Original Article

Benefits of intravenous lidocaine on post-operative pain and acute rehabilitation after laparoscopic nephrectomy

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Abstract

Background and Aims: Intravenous (I.V.) lidocaine has analgesic, antihyperalgesic and anti-inflammatory properties and is known to accelerate the return of bowel function after surgery. We evaluated the effects of I.V. lidocaine on pain management and acute rehabilitation protocol after laparoscopic nephrectomy.

Materials and Methods: A total of 47 patients scheduled to undergo laparoscopic nephrectomy were included in a two-phase observational study where I.V. lidocaine (1.5 mg/kg/h) was introduced, in the second phase, during surgery and for 24 h post-operatively. All patients underwent the same post-operative rehabilitation program. Post-operative pain scores, opioid consumption and extent of hyperalgesia were measured. Time to first flatus and 6 min walking test (6MWT) were recorded.

Results: Patient demographics were similar in the two phases ($n = 22$ in each group). Lidocaine significantly reduced morphine consumption (median [25-75% interquartile range]; 8.5 mg[4-17] vs. 25 mg[19-32]; $P < 0.0001$), post-operative pain scores ($P < 0.05$) and hyperalgesia extent on post-operative day 1-day 2-day 4 (mean ± standard deviation (SD); 1.5 ± 0.9 vs. 4.3 ± 1.2 cm ($P < 0.001$), 0.6 ± 0.5 vs. 2.8 ± 1.2 cm ($P < 0.001$) and 0.13 ± 0.3 vs. 1.2 ± 1 cm ($P < 0.001$), respectively). Time to first flatus (mean ± SD; 29 ± 7 h vs. 48 ± 15 h; $P < 0.001$) and 6MWT at day 4 (189 ± 50 m vs. 151 ± 53 m; $P < 0.001$) were significantly enhanced in patients with i.v. lidocaine.

Conclusion: Intravenous (I.V.) lidocaine could reduce post-operative morphine consumption and improve post-operative pain management and post-operative recovery after laparoscopic nephrectomy. I.V. lidocaine could contribute to better post-operative rehabilitation.

Key words: Analgesia, laparoscopic nephrectomy, lidocaine, post-operative pain

Introduction

Laparoscopic nephrectomy is a common urological procedure with many advantages over traditional open procedures: Less pain, lower complication rates, faster recovery and reduced costs[1] Fast-track surgery and acute rehabilitation programs reduce post-operative morbidity, duration of hospitalization and accelerate post-operative recovery and convalescence.[2,3] Effective post-operative analgesia is the key for early rehabilitation.[2] Epidural analgesia using local anesthetic is particularly appropriate after abdominal surgery because it reduces surgical stress, provides excellent pain relief allowing enforced mobilization and improves gastrointestinal function.[4] However, its benefit-risk ratio may be questionable in laparoscopic nephrectomy.[3] Intravenous (I.V.) lidocaine provides analgesic, antihyperalgesic and anti-inflammatory properties[5-8] and has been reported to accelerate the return of bowel function after surgery.[9] The aims of this study were to evaluate the beneficial effects of I.V. lidocaine on immediate and late post-operative pain management and acute rehabilitation after laparoscopic nephrectomy.

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Materials and Methods

We conducted an observational study in a single center. Our Institutional Ethics Committee was consulted and considered that this study was observational and was in accordance with

good recommended practices. After obtaining informed and written consent, patients American Society of Anesthesiologists physical status I/II/III, scheduled to undergo laparoscopic nephrectomy (three ports plus an incision for kidney removal) were consecutively enrolled in two phases with the introduction of I.V. lidocaine in the second phase. Exclusion criteria were anti-arrhythmic drug intake within 1 week before surgery, renal and hepatic insufficiency, psychiatric disorders, steroid and/or chronic opioid treatments and inability to understand the patient-controlled analgesia (PCA) device. During the anesthesia consultation, patients were instructed by an anesthesiologist in the use of a standardized horizontal 100 mm linear visual analogue scale (VAS), identifying 0 as "no pain" and 10 as "worst imaginable pain" and in the use of a PCA device.

Anesthesia protocol

Patients were classified into two groups according to their period of enrolment. In phase 1, from September to December 2009 (Reference group), patients were premedicated with oral hydroxyzine 100 mg 1 h before surgery. Anesthesia was induced using i.v. propofol 2.5 mg/kg and a target-controlled infusion of sufentanil, Gepts *et al*. pharmacokinetic model[10] at an initial effect-site concentration of 0.5 ng/ml. Orotracheal intubation was facilitated with cisatracurium 0.15 mg/kg. Anesthesia was maintained with sevoflurane at an end-tidal concentration of 1.5-2.5% using a closed circuit with 1.5 l/min fresh gas flow and sufentanil at a target concentration of 0.2-0.5 ng/ml, adjusted to maintain the bispectral index (BIS-XPTM monitor, Aspect Medical Systems, Natick, MA, USA) between 40 and 50. Neuromuscular block was maintained by a continuous infusion of cisatracurium adapted to obtain no response to train-of-four stimulation during surgery (TOF-WATCH® Organon, Dublin, Ireland). Patients were mechanically ventilated with an air-oxygen mixture (50/50) and ventilation was adjusted to maintain end-tidal carbon dioxide between 35 and 45 mmHg. Isotonic saline was infused at 10-15 ml/kg/h. Heart rate, non-invasive blood pressure, SpO_2 and esophageal temperature were recorded at 5-min intervals throughout the surgical procedure. Normothermia was maintained with a forced warm device covering the upper part of the body throughout anesthesia. At the time of skin closure, infusion of sufentanil and cisatracurium were stopped. Wound infiltration was performed in each patient in both groups with a single bolus of 20 ml ropivacaine 2 mg/ml plus 20 ml ropivacaine 7.5 mg/ml as currently used in our institution[11] I.V. acetaminophen 1 g, tramadol 100 mg and ketoprofen 50 mg were infused for 20 min at the same time. In phase 2, from January to April 2010, patients (lidocaine group) underwent the same protocol as in phase 1 with the addition of a continuous infusion of lidocaine, 1.5 mg/kg/h, at induction of anesthesia, before incision, throughout surgery and for 24 h post-operatively. The lidocaine infusion was connected to the distal part of the line to avoid accidental bolus administration.

Postoperative pain management and acute rehabilitation

After surgery, patients were transferred for the first post-operative 24 h to the post anesthetic care unit (PACU). Tracheal extubation was performed in conscious normothermic patients without residual muscle weakness (TOF ratio T4/T1 >0.9). Post-operative analgesia was provided in both groups by the combination of I.V. acetaminophen (1 g every 6 h), morphine titration if needed and a PCA device with morphine 1 mg/ml and droperidol 0.05 mg/ml, set to deliver 1 mg bolus dose of morphine with a 7 min lockout interval and no continuous infusion. PCA was maintained for 48 h post-operatively. The level of pain score was assessed at rest and during coughing every 3 h the 1st day and every 12 h the 2nd day. Morphine consumption was noted at the same time during the period study. In both groups, I.V. tramadol 100 mg was given as analgesic rescue (VAS >5) and i.v. ondansetron 4 mg was administered when patients complained of nausea, retching or emetic episodes. Sedation was assessed using a four-point scale:

1. No sedation (awake);
2. Light sedation (awake with verbal stimulation);
3. Moderate sedation (awake with multiple verbal stimulation);
4. Deep sedation (awake only with painful stimulation).

The gastrointestinal tube was removed at the end of surgery after aspiration of gastric contents. An abdominal drain was left for 48 h. The bladder catheter was removed and oral fluids were started on the 1st post-operative day. If patients did not report nausea or vomiting, solid meals were given the day after I.V. perfusions were stopped. The patients started active mobilization in bed on the 1st day, sitting the 2nd day and assisted ambulation the 3rd day.

Study parameters

Evaluation started when patients were in the PACU (hour zero). The primary endpoint was total morphine consumption at the end of post-operative day 2. Secondary outcome measures were as follows:

- Number of patients requiring morphine titration in the PACU and dose of morphine administered;
- Pain level assessed by VAS score at rest and during coughing;
- Punctuate hyperalgesia and extent of hyperalgesia were measured prior to surgery on days 1, 2 and 4 and at 3 months using the von Frey filament technique as previously described.[12] The threshold for punctuate hyperalgesia was measured with calibrated von Frey filaments. Each of the 20

filaments has a different diameter (0.06-1.14 mm) to which a calibration value corresponding to the log of 10 times the strength required to bend the filament in half-circle is assigned. The filaments were applied perpendicularly at 2 cm from the medial side of the incision at 3 sites corresponding to the middle of the incision, 5 cm above and 5 cm below the middle of the incision. At the first test, the regions were marked. The subjects were instructed to close their eyes during the procedure. Von Frey filament applications to the designated point on the skin for approximately 1 s were separated by at least 15 s to avoid temporal summation. The von Frey filaments were applied in ascending order of stiffness. Tactile pain threshold was defined as the smallest force (g/mm^2) necessary to bend a von Frey filament, which was just perceived as painful. If the strongest hair did not elicit a response, the threshold was recorded as 281 g/mm^2. A mean value for the three regions (right, middle, left) was finally calculated and used for statistical comparisons. The extent of hyperalgesia was assessed with a 100 g/mm^2 von Frey filament. After removal of the surgical dressing, stimulation was started 10 cm from the medial side of the incision on three parallel lines at right angles to the middle of the surgical incision, 5 cm above and 5 cm below. Stimulation continued toward the incision in 5 mm steps at 1-s intervals until the patient reported a clear change in sensation. The first point where a "painful", "sore' or "sharp" feeling appeared was noted and the distance to the incision was measured with an accuracy of 0.5 cm. If no change in sensation appeared, stimulation was stopped 0.5 cm from the incision. A mean value for the three assessments was calculated and used for statistical comparisons.

- Gastrointestinal discomfort was assessed by the presence of abdominal fullness during the 1st post-operative day[13]
- Detection of first flatus time and oral intake were routinely checked by the nurses;
- The 6 min walking test (6MWT) the day before surgery and on day 4 and at hospital discharge[14,15]
- Mental function assessed by the digit symbol substitution test (DSST)[16] on a daily basis until patients attained the score noted the day before surgery;
- Side-effects such as nausea or vomiting, sedation;
- Signs of systemic toxicity of lidocaine such as perioral numbness and metallic taste were checked by the nurses in the PACU besides hypotension and bradycardia (continuous cardiovascular monitoring). In the first 11 patients in the lidocaine group, blood samples were drawn at the end of the 24-h infusion to measure unbound plasma lidocaine concentrations, using an Ultra Performance Liquid Chromatography-tandem mass spectrometry method (linearity between 0,05 and 10 μg/ml, bias and precision <15%);
- Duration of hospital stay.

Statistical analysis

The calculation of the sample size was based on the primary endpoint (morphine consumption during the first 2 post-operative days). From retrospective data from our institution, morphine consumption was 40 ± 13 mg in a similar population. Thus, a sample size of 21 patients in each group was required to detect as significant a between-group difference of 30% with an α risk of 0.05 and a β risk of 0.2. Patients were enrolled until 22 patients were included in each group. Data are expressed as mean (standard deviation), or as median (25-75% interquartile range) in case of non-parametric distribution. Between-group comparisons were performed with Student's *t*-test for parametric values or with the Mann — Whitney test otherwise. Dichotomous data were analyzed with the Chi-square test or Fisher test when appropriate. Hyperalgesia areas were compared with two-way repeated-measures ANOVA. A $P < 0.05$ was considered to be statistically significant. Statistical analysis was performed with Statview for Windows (version 5.0; SAS Institute Inc., Cary, NC).

Results

A total of 47 patients were included; three patients were excluded because of one surgical conversion (Lidocaine group) and two cases of poor nocturnal PCA management (Reference group). Totally 47 patients ($n = 22$ in each group) completed the study. Demographic and intra-operative data, type and duration of surgery were similar between the groups, as were indications for nephrectomy [Table 1]. Three and 15 patients in the Lidocaine and Reference groups respectively needed I.V. morphine titration in the PACU ($P < 0.001$). The median cumulative doses of I.V. morphine given as

Table 1: Demographic and intra-operative data

Clinical variable	Lidocaine group (n=22)	Reference group (n=22)	P
Age (year)	58 (17)	61 (14)	ns
Sex (M/F)	10/12	11/11	ns
Height (cm)	166 (9)	168 (9)	ns
Weight (kg)	68 (10)	75 (20)	ns
ASA I/II/III	7/12/3	2/16/4	ns
Type of surgery			
Neoplastic kidney	19	20	ns
Small infectious kidney	3	2	ns
Duration surgery (min)	139 (40)	134 (48)	ns
Length of surgical incision (cm)	12 (4)	13 (4)	ns
Pre-operative sufentanil consumption (μg)	139 (40)	121 (32)	ns
Time to tracheal extubation (min)	39 (42)	32 (19)	ns

Data are presented as mean (SD), or number of patients. ASA = American Society of Anesthesiologists, ns = Not significant, SD=Standard deviation

titration in the PACU were 0 and 6 mg [0-9] in the Lidocaine and Reference groups respectively ($P < 0.001$). Median cumulative morphine consumption at the end of post-operative day 2 was 8.5 mg [4-17] in the Lidocaine group and 25 mg[19-32] in the Reference group ($P < 0.0001$) [Figure 1]. Pain intensity was significantly reduced in the Lidocaine group both at rest and during coughing ($P < 0.0001$) throughout the 48-h study [Figure 2].

No major adverse events occurred. No patient in the Lidocaine group and 4 patients in the Reference group experienced nausea (NS). Sedation score was never over 1 in any patient. No urinary retention was noted in both groups at bladder catheter removal. None of the patients required tramadol for analgesic rescue. Post-operative recovery course is presented in Table 2. Time to recover pre-operative mental status (DSST) was similar in both groups. Gastrointestinal discomfort was present in 3 and 15 patients in the Lidocaine and Reference groups respectively ($P < 0.05$). Recovery of intestinal transit assessed by time to first flatus was faster in the Lidocaine group ($P < 0.001$). The 6MWT distance decreased by an average of 15 and 32% when compared with pre-operative data in the Lidocaine and Reference groups, respectively ($P < 0.05$). Pressure pain threshold (punctuate hyperalgesia) was significantly higher on days 1, 2 and 4 in the Lidocaine group when compared with the Reference group ($P < 0.05$) and was normalized on day 4 in the Lidocaine group [Figure 3]. Extent of hyperalgesia proximal to the surgical incision was significantly smaller in the Lidocaine group at all 3 time points [Figure 4]. There was a correlation between the extent of hyperalgesia at 24 h after intervention and total 24 h post-operative PCA morphine consumption ($r^2 = 0.096$, $P < 0.05$).

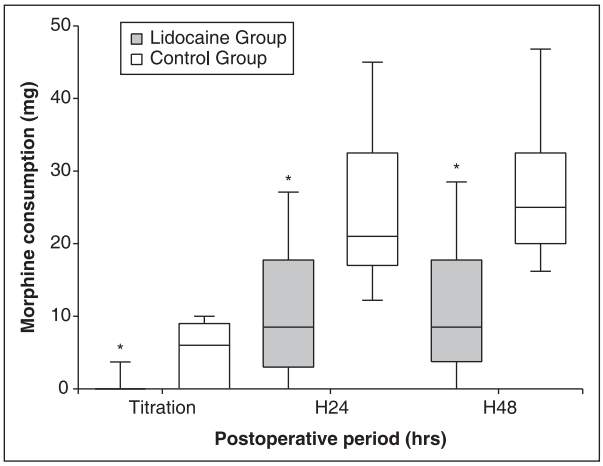

Figure 1: Post-operative morphine consumption during titration and patient-controlled analgesia period at 24 h and 48 h. Results are expressed as box plots with median (line), 25th-75th percentiles (box) and 10th-90th percentiles (whiskers) *$P < 0.001$

No adverse effect of I.V. lidocaine infusion was reported. Mean unbound plasma lidocaine concentration was 3.2 ± 0.9 μg/ml at the end of the 24-h infusion (range: 1.5-3.9 μg/ml), below the toxic level of 5 μg/ml.

Table 2: Recovery parameters

Clinical variable	Lidocaine group (n=22)	Reference group (n=22)	P
Gastrointestinal discomfort (n)	3	15	$P<0.05$
Time to first flatus (h)	29 (7)	48 (15)	$P<0.001$
Time to first meal (h)	36 (7)	58 (19)	$P<0.001$
DSST pre-operative	47 (16)	46 (16)	ns
Day 1	39 (14)	36 16)	ns
Day 2	50 (16)	45 18)	ns
Day 4	57 (12)	54 18)	ns
6MWT pre-operative (m)	222 (57)	220 (50)	ns
Day 4 (m)	189 (50)	151 (53)	$P<0.05$
Discharge (m)	219 (54)	201 (58)	ns
Duration hospital stay (d)	6.5 (1.5)	7.5 (3)	ns

Data are expressed as mean (SD) or number of patients. ns = not significant, DSST = Digit symbol substitution test, 6MWT = 6-min walking test, SD = Standard deviation

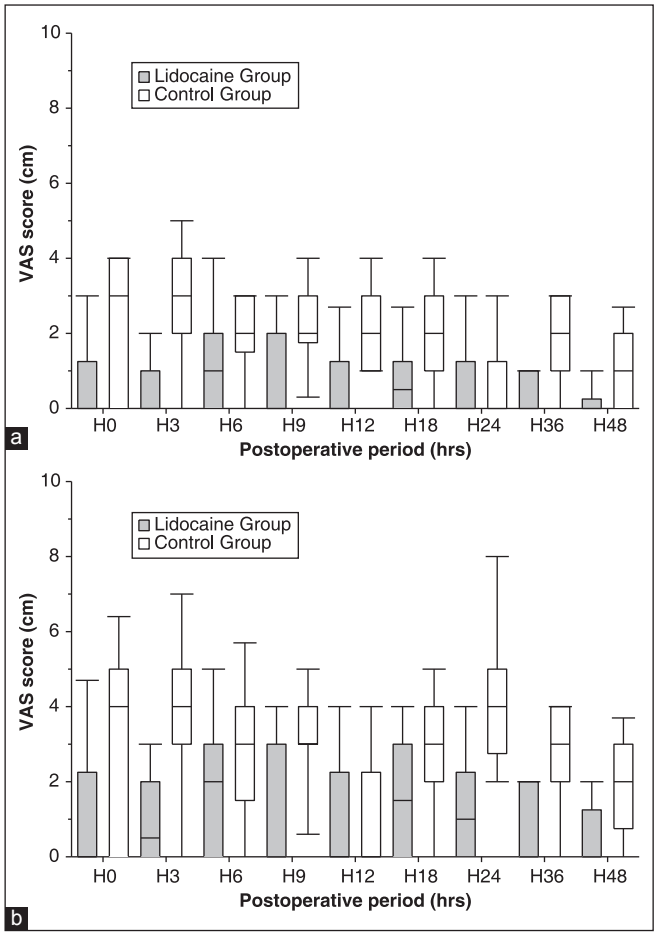

Figure 2: Pain intensity at rest (a) and during coughing (b) assessed using a visual analogue scale. Results are expressed as box plots with median (line), 25th-75th percentiles (box) and 10th-90th percentiles (whiskers) $P < 0.05$ at all times

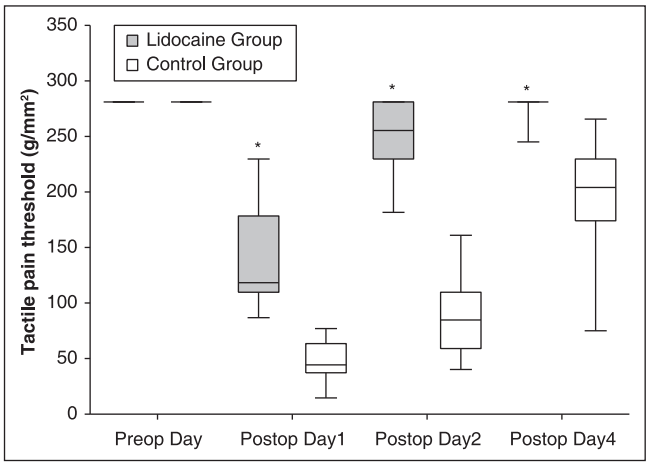

Figure 3: Tactile pain thresholds (g/mm²) determined with von Frey filaments, 2 cm proximal and perpendicular to the middle of the incision, 5 cm above and 5 cm below the middle of the incision during the preoperative (Preop) day and at post-operative (Postop) days 1, 2 and 4. Results are expressed as box plots with median (line), 25th-75th percentiles (box) and 10th-90th percentiles (whiskers) *$P < 0.05$

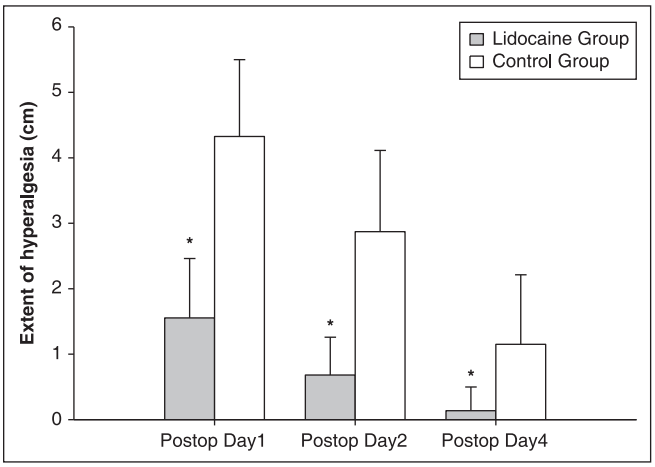

Figure 4: Extent of hyperalgesia (cm) to von Frey filament stimulation proximal to the surgical incision in the post-operative period (mean ± standard deviation) *$P < 0.01$

Discussion

This observational study shows that peri-operative I.V. infusion of non-toxic doses of lidocaine may improve post-operative analgesia, reduce post-operative opioid requirement, accelerate post-operative recovery of bowel function and facilitate acute rehabilitation in patients undergoing laparoscopic nephrectomy.

Our results demonstrate that I.V. lidocaine reduces the overall post-operative morphine consumption by about 66% as well as pain score at rest and during coughing during the first 2 post-operative days. The analgesic effect persisted after lidocaine was discontinued, suggesting a prevention of spinal or peripheral hypersensitivity or both. I.V. lidocaine has analgesic, antihyperalgesic and anti-inflammatory properties mediated by a variety of mechanisms including sodium channel blockade,[5] inhibition of G protein-coupled receptor and N-Methyl-D-Aspartate receptors.[6-8] Moreover, I.V. lidocaine reduced post-operative hyperalgesic areas, hence confirming experimental findings.[17,18] The extent of hyperalgesia itself at 24 h post-operatively suggests that central sensitization may contribute to post-operative pain after laparoscopic nephrectomy. The rostral ventromedial medulla (RVM) is involved in the development and maintenance of central sensitization through the activation of descending pain facilitatory pathways after acute morphine administration. In recent animal studies, microinjection of lidocaine in the RVM totally abolished morphine-induced sensory hypersensitivity as early as the 1st day after morphine administration.[19] This could explain the reduction in post-operative hyperalgesia after I.V. lidocaine in our study. Further studies are warranted to confirm these findings. Abdominal discomfort was significantly reduced in the Lidocaine group due to the ability of lidocaine to reduce visceral pain, as previously shown in animal studies.[20,21] There was no post-operative nausea/vomiting in the Lidocaine group probably in relation to the decrease in morphine consumption. The median cumulative dose was far below the threshold of 20 mg thought to induce clinically meaningful events.[22]

I.V. lidocaine improved post-operative bowel function and first flatus occurred almost 1 day earlier in the Lidocaine group. Factors involved in the post-operative ileus are opioid consumption, visceral inflammation secondary to surgery and post-operative sympathetic stimulation.[23-25] The reduction in ileus duration by I.V. lidocaine may be mediated by the reduction in post-operative morphine consumption, the anti-inflammatory properties of lidocaine and/or direct inhibition of the sympathetic mesenteric plexus. The 6MWT distances were significantly increased in the Lidocaine group, showing the ability of lidocaine to improve the recovery process. Our data are in accordance with those of Lauwick *et al.*[15] where factors involved in faster recovery were lack of pain and low morphine consumption. Post-operative fatigue, sleep disturbance due to post-operative morphine consumption and major surgical aggression are important factors involved in a rehabilitation program.[2]

I.V. lidocaine and laparoscopic surgery may reduce the impact of these factors. These favorable lidocaine-related effects integrated into an acute rehabilitation program could allow the discharge of patients at least 1 day earlier. Although the time factor was not statistically significant, length of stay includes several non-medical factors: Patient and surgeon preferences with regard to discharge home, day of the week

and distance to return home, as well as social factors (e.g., availability of caregivers at home or not). Finally, our results are in line with previous reports on the beneficial effects of I.V. lidocaine on post-operative analgesia and bowel function.[13,21,26,27] However, in orthopedic surgery with a different protocol, I.V. lidocaine failed to improve post-operative analgesia.[28]

No lidocaine-related adverse effects were recorded during surgery and the study period. Mean levels at the end of the 24-h infusion were always below the generally accepted toxic level (5 μg/ml). These findings are comparable with results provided by Kaba *et al.*: 2.7 ± 1.1 μg/ml.[13] Lidocaine infusion should be administered during surgery and continued for 24 h after surgery[13] to induce its actions, rather than only during the intra-operative and immediate post-operative periods.[13,27,28] Moreover, failure to produce analgesic effects has been reported when lidocaine infusion was established in the post-operative period only.[26]

On the basis of these data, epidural analgesia does not seem necessary for post-operative pain management after laparoscopic nephrectomy.[3] I.V. lidocaine and epidural analgesia provide comparable results in terms of post-operative morphine consumption, pain management and rehabilitation in patients undergoing laparoscopic segmental colectomy.[13,29] Plasma lidocaine levels are similar to those reported during prolonged epidural administration of lidocaine: 2-3 μg/ml[30] suggesting that systemic lidocaine rather than nerve block *per se* may play a role in the beneficial effects on post-operative recovery observed with epidural analgesia.[13,31] I.V. lidocaine might be a simple, inexpensive, alternative method providing the same benefits as more invasive and costly techniques.[32]

One limitation of our work was that it was an open observational study; further randomized studies are required to confirm these results.

Conclusions

Lidocaine I.V. reduces post-operative morphine consumption and improves post-operative pain management and post-operative recovery. I.V. lidocaine as a "minimally invasive analgesia" technique could be useful to post-operative rehabilitation programs.

Thus I.V. lidocaine could improve immediate and late post-operative pain management and recovery after laparoscopic nephrectomy. I.V. lidocaine as a "minimally invasive analgesia" technique could contribute to rapid post-operative rehabilitation programs.

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