardiac surgery. Stroke 2009;40:880-7.
18. Eriksson AS, Sinclair R, Cassuto J, Thomsen P. Influence of lidocaine on leukocyte function in the surgical wound. Anesthesiology 1992;77:74-8.
19. De Oliveira GS Jr., Fitzgerald P, Streicher LF, Marcus RJ, McCarthy RJ. Systemic lidocaine to improve postoperative quality of recovery after ambulatory laparoscopic surgery. Anesth Analg 2012;115:262-7.
20. Saadawy IM, Kaki AM, Abd El Latif AA, Abd-Elmaksoud AM, Tolba OM. Lidocaine vs. magnesium: Effect on analgesia after a laparoscopic cholecystectomy. Acta Anaesthesiol Scand 2010;54:549-56.
21. Kaba A, Laurent SR, Detroz BJ, Sessler DI, Durieux ME, Lamy ML, *et al*. Intravenous lidocaine infusion facilitates acute rehabilitation after laparoscopic colectomy. Anesthesiology 2007;106:11-8.
22. Tauzin-Fin P, Bernard O, Sesay M, Biais M, Richebe P, Quinart A, *et al*. Benefits of intravenous lidocaine on post-operative pain and acute rehabilitation after laparoscopic nephrectomy. J Anaesthesiol Clin Pharmacol 2014;30:366-72.
23. Stubhaug A, Breivik H, Eide PK, Kreunen M, Foss A. Mapping of punctuate hyperalgesia around A surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. Acta Anaesthesiol Scand 1997;41:1124-32.

24. Woolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. Pain 1991;44:293-9.
25. Woolf CJ, Chong MS. Preemptive analgesia – Treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 1993;77:362-79.
26. Bell RF, Dahl JB, Moore RA, Kalso E. Peri-operative ketamine for acute post-operative pain: A quantitative and qualitative systematic review (Cochrane review). Acta Anaesthesiol Scand 2005;49:1405-28.
27. Holte K, Kehlet H. Postoperative ileus: A preventable event. Br J Surg 2000;87:1480-93.
28. Luckey A, Livingston E, Taché Y. Mechanisms and treatment of postoperative ileus. Arch Surg 2003;138:206-14.
29. Kurz A, Sessler DI. Opioid-induced bowel dysfunction: Pathophysiology and potential new therapies. Drugs 2003;63:649-71.
30. Martin F, Cherif K, Gentili ME, Enel D, Abe E, Alvarez JC, *et al.* Lack of impact of intravenous lidocaine on analgesia, functional recovery, and nociceptive pain threshold after total hip arthroplasty. Anesthesiology 2008;109:118-23.
31. Insler SR, O'Connor M, Samonte AF, Bazaral MG. Lidocaine and the inhibition of postoperative pain in coronary artery bypass patients. J Cardiothorac Vasc Anesth 1995;9:541-6.
32. Loix S, De Kock M, Henin P. The anti-inflammatory effects of ketamine: State of the art. Acta Anaesthesiol Belg 2011;62:47-58.
33. Dale O, Somogyi AA, Li Y, Sullivan T, Shavit Y. Does intraoperative ketamine attenuate inflammatory reactivity following surgery? A systematic review and meta-analysis. Anesth Analg 2012;115:934-43.
34. Martinez V, Cymerman A, Ben Ammar S, Fiaud JF, Rapon C, Poindessous F, *et al.* The analgesic efficiency of combined pregabalin and ketamine for total hip arthroplasty: A randomised, double-blind, controlled study. Anaesthesia 2014;69:46-52.
35. Grady MV, Mascha E, Sessler DI, Kurz A. The effect of perioperative intravenous lidocaine and ketamine on recovery after abdominal hysterectomy. Anesth Analg 2012;115:1078-84.
36. Mendola C, Cammarota G, Netto R, Cecci G, Pisterna A, Ferrante D, *et al.* S+-ketamine for control of perioperative pain and prevention of post thoracotomy pain syndrome: A randomized, double-blind study. Minerva Anestesiol 2012;78:757-66.
37. Welters ID, Feurer MK, Preiss V, Müller M, Scholz S, Kwapisz M, *et al.* Continuous S-(+)-ketamine administration during elective coronary artery bypass graft surgery attenuates pro-inflammatory cytokine response during and after cardiopulmonary bypass. Br J Anaesth 2011;106:172-9.
38. Loftus RW, Yeager MP, Clark JA, Brown JR, Abdu WA, Sengupta DK, *et al.* Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. Anesthesiology 2010;113:639-46.
39. Lauwick S, Kim DJ, Mistraletti G, Carli F. Functional walking capacity as an outcome measure of laparoscopic prostatectomy: The effect of lidocaine infusion. Br J Anaesth 2009;103:213-9.
40. Vigneault L, Turgeon AF, Côté D, Lauzier F, Zarychanski R, Moore L, *et al.* Perioperative intravenous lidocaine infusion for postoperative pain control: A meta-analysis of randomized controlled trials. Can J Anaesth 2011;58:22-37.
41. Subramaniam K, Subramaniam B, Steinbrook RA. Ketamine as adjuvant analgesic to opioids: A quantitative and qualitative systematic review. Anesth Analg 2004;99:482-95.
42. Elia N, Tramèr MR. Ketamine and postoperative pain – A quantitative systematic review of randomised trials. Pain 2005;113:61-70.
43. Song JW, Shim JK, Song Y, Yang SY, Park SJ, Kwak YL. Effect of ketamine as an adjunct to intravenous patient-controlled analgesia, in patients at high risk of postoperative nausea and vomiting undergoing lumbar spinal surgery. Br J Anaesth 2013;111:630-5.
44. VanDenKerkhof EG, Peters ML, Bruce J. Chronic pain after surgery: Time for standardization? A framework to establish core risk factor and outcome domains for epidemiological studies. Clin J Pain 2013;29:2-8.
45. Gerbershagen HJ, Dagtekin O, Rothe T, Heidenreich A, Gerbershagen K, Sabatowski R, *et al.* Risk factors for acute and chronic postoperative pain in patients with benign and malignant renal disease after nephrectomy. Eur J Pain 2009;13:853-60.
46. Andersen MH, Mathisen L, Oyen O, Edwin B, Digernes R, Kvarstein G, *et al.* Postoperative pain and convalescence in living kidney donors-laparoscopic versus open donor nephrectomy: A randomized study. Am J Transplant 2006;6:1438-43.
47. Perry KT, Freedland SJ, Hu JC, Phelan MW, Kristo B, Gritsch AH, *et al.* Quality of life, pain and return to normal activities following laparoscopic donor nephrectomy versus open mini-incision donor nephrectomy. J Urol 2003;169:2018-21.
48. Owen M, Lorgelly P, Serpell M. Chronic pain following donor nephrectomy – A study of the incidence, nature and impact of chronic post-nephrectomy pain. Eur J Pain 2010;14:732-4.
49. Grigoras A, Lee P, Sattar F, Shorten G. Perioperative intravenous lidocaine decreases the incidence of persistent pain after breast surgery. Clin J Pain 2012;28:567-72.
50. Wu CL, Tella P, Staats PS, Vaslav R, Kazim DA, Wesselmann U, *et al.* Analgesic effects of intravenous lidocaine and morphine on postamputation pain: A randomized double-blind, active placebo-controlled, crossover trial. Anesthesiology 2002;96:841-8.
51. Terkawi AS, Sharma S, Durieux ME, Thammishetti S, Brenin D, Tiouririne M. Perioperative lidocaine infusion reduces the incidence of post-mastectomy chronic pain: A double-blind, placebo-controlled randomized trial. Pain Physician 2015;18:E139-46.
52. Hayes C, Armstrong-Brown A, Burstal R. Perioperative intravenous ketamine infusion for the prevention of persistent post-amputation pain: A randomized, controlled trial. Anaesth Intensive Care 2004;32:330-8.
53. Dualé C, Sibaud F, Guastella V, Vallet L, Gimbert YA, Taheri H, *et al.* Perioperative ketamine does not prevent chronic pain after thoracotomy. Eur J Pain 2009;13:497-505.
54. Chaparro LE, Smith SA, Moore RA, Wiffen PJ, Gilron I. Pharmacotherapy for the prevention of chronic pain after surgery in adults. Cochrane Database Syst Rev 2013;(7):CD008307.
55. Schmid RL, Sandler AN, Katz J. Use and efficacy of low-dose ketamine in the management of acute postoperative pain: A review of current techniques and outcomes. Pain 1999;82:111-25.