

Perioperative Intravenous Lidocaine Has Preventive Effects on Postoperative Pain and Morphine Consumption After Major Abdominal Surgery

Wolfgang Koppert, MD*, Marc Weigand, MD*, Frank Neumann, MD*, Reinhard Sittl, MD*, Jürgen Schuettler, MD*, Martin Schmelz, MD†, and Werner Hering, MD‡

*Department of Anesthesiology, University of Erlangen, Erlangen, Germany; †Department of Anesthesiology Mannheim, University of Heidelberg, Mannheim, Germany; and ‡Department of Anesthesiology, St. Marien Hospital Siegen, Siegen, Germany

Sodium channel blockers are approved for IV administration in the treatment of neuropathic pain states. Pre-clinical studies have suggested antihyperalgesic effects on the peripheral and central nervous system. Our objective in this study was to determine the time course of the analgesic and antihyperalgesic mechanisms of perioperative lidocaine administration. Forty patients undergoing major abdominal surgery participated in this randomized and double-blinded study. Twenty patients received lidocaine 2% (bolus injection of 1.5 mg/kg in 10 min followed by an IV infusion of 1.5 mg · kg⁻¹ · h⁻¹), and 20 patients received saline placebo. The infusion started 30 min before skin incision and was stopped 1 h after the end of surgery. Lidocaine blood concentrations were measured. Postoperative pain ratings (numeric rating scale of 0–10) and morphine

consumption (patient-controlled analgesia) were assessed up to 72 h after surgery. Mean lidocaine levels during surgery were 1.9 ± 0.7 μg/mL. Patient-controlled analgesia with morphine produced good postoperative analgesia (numeric rating scale at rest, ≤3; 90%–95%; no group differences). Patients who received lidocaine reported less pain during movement and needed less morphine during the first 72 h after surgery (103.1 ± 72.0 mg versus 159.0 ± 73.3 mg; Student's *t*-test; *P* < 0.05). Because this opioid-sparing effect was most pronounced on the third postoperative day, IV lidocaine may have a true preventive analgesic activity, most likely by preventing the induction of central hyperalgesia in a clinically relevant manner.

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Preclinical studies revealed analgesic effects of IV sodium channel blockers in experimental models leading to sensitization and increased responses of nociceptive afferents (1–6). Mechanoinensitive nociceptors, a subgroup of nociceptors involved in the generation and maintenance of hyperalgesia, were particularly sensitive to IV lidocaine (4,5). These observations were confirmed by clinical studies showing antinociceptive effects of sodium channel blockers, especially in chronic pain states dominated by hyperalgesia (7–12). It remains unclear whether IV sodium

channel blockers affect postoperative pain. Perioperatively administered systemic lidocaine decreases postoperative pain, whereas lidocaine treatment in the postoperative period only failed to produce analgesic effects (13–16). However, the time course of pain ratings and patient-controlled morphine consumption for a longer period after surgery have not been investigated. Therefore, the aim of this study was to determine the effects of systemic lidocaine on morphine consumption in the postoperative period. Short accounts of this work have previously been published in abstract form (17).

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Address correspondence and reprint requests to Priv.-Doz. Dr. med. W. Koppert, Department of Anesthesiology, University Hospital Erlangen, Krankenhausstrasse 12, D-91054 Erlangen, Germany. Address e-mail to koppert@kfa.imed.uni-erlangen.de.

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Methods

After approval by the Ethics Committee of the Medical Faculty of the University of Erlangen, a prospective, randomized, and double-blinded study of 40 patients undergoing major abdominal surgery was undertaken. Patients were excluded from the study when

immediate tracheal extubation after surgery was not planned, when they regularly took analgesics or had taken opioids or antiarrhythmic drugs within 1 wk of surgery, when they had a history of drug or alcohol abuse, or when there were contraindications to the self-administration of opioids (i.e., they were unable to understand the patient-controlled analgesia [PCA] device). The afternoon before surgery, patients were recruited and, after giving informed consent to take part in the study, were instructed by an anesthesiologist on the use of the verbal rating scale, identifying 0 as "no pain" and 10 as "worst imaginable pain." They were also instructed in the use of a PCA device.

Randomization of the study medication (lidocaine versus saline) was performed with computer-generated codes maintained in sequentially numbered, opaque envelopes. Additional envelopes were provided if patients had to be excluded after recruitment and randomization.

Anesthesia was induced with midazolam 0.05 mg/kg, fentanyl 3 μ g/kg, and etomidate 0.2 mg/kg, followed by cisatracurium 0.1 mg/kg to facilitate orotracheal intubation. After intubation, ventilation was controlled to maintain normocapnia with isoflurane in 35% oxygen with nitrous oxide. The maintenance of anesthesia was left to the discretion of each anesthesiologist, with the exception of the administration of opioids: every patient had to receive at least 6 μ g/kg of fentanyl before surgical incision and no more than 1 μ g/kg of fentanyl per hour. The last dose of fentanyl had to be administered at least 30 min before the end of the surgical procedure. This regimen was performed to minimize the variation of intraoperatively administered opioids as much as possible. Furthermore, all anesthesiologists were instructed to avoid using local anesthetics. The surgical procedures were performed by three general surgeons and two urologists who often worked together, thus limiting surgical variation.

Immediately after orotracheal intubation, patients of the lidocaine group received an IV bolus injection of lidocaine (1.5 mg/kg in 10 min) followed by a continuous IV infusion at 1.5 mg \cdot kg⁻¹ \cdot h⁻¹. At least 30 min was kept between the start of the continuous infusion and surgical incision. The infusion was terminated 60 min after skin closure. Patients of the control group received an infusion of saline in an equal manner. The anesthesiologist, the surgeon, and the nursing staff were all blinded to the group allocations.

All patients were transferred to the postanesthesia care unit for at least 12 h. Both in the postanesthesia care unit and on the surgical ward, the patients were observed by nursing staff members who was blinded to the treatment.

During the first postoperative hours, pain intensity was evaluated every 15 min. If pain intensity exceeded 4 (out of 10), PCA was started, and the time between

skin closure and the first PCA request was noted. The PCA settings were a demand dose of 2 mg of morphine hydrochloride and a lockout of 10 min, with no continuous rate provided. If the pain intensity exceeded 6 (out of 10) for at least 30 min, the demand dose was doubled for at least 12 h. Patients were monitored for sedation via a four-point categorical scale (0, alert; 1, sleepy but arousable; 2, stupor; 3, coma) and for episodes of desaturation via pulse oximetry. After discontinuation of the PCA pump, morphine consumption and the time and number of positive and negative PCA requests were recorded via dedicated software.

Pain intensities at rest and during movement (i.e., deep inspiration, coughing, and walking) were monitored every 2 h until the first postoperative day and then every 4 h until the end of the observation period. Furthermore, the patients were asked to report side effects such as light-headedness, perioral numbness, sedation, nausea, vomiting, obstipation, and pruritus.

Arterial blood samples were taken from an arterial line on the noninfused arm before and immediately after bolus infusion and then during and 1 h after continuous infusion. Plasma was stored at -72°C for later analysis. Lidocaine levels were analyzed with a validated high-pressure liquid chromatography method by using a C-18 reverse-phase column. The mobile phase was 30% methanol and 70% water and contained 2 g of sodium acetate (pH 3). Detection was performed at 220 nm with a Waters 484 ultraviolet detector. Plasma samples were extracted with C-18 solid-phase extraction columns by using etidocaine as an internal standard. The columns were rinsed twice with methanol and buffer (20 mL of 1 M Na₂CO₃ in 200 mL of water). One milliliter of plasma together with the internal standard was added to the column and rinsed twice with buffer. Elution of lidocaine was performed with 200 μ L of methanol. The method was linear up to 10,000 ng/mL, with a recovery rate of more than 90% and an interassay variability of 6%.

Our experience with this type of surgery indicated that PCA morphine consumption over the initial 72 postoperative hours after major abdominal surgery is approximately 150 \pm 75 mg. A sample size estimate indicated that 18 patients per group would give a power of 80% at an α level of 0.05 for detecting a difference in morphine consumption of at least 35%. The study size was thus prospectively set to 40 patients.

Age, weight, height, duration of the infusion, and cumulative morphine consumption were compared by using unpaired Student's *t*-tests. The frequencies of gender, ASA status, and PCA requests, as well as the incidence of side effects, were analyzed by using Fisher's exact tests. The fraction of patients not requiring supplemental postoperative morphine was evaluated with survival curves and was compared by using the

Kaplan-Meier log-rank test. Morphine consumption and pain ratings over time were statistically evaluated with Student's *t*-test and the Mann-Whitney *U*-test, respectively, and corrected with the Bonferroni procedure. Significance levels throughout this study were $P < 0.05$; all data were presented as mean \pm SD or median and 25%–75% interquartile ranges. The Statistica software package (StatSoft, Tulsa, OK) was used for statistical analyses.

Results

Three patients were excluded during the study because of hypothermia that required prolonged mechanical ventilation ($n = 2$, one in each group) or because of surgical complications that required another procedure on the second postoperative day ($n = 1$ patient from the control group). They were replaced according to the previously described procedure. Finally, 8 women and 32 men finished the study protocol; their average age (\pm SD) was 57 ± 12 yr (range, 31–71 yr). Both groups were comparable with regard to age, weight, height, and the distribution of sex (Table 1). The type and lengths of the surgical procedures were similar, leading to a mean duration of infusion of approximately 6 ± 2 h in both groups (Table 1). There was no perioperative mortality (<30 days) among the 40 patients enrolled in our study.

The lidocaine infusion started 51 ± 13 min (range, 35–80 min) before surgical incision. Arterial plasma levels of lidocaine were stable during infusion, and mean levels were 1.9 ± 0.7 $\mu\text{g}/\text{mL}$ (Fig. 1). In no case did lidocaine plasma concentrations approach a toxic level (>5 $\mu\text{g}/\text{mL}$). One hour after termination of the infusion, mean lidocaine plasma levels decreased to 0.9 ± 0.6 $\mu\text{g}/\text{mL}$. No anesthesiologist noted adverse events related to the lidocaine infusion during surgery. Furthermore, no patient after having regained consciousness complained of lidocaine-related side effects such as perioral numbness or metallic taste. The incidences of drowsiness, light-headedness, and nausea were comparable in the lidocaine and control groups. At no time point were lidocaine plasma concentrations detected in the control group.

The survival curve analysis of the first morphine administration revealed no difference ($P > 0.1$). Furthermore, the median time to the first PCA use was similar in both groups ($P > 0.5$) (Table 2). However, the request for morphine during the observation period of 72 h was significantly smaller in the lidocaine group ($P < 0.05$), resulting in a reduced overall morphine consumption ($P < 0.05$) (Table 2). This reduction was primarily based on smaller morphine requirements in the lidocaine group throughout the second half of the observation period ($P < 0.05$) (Fig. 2).

PCA provided adequate analgesia in both groups: the pain intensity at rest was not different between groups, with a median pain intensity score not exceeding 1 of 10 ($P > 0.1$) (Fig. 3). However, the control group exhibited significantly more pain during movement, especially during the second and third postoperative 24 h ($P < 0.05$) (Fig. 3). In this group, pain intensities exceeded 4 of 10 and reached this acceptable level only at the end of the observation period.

The severity of side effects was mild in general. The incidence of side effects was similar in the lidocaine and the control groups (Table 3). Furthermore, the grade of obstipation was similar in both groups; lidocaine-treated patients had their first bowel movement 79 h (66–84 h) after surgery, and the control patients had their first bowel movement 85 h (68–96 h) after surgery ($P = 0.16$).

Discussion

In our study, the analgesic and antihyperalgesic effects of systemic lidocaine on postoperative pain intensity and morphine consumption were investigated. Consistent with previous studies, we found that systemic lidocaine reduced postoperative pain and morphine consumption when applied perioperatively (13,16). However, the effects were most prominent at 36 hours after surgery. Therefore, the perioperative period seems to be of particular importance for lidocaine-sensitive mechanisms of postoperative pain. The time course of the analgesic and antihyperalgesic effects suggests that these mechanisms prevent the induction of central hyperalgesia, leading to enhanced postoperative pain therapy.

Although the analgesic effects of systemic lidocaine have been proven for chronic pain, especially for neuropathic pain states (8–10,12,18,19), conflicting results have been achieved in acute pain, such as postoperative pain (13–16,20,21). When IV lidocaine was administered during surgery at doses large enough to induce toxic side effects (>5 $\mu\text{g}/\text{mL}$), direct analgesic and morphine-sparing effects were observed (20,21). To minimize adverse reactions, Cassuto et al. (13) administered lidocaine in a small-dose regimen (2 mg/min) starting 30 minutes before surgery and continuing for 24 hours after surgery. They found significant relief of postoperative pain and a decrease in opioid consumption during the first and second postoperative days. In contrast, if a small-dose lidocaine infusion was established in the postoperative period only, lidocaine failed to produce analgesic effects (14,15). Although the observation period was limited to the early postoperative phase, the results suggest that lidocaine might have its best effects when administered during surgery, i.e., during the presence of significant nociceptive input.

Table 1. Morphometric and Demographic Data, Surgical Procedures, and Duration of Infusions

Variable	Saline	Lidocaine
Age (yr)	56 ± 12	58 ± 12
Weight (kg)	76.8 ± 11.3	75.6 ± 11.8
Height (cm)	172.6 ± 7.8	174.3 ± 7.5
Sex (men/women)	16/4	16/4
ASA status (I/II/III)	3/13/4	2/12/6
Procedure		
Prostatectomy with lymph node dissection	9	10
Cystectomy with lymph node dissection	3	2
Abdominal nephrectomy with lymph node dissection	3	2
Colectomy with lymph node dissection	2	3
Lymph node dissection	3	3
Duration of infusion (h)	6.2 ± 1.9	6.2 ± 2.1
Duration of hospital stay (d)	14.2 ± 3.1	12.8 ± 4.2

Values are mean ± SD or number of patients. There were no significant differences between the groups.

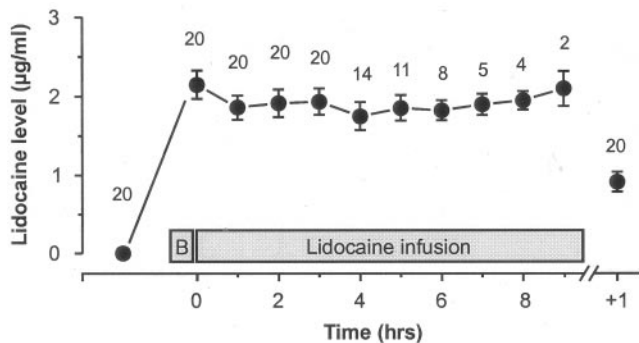


Figure 1. Lidocaine plasma levels before and immediately after bolus infusion of 1.5 mg/kg (B) and during and 1 h after continuous infusion of 1.5 mg · kg⁻¹ · h⁻¹. Figures indicate the number of patients receiving the infusion; values are mean ± SEM.

Table 2. Data of Patient-Controlled Analgesia (PCA)

Variable	Saline	Lidocaine
Total morphine consumption (mg)	159.0 ± 73.3	103.1 ± 72.0*
Time to first PCA use (min)	30 (15-71)	49 (21-68)
Total PCA requests	68 (49-90)	38 (22-65)*
Positive PCA requests	47 (38-63)	33 (20-50)*
Negative PCA requests (% of total PCA requests)	25 (11-35)	18 (11-26)

Values are mean ± SD or median (25%-75% interquartile range). Statistically significant differences between the groups: * *P* < 0.05.

The benefit of a continuous small-dose lidocaine infusion during surgery was confirmed by Groudine et al. (16). Their study was optimized to reach an early hospital discharge in patients undergoing radical retropubic prostatectomy. All patients received ketorolac as standard pain medication, and morphine was additionally applied for breakthrough pain and for those patients not receiving ketorolac. They found that perioperative administration of lidocaine resulted in a faster return of bowel function and less overall pain, which resulted in a shorter hospital stay (4 ± 0.7 days versus 5.1 ± 2.9 days; *P* < 0.05).

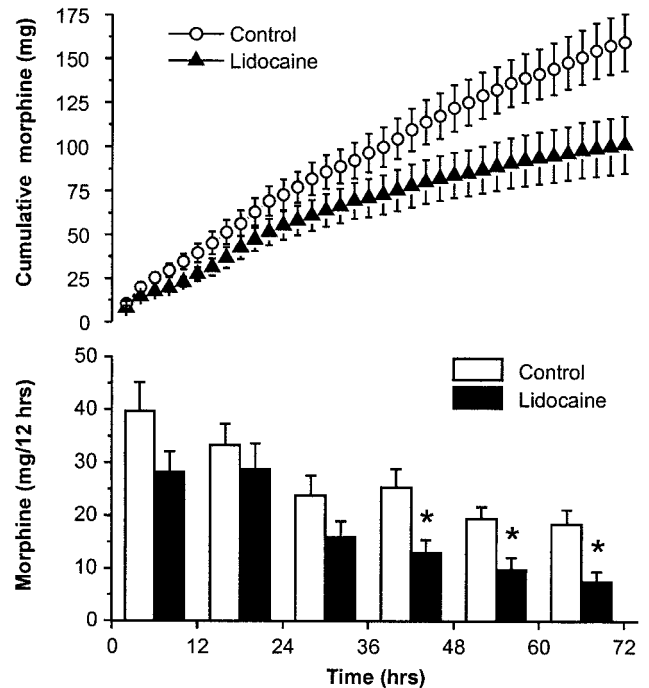


Figure 2. Upper panel: cumulative postoperative morphine consumption in the two groups during 72 h after connection of the patient-controlled analgesia pump. Lower panel: morphine consumption in 12-h intervals in the two groups. Values are mean ± SEM. * *P* < 0.01; unpaired Student's *t*-test corrected with the Bonferroni procedure.

In our study, different surgical procedures were included. All were major abdominal surgeries with extended tissue trauma and without additional regional anesthesia. Thus, a longer time was needed for recovery, which was reflected in an extended hospital stay (12.8 ± 4.2 days versus 14.2 ± 3.1 days; not significant). Furthermore, the design was optimized to determine the time course of the analgesic and anti-hyperalgesic effects of small-dose lidocaine. Therefore, a PCA device was used with small boluses of morphine and a lockout of 10 minutes. This method

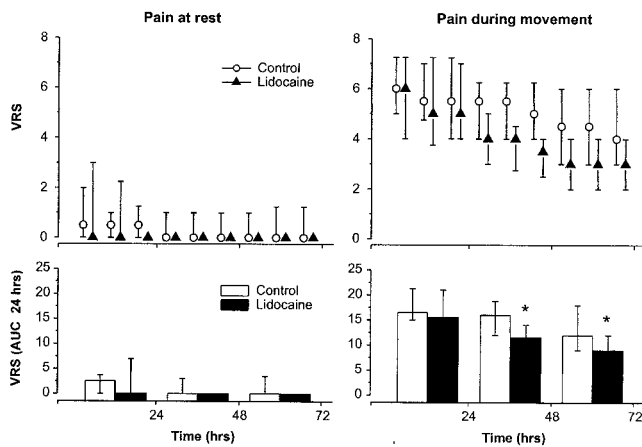


Figure 3. Pain ratings at rest and during movement in the two groups. Upper panels: mean ratings were calculated three times per day, representing 8-h intervals. Lower panels: areas under the curve (AUCs) of pain ratings during 12-h intervals. Values are median and 25%-75% interquartile ranges. **P* < 0.01; Mann-Whitney *U*-test corrected with the Bonferroni procedure. VRS = verbal rating scale.

Table 3. Incidence of Sedation, Nausea, Vomiting, Obstipation, and Pruritus

Variable	Saline	Lidocaine
Sedation	7/2/0	4/2/0
Nausea	12/5/0	9/4/0
Vomiting	5/1/0	4/1/0
Pruritus	1/2/2	0/2/0
Obstipation	20/20/15	20/19/14

Values are the number of patients having the observed effects during the first, second, and third 24-h intervals. There were no statistically significant differences between the groups.

was proven to detect differences in morphine requirements, especially in the postoperative period. Additionally, pain ratings at rest and with movement were obtained three times per day.

Because the perioperative period was found to be of particular importance for lidocaine-sensitive mechanisms, the infusion was started at least 30 minutes before surgery and was terminated 1 hour after surgery. A bolus injection of lidocaine 1.5 mg/kg followed by a continuous infusion of 1.5 mg · kg⁻¹ · h⁻¹ led to lidocaine plasma levels of approximately 2 μg/mL. Although lidocaine levels varied in a wide range, no lidocaine plasma level more than 3.8 μg/mL was found except in one patient, in whom a plasma level of 4.5 μg/mL was observed immediately after bolus injection. These findings are in accordance with previous studies, in which a continuous infusion of lidocaine 1.5–2.0 mg/kg led to variable plasma levels between 1.3 and 4.0 μg/mL (14,16). No lidocaine-related side effects were observed. After recovery of anesthesia, all patients felt sedated one hour later. Shortly after termination of the infusion, the incidence of nausea and vomiting was similar in both treatment

groups. Therefore, the results underline the safety of systemic lidocaine for perioperative use.

The time to first PCA use was similar in both groups. Although a delayed demand for morphine was observed in the lidocaine group, no lasting, direct analgesic effects of the lidocaine infusion were determined in our study. Therefore, small-dose lidocaine failed to show the additive effect observed after the administration of large-dose lidocaine (20,21). However, we cannot exclude that the power in our study was too low to detect these effects, because they might be more prominent in a larger sample.

However, the overall morphine consumption was clearly reduced in the lidocaine group. This reduction was based on smaller morphine requirements during the second and, above all, during the third postoperative day. We therefore suggest that these observations reflect clinical relevance to experimental findings in which lidocaine was considered as antihyperalgesic rather than as analgesic (4–6).

This is confirmed by the pain intensities observed in both treatment groups. Both groups had similar pain ratings at rest, with a rating of ≤3 in 90%–95% of the patients; this reflects adequate pain therapy with the PCA. However, pain ratings during movement differed between the treatment groups; activities such as deep inspiration, coughing, and walking led to significantly smaller pain ratings in the lidocaine group as compared with the control group. Again, this effect was most pronounced on the second and third postoperative day, despite a smaller morphine requirement in this group.

The mechanisms and the site of action of systemic lidocaine are still unclear. Systemic lidocaine can inhibit peripheral neuropeptide release (5); however, it is assumed that the main therapeutic effect can be attributed to a central antihyperalgesic effect (22). In abdominal surgery with extended tissue damage, there is major input from chemonociceptors to the central nervous system. In humans, especially, the mechanoinsensitive nociceptors are known to be tonically activated by chemicals (23). This class of nociceptors has also been linked to the induction of central sensitization in experimental (23,24) and clinical (25) settings. In line with these results, mechanoinsensitive nociceptors were particularly sensitive to small-dose lidocaine (4,5), thus preventing the induction of central hyperalgesia and improving the postoperative pain therapy.

However, the results are partly in contrast to the findings of Groudine et al. (16), who reported an opioid-sparing effect in the early postoperative period only, whereas the total consumption of pain medication failed to reach statistical significance. This might be explained by the type of surgery they studied, i.e., without extended tissue trauma, leading to a lesser pain experience in their patients and thus less need for

the breakthrough pain medication, morphine (they showed approximately one tenth of the morphine consumption observed in our study). We therefore suggest that the perioperative administration of systemic lidocaine is most effective in surgery associated with the development of pronounced central hyperalgesia, i.e., intestinal and bowel surgery. The pain experience after these types of surgery can be attenuated by lidocaine in a clinically relevant manner.

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