Intraperitoneal Local Anesthetics Have Predominant Local Analgesic Effect

A Randomized, Double-blind Study

Andrea Perniola, M.D., Ph.D., Anders Magnuson, B.Sc., Kjell Axelsson, M.D., Ph.D., Anil Gupta, F.R.C.A., M.D., Ph.D.

ABSTRACT

Background: It remains unclear whether analgesia from intraperitoneal local anesthetics is *via* local or central mechanisms. This double-blind clinical trial tests the hypothesis that intraperitoneal local anesthetic is superior to continuous IV infusion for pain management. Primary outcome was morphine consumption during 0 to 24 h.

Methods: Informed consent was obtained from 60 patients, age 30 to 75 yr, American Society of Anesthesiologists physical status I to II, undergoing abdominal hysterectomy. A computer-generated program randomized patients in parallel arms to group IV: continuous infusion of lidocaine 50 mg/h (10 ml) IV and saline 10 ml/h intermittently intraperitoneal; group IP: injection of lidocaine 50 mg/h (10 ml) once every hour intraperitoneally and continuous infusion of saline 10 ml/h intravenously; and group P (placebo): saline 10 ml/h both intravenously and intermittent intraperitoneal injection. Postoperative morphine consumption, pain intensity, recovery, home discharge, and lidocaine concentrations were measured.

Results: Morphine consumption during 0 to 24 h was lower in group IP *versus* group IV, mean difference −22.6 mg (95% CI, 11.4 to 33.8; $P < 0.01$). No difference was seen between group IV and group P. The total mean plasma concentration of lidocaine in group IP was significantly lower than group IV, 0 to 4.5 h postoperatively ($P = 0.03$) with no evidence of systemic toxicity. Pain intensity and other recovery parameters were similar between the groups.

Conclusion: The lower supplemental morphine consumption and plasma lidocaine concentration in group IP would confirm that the effects of local anesthetics are likely to be predominant *via* local intraperitoneal receptors or anti-inflammatory effects and not *via* central mechanisms alone. **(ANESTHESIOLOGY 2014; 121:352-61)**

LOCAL anesthetics (LAs) have been used for postoperative pain management for decades. Not only do they act on peripheral nerves by preventing sodium influx, and systemically when administered intravenously or by absorption when injected locally, recent evidence even suggests that LAs have an anti-inflammatory effect.[1,2] Further improvement in postoperative analgesia has been made possible by the use of multi-hole catheters and intermittent injection of LA injected intra-abdominally, a method that is rapidly evolving currently. Several authors have successfully used LA for pain management after major abdominal operations, including abdominal hysterectomy,[3,4] open colorectal surgery,[5] and open radical prostatectomy.[6] Specifically, the use of LA injected *via* catheters placed preperitoneally or intraperitoneally has been found to reduce supplemental postoperative analgesic requirement and sometimes even side effects of opiates postoperatively.[1,2,5] The exact mechanism for this pain reduction remains unclear, but several explanations have been proposed, including sensory-neural block of peritoneal pain receptors,[2,7] vagal afferent nerve block transmitting sensory visceral information into the central nervous system[5] or *via* the antiinflammatory analgesic effect of LAs.[2] Additionally, because LA is absorbed into the systemic circulation when injected intraperitoneally, a central effect has also been proposed, similar to

What We Already Know about This Topic

- It remains unclear whether intraperitoneal administration of local anesthetic acts peripherally or centrally for analgesia after laparotomy

What This Article Tells Us That Is New

- In 60 patients undergoing open abdominal hysterectomy, morphine consumption was lower in women receiving lidocaine intraperitoneally than intravenously, indicating a peripheral action

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that *via* IV infusion. In two recent reviews[8,9] the authors argue that IV lidocaine in the perioperative period may reduce postoperative analgesic requirements and thereby promote faster return of bowel function and shorten hospital stay. However, it remains unclear whether the mechanism of action of LA injected intraabdominally is *via* local somatosensory or antiinflammatory mechanisms intraperitoneally or through their systemic absorption and a central effect.

Our hypothesis was that LAs injected intraperitoneally reduce postoperative pain *via* local mechanisms and not primarily by systemic absorption and a central effect. This randomized-controlled trial was therefore performed with the primary aim of assessing analgesic consumption during the first 24 h after abdominal hysterectomy in patients receiving the same dose of LA given either intravenously or intraperitoneally. Normal saline was administered in a third group of patients as placebo control and rescue analgesics given to all patients *via* a patient-controlled analgesic pump. The secondary aims were to assess pain scores, recovery parameters, side effects/complications, and venous plasma concentrations of LA.

Materials and Methods

This study was approved by the Regional Ethics Committee, Uppsala, and the Swedish agency for Foods and Drugs (Uppsala, Sweden), as well as registered in a clinical trials database, ClinicalTrials.gov (identification number NCT01492179) before patient recruitment. The study was also monitored and quality controlled by an independent, hospital-based clinical trials group. The study was double blind, randomized, parallel arm, superiority design, and patients were allocated in a 1:1:1 ratio according to a computer-generated program. All patients provided written informed consent before enrollment. A total of 60 patients of the American Society of Anesthesiology physical status classification system I to II, aged 30 to 75 yr, scheduled for abdominal hysterectomy with or without salpingo-oophorectomy and operated at the Örebro University Hospital between November 2011 and April 2013 were included in this study through the hospital-based data system. Exclusion criteria were allergy to LAs, chronic pain requiring opioid analgesics, patients with Atrioventricular block II, patients treated with class III antiarrhythmics, and those with severe renal and/or hepatic disease.

On the day of surgery, the Hospital Pharmacy randomized patients into three groups (20 patients in each group) using computer-generated randomized numbers inserted into sealed opaque envelopes and marked 1 to 60. Block randomization was used with two blocks of 30 patients each so that plasma concentration of lidocaine could be analyzed after the first 30 patients were recruited. All personnel involved in patient management as well as patients and study investigators were fully blinded to the method of analgesia until the study was complete.

Study Protocol

On the day of surgery, all patients received information about the pain scale, the numeric rating scale where the patients evaluated their pain on a scale from 0 to 10, with 0 = no pain and 10 = worst imaginable pain. They were also informed about how to use the patient-controlled analgesia morphine pump before surgery. The study drugs for initial bolus injection were prepared in two syringes, 20 ml in each, marked in blue for IV use and yellow for intraperitoneal use. The syringe contained lidocaine or saline, based on study group assignment. Additionally, two bags, 240 ml each, marked in blue for IV use and yellow for intraperitoneal use, were prepared for continuous infusion after surgery, and they contained the respective study drugs according to study group assignment. The drugs were administered according to the following protocol:

Group IV. The surgeon injected 20 ml of saline into the abdominal cavity after opening the peritoneum, moving the small intestines and exposing the uterus. The surgical procedure was thereafter stopped during 10 min. At the same time, 5 mg/ml lidocaine 100 mg (20 ml) was injected as an IV bolus during 10 min (120 ml/h) by one of the investigators. On arrival in the postanesthesia care unit (PACU), a continuous IV infusion of lidocaine 5 mg/ml (10 ml/h) was started and every hour thereafter, 10 ml saline was injected once per hour during 10 min *via* the intraperitoneal catheter.

Group IP. The surgeon injected 100 mg lidocaine 5 mg/ml (20 ml) into the abdominal cavity after opening the peritoneum, moving the small intestines and exposing the uterus. At the same time, 20 ml of saline was injected as an IV bolus during 10 min (120 ml/h). On arrival in the PACU, a continuous IV infusion of saline (10 ml/h) was started, and every hour thereafter, 5 mg/ml lidocaine 50 mg (10 ml) was injected during 10 min *via* the intraperitoneal catheter using an automated pump.

Group P. The surgeon injected 20 ml of saline into the abdominal cavity after opening the peritoneum, moving the small intestines and exposing the uterus. At the same time, 20 ml of saline was injected as an IV bolus during 10 min (120 ml/h). On arrival in the PACU, a continuous IV infusion of saline (10 ml/h) was started, and every hour thereafter, 10 ml saline was injected once per hour during 10 min *via* the intraperitoneal catheter.

The multihole catheter was inserted percutaneously by the surgeon at the end of surgery approximately 1 to 2 cm away from the edge of the incision, and the tip of the catheter was placed supravaginally in an identical way as described in a previous study.[3] All patients received 2 mg morphine intravenously and 20 ml of lidocaine 5 mg/ml at the wound edges at the end of surgery. Both the continuous infusion and the intermittent injections were stopped 24 h postoperatively. Alaris®-GW volumetric pump (Cardinal Health, San Diego, CA) was used to administer continuous IV infusion, whereas the intraperitoneal catheter was connected to a CADD®-Solis Ambulatory Infusion Pumps 5200 (Upper

Metro Place, Dublin, OH) for "automatic intermittent" bolus injections every hour, as described earlier. The multihole catheter was removed 24 h after surgery. The time to arrival in the PACU was considered to be 0 (t = 0) for all recordings made thereafter.

Anesthetic and Surgical Technique

All patients were premedicated with oral midazolam (0.05 to 0.1 mg/kg), and paracetamol (1 g) was given orally approximately 1 h before scheduled surgery. Anesthesia was induced with propofol (1 to 2 mg/kg) and fentanyl (1 to 2 μg/kg). Rocuronium (0.5 mg/kg) was used as muscle relaxant for tracheal intubation. General anesthesia was maintained with 1 to 3% sevoflurane and oxygen 33% in air. Mechanical ventilation was used in a low-flow system to maintain an end-tidal carbon dioxide of between 4.5 and 5.5 kPa. Sevoflurane concentration was adjusted to maintain adequate anesthesia depth assessed clinically, and fentanyl was given intermittently IV. When required for analgesic during surgery. At the end of surgery, muscle relaxation was reversed using glycopyrrolate (0.2 mg) and neostigmine (2.5 mg), and the gases were turned off. Monitoring included noninvasive blood pressure, pulse frequency, peripheral oxygen saturation, end-tidal gas monitoring, electrocardiography, and train-of-four stimulation. Surgery was performed in a standardized way using either a lower-abdominal midline incision or a Pfannenstiel incision depending on the choice of the operator and expected degree of surgical difficulty. Postoperatively, electrocardiography, blood pressure, and oxygen saturation were monitored routinely in the PACU for 24 h before the patient was transferred to the gynecological ward. The nurses recorded any signs and symptoms of systemic toxicity of LA, using a standardized questionnaire. In case of persistent pain unrelieved by intraperitoneal bolus or IV continuous infusion of study medication, the nurses administered IV morphine as "rescue" medication to all patients during the first 4 postoperative hours so that the numeric rating scale was 3 or less. Thereafter, and when the patient was fully awake, a patient-controlled analgesia pump was connected according to the hospital routines (bolus dose 1 mg, lock-out time 6 min), and all patients were encouraged in using this pump so that the pain was mild (numeric rating scale ≤3). When nausea and vomiting occurred postoperatively, ondansetron 4 mg IV was used as the drug of first choice followed by droperidol 0.625 mg IV if the nausea/vomiting persisted.

Recording and Measurements

The primary endpoint of this study was morphine consumption during 0 to 24 h. The secondary endpoints were lidocaine concentration, pain at the incision site, deep pain and pain on coughing, time to recovery, nonsteroidal anti-inflammatory drug consumption, postoperative nausea and vomiting, antiemetics administered, and sedation scores.

In addition to the routine postoperative protocols, the following data were recorded:

Rescue analgesic morphine consumption during 0 to 4, 0 to 24, and 24 to 48 h. Fentanyl and nonsteroidal anti-inflammatory drugs given intra- and postoperatively.

Pain intensity with numeric rating scale at the site of the incision, "deep" (visceral) pain and pain on coughing at 1, 4, 8, 24, and 48 h.

Time to recovery such as the ability to walk with and without support, gastrointestinal function (time to start drinking, eating, and intestinal motility), and postoperative home readiness/discharge, twice each day. All patients followed the enhanced recovery after surgery program and standardized criteria for early recovery after major surgery.

Side effects including nausea and/or vomiting (0 to 4, 4 to 24, and 24 to 48 h), antiemetics administered (0 to 24 and 24 to 48 h), grade of sedation (0 to 10 scale, where 0 = awake and 10 = aroused on stimulation), and other side effects and symptoms of LA toxicity.

Plasma Lidocaine Concentration

In the first 30 patients, 7 ml of venous blood was drawn in heparinized tubes intraoperatively at 15 min, 1 h after IV bolus injection of the saline or lidocaine and postoperatively at 4.5, 24.5, and 26.5 h after surgery. The blood was centrifuged to separate the plasma, which was frozen to −20°C. The plasma concentration of lidocaine was analyzed using liquid chromatography-mass spectrometry.[10] The limit of detection of lidocaine in the current study was 5 ng/ml (signal/noise-ratio >10).

Statistical Analysis

In a previous study,[11] the mean (SD) consumption of morphine during 24 h was 36 (17) mg in a group of patients receiving lidocaine intravenously. From our previous study, we think that this can be reduced by 50% in the group receiving intermittent intraperitoneal lidocaine compared with the group receiving continuous infusion of lidocaine intravenously.[4] Assuming $\beta = 0.1$ (power 90%) and $\alpha = 0.05$, we calculated that we needed 20 patients per group to be able to detect a statistical significant difference between the two active groups for the primary endpoint using unpaired t test. Mean (SD) is used to summarize continuous variables while categorical variables are presented as numbers (%). The primary endpoint, 0 to 24 h morphine consumption, was evaluated with one-way ANOVA comparing all the study groups, followed by Tukey-corrected *post hoc* test for pairwise group comparison. The *post hoc* tests are reported with corrected P values and 95% CIs. A similar analysis was also performed for intraoperative fentanyl and different markers for postoperative functional recovery. Morphine consumption was also evaluated by repeated measures over time: 0 to 4, 4 to 24, and 24 to 48 h using mixed model because of minor loss of data missing at random and Bonferroni corrected *post hoc* test for pairwise comparison between study groups at each time point, reported with corrected P values and 95%

CI. Normality assumption was evaluated with Shapiro–Wilk test, and if violation was present, log transformation, outlier exclusion, or nonparametric methods was performed for sensitivity analysis. Because the sensitivity analysis did not change any study conclusions, they are not reported in the result section. The same strategy of analysis for repeated measurements with mixed model was also applied for sedation, lidocaine concentration, pain at the incision site, deep pain, and pain on coughing. Categorical variables such as nonsteroidal anti-inflammatory drug consumption, postoperative nausea, postoperative vomiting, and antiemetics given (yes/no) were analyzed with an overall chi-square test, or Fischer exact test as appropriate, comparing all three study groups and then comparing pairwise between study groups with the same statistical test method corrected with Bonferroni method. Two-tailed *P* value less than 0.05 was considered to be statistically significant. All statistical analyses were performed using the SPSS version 17 (IBM SPSS Statistics, Chicago, IL) and STATA release 11 (Stata Corp., College Station, TX).

Results

Of the 95 patients interviewed for possible inclusion, 35 patients did not meet the inclusion criteria or refused to participate in the study (fig. 1). Of the 60 patients randomized, one patient in group IV was excluded after randomization because of the presence of first-degree atrioventricular block. The demographic and surgical characteristics in the groups are shown in table 1.

During the time period 0 to 24 h, the mean (SD) morphine consumption was significantly lower in group IP compared with that in group IV: 23.2 (12.1) *versus* 44.3 (17.3),

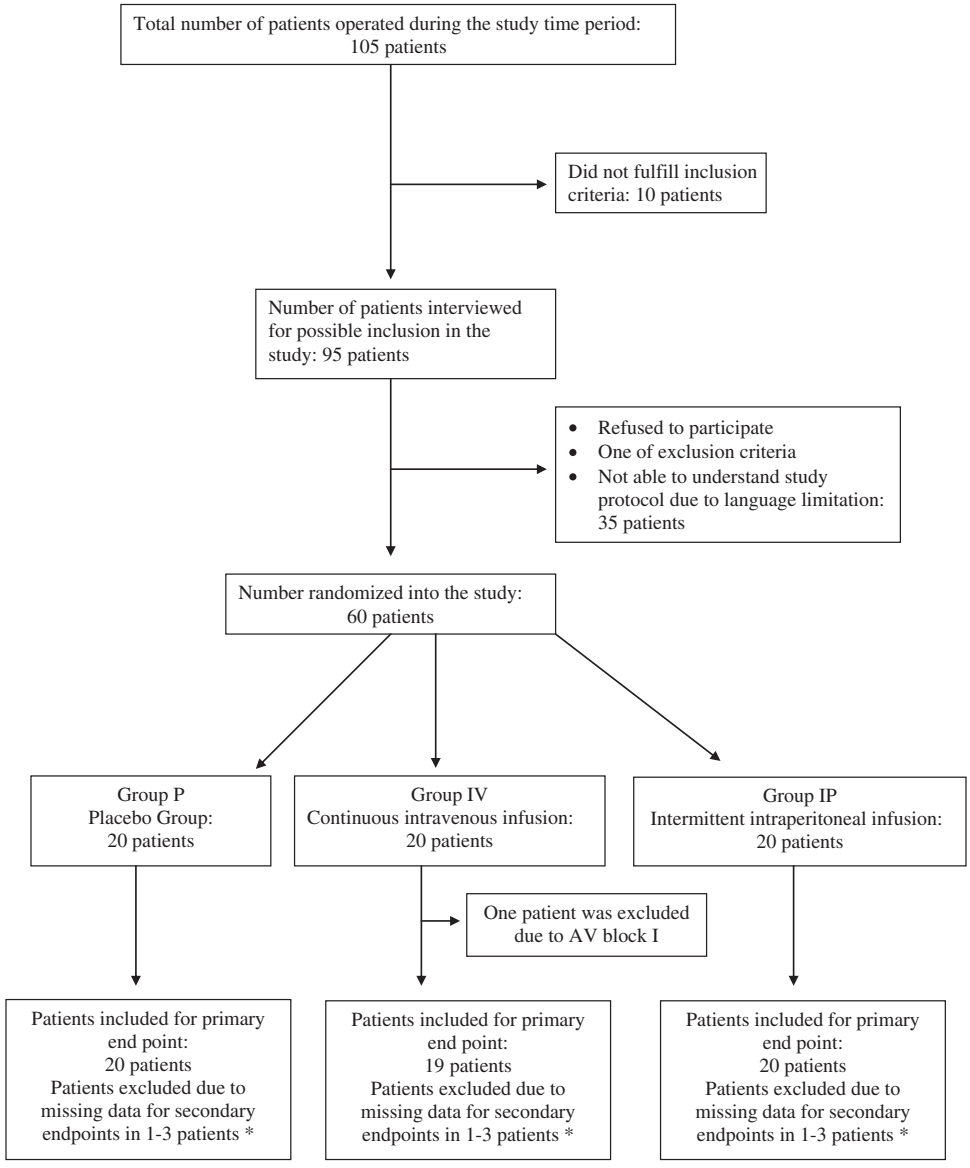

Fig. 1. Flow diagram of screened, excluded, and recruited patients. AV = atrioventricular; Group IP = intermittent intraperitoneal lidocaine; group IV = continuous intravenous lidocaine; group P = placebo. *See tables for details.

P value less than 0.01 during 0 to 24 h, 12.7 (7.4) *versus* 20.2 (8.3) during 0 to 4 h, $P = 0.02$ and $P = 10.6$ (6.8) *versus* 23.9 (14.3), $P = 0.03$ during 4 to 24 h, respectively (table 2). Pain intensity is shown in figure 2, A–C. In general, median pain intensity score in incisional and deep pain was 4 or less except during the first hour postoperatively. In deep pain, a significantly lower pain score was observed in group IP compared with group IV at 48 h postoperatively with a mean difference of 2.3 (95% CI 0.4 to 4.2, $P = 0.01$). On coughing, pain scores varied from 4 to 8 without any statistical differences between the groups. The patients in group P consumed significantly more morphine than patients in group IP, but there were no significant differences between group P and group IV 0 to 24 h postoperatively. During 24 to 48 h, no significant differences were found between the three groups. The intensity of postoperative pain did not differ between group P and the other two groups at any time.

No differences were found between the groups in the recovery parameters as well as in time to home readiness and length of hospital stay (table 3). No differences were seen between the groups in nausea/vomiting or the number of patients who received antiemetics during the time period 0 to 48 h. The patients in group IP and IV had statistically lower sedation score as compared with patients in group P ($P = 0.049$ and $P = 0.045$, respectively) (table 4).

No patient had any signs or symptoms of LA toxicity. The mean plasma concentration of lidocaine in group IP was significantly less than group IV at 15 min, 1 h, and 4.5 h (fig. 3). The mean difference, the 95% CI and *P* values were, respectively, 0.8 (0.6 to 0.9, $P < 0.01$); 0.3 (0.2 to 0.5, $P < 0.01$); and 0.7 (0.07 to 1.4, $P = 0.03$). No statistical differences were seen between these groups at 24.5 or 26.5 h.

Table 1. Demographic Data, Duration of Anesthesia, and Operation

	Group IV (n = 19)	Group IP (n = 20)	Group P (n = 20)
Age (yr)	55 (11)	47 (8)	54 (11)
Weight (kg)	76 (26)	75 (26)	78 (25)
Height (cm)	161 (18)	162 (23)	160 (20)
ASA physical status (1/2)	13/6	16/4	11/9
Duration of operation (min)	99 (35)	104 (24)	109 (44)
Duration of anesthesia (min)	141 (32)	148 (28)	153 (46)
Type of operation			
Total hysterectomy	11 (58%)	13 (65%)	10 (50%)
+Salpingo-oophorectomy	8 (42%)	7 (35%)	10 (50%)
Type of incision			
Pfannenstiel	9 (47%)	11 (55%)	6 (30%)
Lower midline	10 (52%)	9 (45%)	14 (70%)

Demographic data, duration of anesthesia, and operation are shown as mean (SD). All other data are shown as numbers (%) as appropriate.

ASA = American Society of Anesthesiologists; group IP = intermittent intraperitoneal lidocaine; group IV = continuous intravenous lidocaine; group P = placebo.

Table 2. Opioids and Rescue Analgesia Consumption

	Group IV	Group IP	Group P						
	n = 19	n = 20	n = 20	IV – IP		IV – P		IP – P	
	Mean (SD) Range	Mean (SD) Range	Mean (SD) Range	Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI)	*P* Value
Morphine consumption, mg									
0–4 h	20.3 (8.4) (6–34)	12.8 (7.4) (2–28)	21.3 (8.9) (7–37)	7.5 (1.0–14.0)	0.02	–1.1 (–7.6 to 5.5)	1.00	–8.6 (–15.0 to –2.1)	<0.01
4–24 h	23.9 (14.3) (6–59)	10.6 (6.8) (0–21)	28.2 (13.8) (7–59)	13.3 (3.8–22.9)	<0.01	–4.2 (–13.8 to 5.3)	0.84	–17.6 (–27.0 to –8.1)	<0.01
24–48 h	5.3 (7.8) (0–28)	11.2 (20.0) (0–82)	4.5 (5.5) (0–21)	–5.9 (–16.3 to 4.5)	0.51	0.8 (–9.6 to 11.2)	1.00	6.7 (–3.4 to 16.8)	0.32
0–24 h (primary endpoint)	44.3 (17.3) (16–80)	23.3 (12.2) (6–49)	50.9 (14.9) (17–89)	21.1 (9.6–32.6)	<0.01	–6.6 (–18.1 to 4.9)	0.36	–27.6 (–39.0 to –16.3)	<0.01
Intraoperative fentanyl, µg	264 (61)	261 (65)	239 (60)	3 (–45 to 51)	0.99	26 (–22 to 74)	0.41	22 (–25 to 70)	0.49
NSAID (0–24 h), n (%)	2 (10%)	3 (15%)	3 (15%)	NA	1.00	NA	1.00	NA	1.00

Morphine consumption 0–24 h was analyzed using one-way ANOVA with overall group difference $P < 0.01$ and results presented as group differences with CI, and *P* values corrected for multiple comparisons with Tukey method. Repeated measurement of morphine consumption 0–4, 4–24, and 24–48 h were analyzed with mixed model and presented as group differences with CI, and corrected *P* values for multiple comparison using Bonferroni method. NSAIDs are analyzed with Fischer exact test corrected for multiple comparisons using Bonferroni method.

Group IP = intermittent intraperitoneal lidocaine; group IV = continuous intravenous lidocaine; group P = placebo; NA = not available; NSAID = nonsteroidal antiinflammatory drugs.

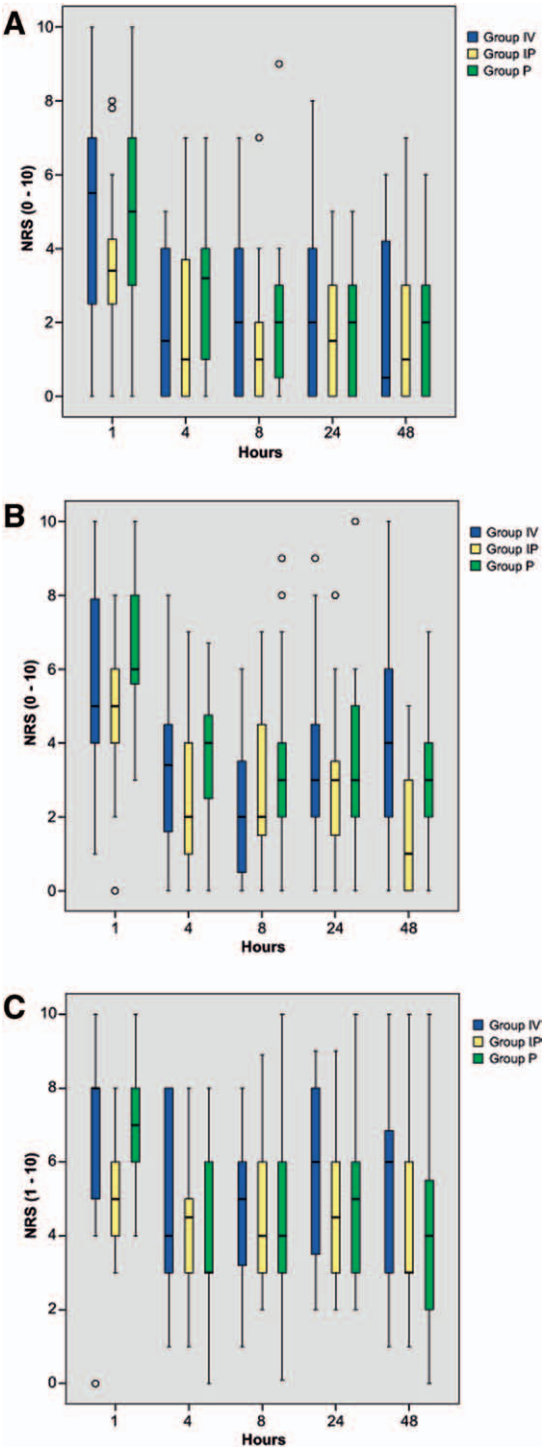

Fig. 2. (*A–C*) Pain at the incision site, deep pain, and pain on coughing. Distributions are shown as *box plots* and interquartile range. Group IP = intermittent intraperitoneal lidocaine; group IV = continuous intravenous lidocaine; group P = placebo; NRS = numeric rating scale; ° = outliers. The *whiskers* represent minimum and maximum values if outliers are not present.

Discussion

In this prospective, randomized, double-blind study, we found lower morphine consumption and a lower plasma concentration of total lidocaine concentration in patients receiving intraperitoneal LA compared with IV LAs, and no signs or symptoms of LA toxicity in any patient. Additionally, there were no differences in recovery parameters between the groups. In the doses administered, IV LA has a weak analgesic effect, and therefore, it is likely that intraperitoneally administered LAs have local effects that are predominantly central. In other words, despite achieving higher plasma concentration of lidocaine in patients given IV lidocaine compared with intraperitoneal, the pain was greater because rescue analgesic consumption was higher in this group.

There are several features of this study that are important to discuss. We used lidocaine as the LA because it can be administered intravenously, and the analgesic doses are known and well described. Although higher doses of LA do not seem to improve analgesia,[3] we agreed to use the same doses intraperitoneally as intravenously so that any dose-related analgesic effect could be excluded. We also measured plasma concentrations of LA to assess whether a slower absorption from intraperitoneal injection may subsequently prolong the duration of analgesia and if any toxic concentrations may result after intermittent intraperitoneal injections. We double blinded the current study to ensure that no source of bias could affect our results. We used patient-controlled rescue analgesia so that we have an objective and correct measure of analgesic consumption instead of nurse administered analgesia. Finally, we used a control group to study whether we could replicate our previous results and to compare analgesic efficacy of intraperitoneal *versus* IV administered lidocaine.

In a large prospective cohort study evaluating a total of 50,523 patients undergoing 179 different surgical procedures, abdominal hysterectomy was ranked as one that was associated with the poorest postoperative pain control,[12] and therefore a good model to study analgesic efficacy of lidocaine. Not only is pain after abdominal hysterectomy poorly treated,[12] many patients have a high incidence of nausea,[13] fatigue, and constipation. Additionally, chronic pain has been reported by 5 to 35% of women undergoing abdominal hysterectomy and has been found to be related to preexisting pain before surgery[14,15] and poor postoperative pain management.[16] Several studies have found that LA administered intravenously during the perioperative period reduces pain intensity and postoperative analgesic requirements[11,17] in different patient populations and a variety of surgeries.[8,9] However, when using IV LA, the dose has to be carefully controlled to detect systemic LA toxicity. Therefore, intravenously administered LA has not been used routinely for postoperative pain management.[18] Because of its simplicity and efficacy in treating postoperative pain, several authors have instead recommended the peripheral route of LA administration.[7,19,20] Mixed results have, however, been obtained when intraperitoneal LA has been administered as a single dose intraoperatively.[21,22] In contrast, LA is efficacious when administered by catheters placed intraperitoneally.[23] In

Table 3. Postoperative Functional Recovery

	Group IV (n = 19)	Group IP (n = 20)	Group P (n = 20)	*P* Value
Time to walk with help, h	24 (17–27) n = 14	20 (6–25) n = 14	23 (21–26) n = 16	0.24
Time to walk without help, h	25 (23–28) n = 16	22 (15–26) n = 14	24 (22–42) n = 15	0.17
Time to start drinking, h	2 (2–3) n = 18	3 (1–5) n = 19	3 (2–6) n = 19	0.11
Time to start eating, h	17 (7–25) n = 17	15 (6–22) n = 16	22 (18–25) n = 17	0.05
Home readiness, days	1 (1–2)	1 (1–2) n = 17	1 (1–2)	0.86
Length of hospital stay, days	2 (2–3)	2 (2–3) n = 17	2 (2–3)	0.61
Return of G-I function, days	1 (1–1)	1 (1–1) n = 18	1 (1–1) n = 17	0.17

All data are shown as median (IQR). All variables were analyzed using Kruskal–Wallis test. Because no group differences were statistically significant after correction for multiple comparisons with Bonferroni method, only Kruskal–Wallis *P* values are presented.

G-I = gastrointestinal; group IP = intermittent intraperitoneal lidocaine; group IV = continuous intravenous lidocaine; group P = placebo; IQR = interquartile range.

Table 4. Side Effect

	Group IV (n = 19)	Group IP (n = 20)	Group P (n = 20)	IV *vs.* IP *P* Value	IV *vs.* P *P* Value	IP *vs.* P *P* Value
PON						
0–4 h	9 (47%)	8 (42%) n = 19	10 (50%)	1.00	1.00	1.00
4–24 h	1 (5%)	4 (20%)	8 (40%)	0.54	0.06	0.90
24–48 h	1 (6%) n = 16	1 (7%) n = 14	1 (6%) n = 17	1.00	1.00	1.00
POV						
0–4 h	5 (26%)	1 (5%)	1 (5%)	0.54	0.54	1.00
4–24 h	1 (5%)	0 (0%)	4 (20%)	1.00	1.00	0.30
24–48 h	0 (0%)	0 (0%)	0 (0%)	NA	NA	NA
Antiemetics given (0–24 h)	14 (73%)	12 (66%) n = 18	15 (75%)	1.00	1.00	1.00
Antiemetics given (24–48 h)	10 (52%)	6 (30%)	10 (50%)	0.72	1.00	0.72
Sedation (NRS)						
4 h	5.0 (2.4)	5.7 (2.2) n = 18	5.6 (2.7)	1.00	1.00	1.00
24 h	4.7 (3.0)	4.7 (2.4) n = 19	6.8 (2.4)	1.00	0.049	0.045
48 h	4.7 (3.1) n = 16	3.3 (2.7) n = 14	3.9 (2.3) n = 16	0.88	1.00	1.00

All results are shown as number of patients n (%) unless otherwise stated. PON and POV were analyzed using chi-square test or Fischer exact test, as appropriate, corrected for multiple comparison with Bonferroni method. Sedation is shown as mean (SD) and analyzed using mixed model and presented as group differences with *P* values, corrected for multiple comparison with Bonferroni method.

Group IP = intraperitoneal lidocaine; group IV = continuous intravenous lidocaine; group P = placebo; NA = not applicable; NRS = numeric rating scale (0 = fully awake and 10 = deep asleep); PON = postoperative nausea; POV = postoperative vomiting.

an earlier study in patients having LA by continuous infusion intraperitoneally, we were able to show a greater than 40% reduction in analgesic requirements compared with placebo during the first postoperative day.[10] In subsequent studies, we were also able to show that 12.5 mg levobupivacaine by continuous intraperitoneal infusion is optimal, and increasing the dose does not improve analgesia.[3] Furthermore, intermittent injection of LA intraperitoneally reduced analgesic requirements by greater than 30% compared with continuous intraperitoneal infusion.[4] The question that remains unanswered is whether the analgesia seen in several of these studies is *via* systemic absorption of LA and a "central effect," as with IV infusion of LA, or a "peripheral" (local) effect intraperitoneally.

Our findings were that pain intensity was similar in all groups at all-time points studied. In other words, patients had good analgesia, except during the first postoperative hour, with similar pain intensity in all three groups during the postoperative observation period. This is important because it confirms that the pain intensity when using the patient-controlled analgesia technique was similar in all three groups. However, the rescue analgesic consumption was considerably higher during 0 to 24 h when LA or saline was administered intravenously compared with intraperitoneal LA. IV LAs have been shown to be efficacious in some studies,[24–26] but not all.[27–29] The absence of any significant effect of IV LA in our current study may be because of inadequate dose of lidocaine or inappropriate technique of IV administration. This is discussed further below under Study Limitations; we could, however, verify that intraperitoneal LAs provide good analgesia, and that the mean morphine consumption could be reduced by greater than 50%, compared with those receiving placebo. These findings are consistent with our previous study where intermittent injection of LA was better than by continuous infusion.[4] It remains uncertain how LA relieves pain when injected through a catheter into the intraperitoneal cavity. It is possible that LAs block peritoneal afferent nerve endings, or the vagal afferent fibers that carry sensory input

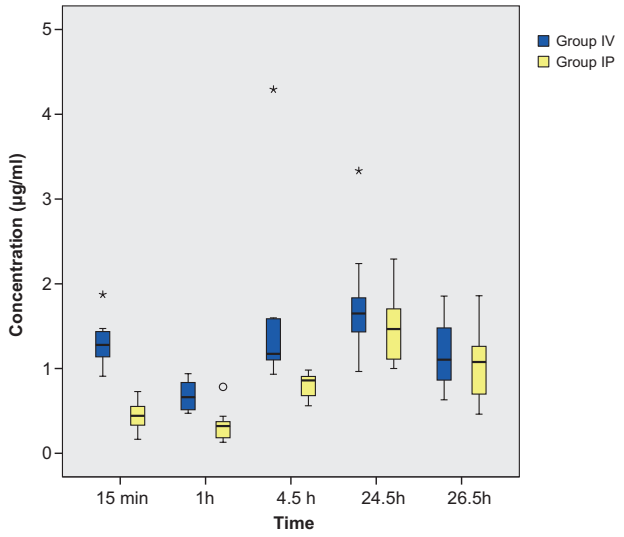

Fig. 3. Plasma lidocaine concentration. Distributions are shown as *box plots* with median and interquartile range. Group IP = intermittent intraperitoneal lidocaine; group IV = continuous intravenous lidocaine; ° = outliers; **P* < 0.05. The *whiskers* represent minimum and maximum values if outliers are not present.

from the gut and peritoneum, or that the systemic absorption from the abdominal cavity may have a mild central effect. An anti-inflammatory action of LA has also been suggested as a possible mechanism of action by several investigators.[1,2,4,7,30] It is thought that LAs may inhibit vagal afferents to the brain, thereby decreasing inflammatory signaling pathways and central pain mechanisms, which may be an important area for research in the future. Unfortunately, we did not measure cytokine concentrations in the plasma.

We measured LA concentration in plasma at defined time intervals in both groups receiving lidocaine and found much lower concentration than that known to be associated with LA toxicity (>5 µg/ml).[31] Additionally, no patient in either group had any signs or symptoms of LA toxicity. The problem of postoperative nausea after abdominal hysterectomy is well known.[13] Although many investigators have confirmed the association between nausea and morphine consumption,[32–34] we did not find a lower frequency of nausea in the intraperitoneal group where morphine consumption was lower. We found a significantly lower sedation score in groups IV and IP compared with group P where morphine consumption was higher. This is significant and important because lower morphine consumption may also reduce sedation. Finally, we could not see any difference in home readiness/discharge between the groups. The introduction of the enhanced recovery after surgery program at our hospital in the last few years has radically changed the practice of discharging patients because majority are home within 2 to 3 days after surgery.

Study Limitations

One important limitation of this study was that the plasma lidocaine concentration was not measured between 4.5 and 24.5 h. However, the total mean plasma concentration of lidocaine in group IP was lower than that in group IV even at 24.5 h, although this did not reach statistical significance. It has previously been shown that a plateau concentration is reached 10 to 20 min after an intraperitoneal bolus administration of 0.375% bupivacaine.[23,35] Because the blood sample was taken 30 min after the 24-h postoperative injection of LA/saline, the plasma concentration at this point should represent the peak values. Therefore, the probability of finding higher concentrations at another time point in group IP is unlikely, and therefore our conclusions remain valid.

Another limitation of this study may be the dose and timing of LA infused intravenously. Some investigators have found that lidocaine is effective when plasma concentration is between 1.75 and 2.7 µg/ml.[17,31,36] In our study, the mean total plasma concentration after IV administration was 1.75 µg/ml or less, which could be considered to be low. Additionally, to be effective in managing postoperative pain, LA infusion has to be started at least 30 min before incision and should be continued intra- and postoperatively.[31] Because the aim of this study was to test the hypothesis whether the analgesic effect of LA was attributable to a systemic absorption or *via* peripheral mechanism, we administered *a priori*, the same dose of lidocaine IV and intraperitoneal. Thus, the low dose of LA administered to patients in group IV may explain the lack of statistical significant difference between group IV and group P, although the morphine consumption was lower (44.3 mg) in the IV group compared with that in the placebo group (50.9 mg). Possibly, adequate doses of LA administered intravenously may have led to a morphine-sparing effect, as has been shown in previous studies[17,31] Finally, we did not confirm the position of the catheter tip by contrast injection. Migration of the catheter is possible during mobilization, and the precise spread of LA after a bolus injection remains unknown. However, considering that the study was randomized and blinded, it is unlikely that there is a systemic bias in catheter placement by the surgeon.

Conclusions

We found a significant opioid-sparing effect when intermittent intraperitoneal injection of LA was administered as compared with continuous IV infusion. The plasma concentration of LA was lower when given intraperitoneally compared with the same dose administered intravenously. The analgesic effects of intraperitoneal LAs are likely to be predominantly *via* local intraperitoneal receptors or anti-inflammatory effects, and not *via* central mechanisms alone.

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Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Perniola: Department of Anesthesiology and Intensive Care, University Hospital, SE 701 85 Örebro, Sweden. perniola.d@gmail.com. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

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