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Lack of Impact of Intravenous Lidocaine on Analgesia, Functional Recovery, and Nociceptive Pain Threshold after Total Hip Arthroplasty

Frédéric Martin, M.D., Kamel Cherif, M.D.,† Marc Emile Gentili, M.D., Ph.D.,‡ Dominique Enel, M.D.,‡ Emuri Abe, Pharm.D.,§ Jean Claude Alvarez, Pharm.D., Ph.D.,‖ Jean Xavier Mazoit, M.D., Ph.D.,# Marcel Chauvin, M.D., Ph.D.,** Didier Bouhassira, M.D., Ph.D.,†† Dominique Fletcher, M.D., Ph.D.***

Background: **The analgesic effect of perioperative low doses of intravenous lidocaine has been demonstrated after abdominal surgery. This study aimed to evaluate whether a continuous intravenous low-dose lidocaine infusion reduced postoperative pain and modified nociceptive pain threshold after total hip arthroplasty.**

Methods: **Sixty patients participated in this randomized double-blinded study. Patients received lidocaine 1% (lidocaine group) with a 1.5 mg/kg^{-1} intravenous bolus in 10 min followed by a 1.5 mg · kg^{-1} · h^{-1} intravenous infusion or saline (control group). These regimens were started 30 min before surgical incision and stopped 1h after skin closure. Lidocaine blood concentrations were measured at the end of administration. In both groups, postoperative analgesia was provided exclusively by patient-controlled intravenous morphine. Pain scores, morphine consumption, and operative hip flexion were recorded over 48 h. In addition, pressure pain thresholds and the extent of hyperalgesia around surgical incision were systematically measured at 24 and 48 h.**

Results: **In comparison with the placebo, lidocaine did not induce any opioid-sparing effect during the first 24 h (median [25–75% interquartile range]; 17 mg [9–28] *vs.* 15 mg [8–23]; P = 0.54). There was no significant difference regarding the effects of lidocaine and placebo on pain score, pressure pain thresholds, extent in the area of hyperalgesia, and maximal degree of active hip flexion tolerated. Mean plasma lidocaine concentration was 2.1 ± 0.4 μg/ml.**

Conclusion: **Low dose perioperative intravenous lidocaine after total hip arthroplasty offers no beneficial effect on postoperative analgesia and does not modify pressure and tactile pain thresholds.**

PATIENTS experience moderate to severe pain after total hip arthroplasty. Adequate control of postoperative pain facilitates earlier mobilization and rehabilitation. Patient-controlled analgesia is effective to treat pain at rest, but seems to be inadequate for dynamic analgesia and may also elicit side effects that may delay hospital discharge. In addition, recent data suggest that extensive use of opioids is associated with hyperalgesia and allodynia.[1] Thus, to reduce opioid consumption and because acute pain is mediated by activation of numerous biochemical and anatomical pathways, practitioners are turning to alternatives to systemic opioids leading to balanced analgesia concept.[2]

Among coanalgesics that have been recently studied for postoperative pain treatment, systemic administration of local anesthetics has been shown to have both analgesic[3–5] and antihyperalgesic actions.[6] Analgesic action has been suggested to result both from a specific peripheral blockade of ectopic discharges in neurones involved in nociception[7] and a direct action on spinal transmission in the spinal cord.[8] Moreover, lidocaine has significant antiinflammatory properties,[9] blocking neutrophil accumulation at the injury site and decreasing the release of inflammatory mediators.[10]

Recent clinical studies demonstrated a morphine-sparing effect of intravenous lidocaine after major abdominal surgery. Among beneficial effects of lidocaine, authors reported a faster return of bowel function,[11,12] an improved dynamic analgesia, and a reduced hospital stay.[4,12,13] Most trials have been carried out after major urologic or abdominal surgery. There is no data about systemic lidocaine effect after orthopedic surgery.

The aim of the present randomized, double-blind, placebo-controlled study was to evaluate the analgesic effect of continuous intravenous (IV) lidocaine after total hip arthroplasty and analyze its effects on periincisional mechanical hyperalgesia.

Materials and Methods

After approval of the Local Ethics Committee (Comité de Protection des Personnes pour la Recherche Biomédicale, Hôpital Ambroise Paré, Boulogne, France) and patient's informed consent, a prospective two-center, randomized, double-blinded study including patients undergoing total hip arthroplasty was undertaken. American Society of Anesthesiologists physical status I-III patients between 18 and 80 yr scheduled for hip arthroplasty under general anesthesia were included. Exclusion criteria were anterior surgical approach; regional anesthesia; contraindications for lidocaine or morphine use; severe cardiac, renal or hepatic diseases; and preoperative use of analgesics (corticosteroids or opioid).

* Anaesthesia Fellow, † Anaesthesia Resident, ** Professor of Anaesthesia, Service d'anesthésie, § Pharmacology Resident, ‖ Associate Professor of Pharmacology, Service pharmacologie toxicologie, Assistance Publique Hôpitaux de Paris, Hôpital Raymond Poincaré, Garches, France. ‡ Staff Anesthesiologist, Service d'anesthésie, Centre Hospitalier St. Grégoire, St. Grégoire, France. †† Neurologist and Director of Research, Institut National de la Santé et de Recherche Médicale, Hôpital Ambroise Paré, Centre d'Evaluation et de Traitement de la Douleur, Versailles, France. # Staff Anesthesiologist, Université Paris-Sud, Laboratoire d'anesthésie, Faculté de Médecine, Le Kremlin-Bicêtre, France.

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Address correspondence to Dr. Fletcher: Service d'anesthésie, Hôpital Raymond Poincaré, Garches, Assistance Publique Hôpitaux de Paris, F-92380 France. dominique.fletcher@rpc.aphp.fr.

We chose as the primary endpoint the morphine consumption over the initial postoperative 24 h. A clinically significant morphine-sparing effect was considered to be 15 mg over 24 h. According to previous data (SD: 19)[14] for α risk of 0.05 with a power of 80%, we calculated that it was necessary to include at least 25 patients per group. Thus, it was decided to include 60 patients to account for drop-outs. The study began in January 2006 and ended March 2007.

Protocol

Before the study began, a randomization list balanced by center was established and each center enrolled patients and assigned treatments consecutively. For each patient, an envelope containing the group assignment was prepared, sealed, and sequentially numbered. On the morning of surgery and before induction of anesthesia, a "blinded" nurse prepared lidocaine or saline solution syringes. None of the other investigators involved in patient management or data collection were aware of the group assignment. Patients scheduled to receive lidocaine 10 mg/ml (lidocaine group) were given an intravenous bolus injection of 1.5 mg/kg of lidocaine in 10 min (30 min before surgical incision) followed by a continuous IV infusion of 1.5 mg · kg · h. The infusion ended 60 min after skin closure. In the control group, patients were given equal volumes of saline.

Anesthesia

Patients were premedicated with 1–2 mg/kg hydroxyzine orally 2 h before anesthesia. General anesthesia was induced with 0.2 μg/kg sufentanil followed by 5 mg/kg thiopental and 0.5 mg/kg atracurium to facilitate orotracheal intubation. Then, patients were ventilated to normocapnia with 50% oxygen and without nitrous oxide. Anesthesia was maintained with sufentanil (0.2 μg · kg · h) and sevoflurane at an initial end-tidal concentration of 1 minimum alveolar concentration, adjusted to age. Inspired sevoflurane concentration was fixed and sufentanil infusion was adjusted to maintain heart rate within 15% of the preinduction value and systolic arterial blood pressure within 20% of the baseline value (step of $\pm$ 0.05 μg · kg · h). Sufentanil was stopped 30 min before end of surgery. Patient's trachea was extubated when response to verbal commands, spontaneous respiratory rate exceeding 12 breaths/min, and end-tidal carbon dioxide partial pressure less than 45 mmHg were observed. Patients were admitted to the postanesthesia care unit (PACU) within 5 min of tracheal extubation. In the PACU, patients were asked to report any lidocaine toxicity side effects such as light headedness, drowsiness, metal taste, perioral numbness, and visual disturbances.

Postoperative Analgesia

Postoperative analgesia was provided in both groups only with IV patient controlled morphine. No others coanalgesics were prescribed. After the patient arrived in the PACU, pain was evaluated every 5 min using a 4-point verbal rating scale for pain (0 = no pain; 1 = slight pain; 2 = moderate pain; 3 = intense or severe pain). If the score was greater than 2, patients under 65 yr received morphine 3 mg while older patients were given 2 mg, every 5 min, if permitted according to the respiration rate (respiratory rate $>$ 10 breaths/min) and sedation score (score $<$ 1), until a verbal rating scale score of 0 or 1 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. Once a verbal rating scale less than 1 had been achieved, spontaneously or after a loading dose of morphine, patients were connected to a patient-controlled analgesia device set to deliver 1 mg morphine as an intravenous bolus with a 5-min lockout interval; continuous infusion was not allowed.

Patient-controlled analgesia was stopped in both groups at the 48th hour, and further analgesia was provided by combination of paracetamol, nonsteroidal antiinflammatory drugs and subcutaneous morphine as needed.

Evaluation

The cumulative dose of morphine given postoperatively (titration and patient-controlled analgesia during the 24-h and 48-h observation period) was measured, as were the 100-mm visual analog scale pain score (0: no pain to 100: worst possible pain) and the verbal rating scale pain score. Both scores were monitored at rest and during hip flexion. The hip flexion angle was also evaluated during the hospitalization and at the third postsurgical month.

During the preoperative anesthetic evaluation, patients were instructed in the use of quantitative sensory tests (punctuate and pressure pain detection thresholds). These measurements were performed in the morning of the first and the second day after surgery.

The punctuate pain detection threshold for mechanical static stimuli was assessed using calibrated von Frey hairs (0.057–178 g/mm^2). The patients were instructed to close their eyes during the procedure. Care was taken to avoid stroking the skin with the hair and to apply only a pressure stimulus. Filaments were applied to the designated point on the skin for 1 s. Von Frey hair applications were separated by at least 30 s to reduce the likelihood of anticipatory responses. The von Frey filaments were applied in ascending order of stiffness. Punctuate pain threshold was defined as the smallest force (g/mm^2) necessary to bend a von Frey hair, which was just perceived as painful. Three determinations with an

interval of 30 s were made during each assessment, and the pain threshold was calculated as the mean of the values obtained for the three measurements.

A handheld electronic pressure algometer (Somedic AB, Stockholm, Sweden) with a 0.28-cm^2 probe area was used to determine pressure pain detection threshold. The patients were instructed to immediately activate a push button, which freezes the digital display, when pain was perceived. The average of three measurements with an interstimulus interval of 60 s was defined as pressure pain threshold value. Values were expressed in kPa. A mean value for the three periincisional regions was calculated and used for statistical comparisons.

Punctuate and pressure pain thresholds were measured at 2–3 cm from the incision at three levels (top, middle, and bottom) and on the opposite thigh the day before the surgery and at the 24th and 48th hours. A mean value was calculated for statistical comparisons.

The extent of mechanical hyperalgesia to von Frey hair stimulation around the surgical wound was assessed with von Frey hair No. 16 (pressure: 122 g/mm^2) according to the method previously described.[1,15] Hyperalgesia was determined by stimulating along three linear paths at right angles to the top, middle, and bottom sides of the surgical incision in steps of 5 mm at 1-s intervals, starting well outside the hyperalgesic area (5 cm). Stimulations continued toward the incision until patients reported a clear change in sensation (*e.g.*, burning, tenderness, or pricking). The distance (in cm) from the incision to where sensations changed was measured, and a sum of the three assessments (top, middle, and bottom) was calculated and used for statistical comparisons.

Blood samples were drawn at 60 min after the skin closure in the PACU to measure plasma lidocaine concentrations. Lidocaine and its active metabolite monoethylglycinexylidide were quantified in plasma using liquid chromatography ion-trap mass spectrometry detection with electrospray ionization interface, after basic liquid/liquid extraction using ropivacaine as an internal standard. Data were collected in full-scan tandem mass spectrometry mode, selecting the ion *m/z* 235.1 for lidocaine, *m/z* 207.1 for monoethylglycinexylidide, and *m/z* 275.1 for ropivacaine for quantification. Retention times were 3.75, 3.05, and 5.60 min for lidocaine, monoethylglycinexylidide, and ropivacaine, respectively. Calibration curves were linear in the 200–5000 ng/ml and 20–500 ng/ml ranges for lidocaine and monoethylglycinexylidide, respectively. The intra- and interassay precisions evaluated at 800 and 3000 ng/ml for lidocaine and 80 and 300 ng/ml for monoethylglycinexylidide were all less than 9.8%, and the intra- and interassay accuracies were in the 93.6–102.0% range. Stability assay after three freeze-thaw cycles have shown no significant changes of the lidocaine and monoethylglycinexylidide plasma concentrations.

Statistical Analysis

The primary criterion was the patient's controlled morphine consumption over 24 h. Secondary criteria were perioperative sufentanil dose, morphine given in PACU, cumulative postoperative morphine consumption at the 48th hour, visual analog scale pain score at rest and when moving, punctuate and pressure pain threshold, extent of hyperalgesia, postoperative hip flexion, and duration of hospital stay.

Continuous variables are presented as mean ± SD and were compared with an unpaired Student *t* test. Morphine consumption was presented as median [25–75% interquartile range] and compared with the Mann–Whitney test. The 95% confidence interval (CI) of the median for morphine consumption over the first postoperative 24 h was calculated by bootstrapping the raw data with 1,000 replications. Pain thresholds and the 100-mm visual analog scale pain scores for 48 h were analyzed with two-way analysis of variance for repeated measures. Categorical data were analyzed with chi-square tests. Statistical analysis was performed with Statview for Windows (version 5.0; SAS Institute, Cary, NC); $P < 0.05$ was considered statistically significant.

Results

Of sixty patients included, two were excluded in the lidocaine group. They decided to leave the study in the PACU because of extreme pain. Patient's characteristics and operative data were comparable in the two treatment groups (table 1). There were no significant differences between lidocaine and placebo groups considering morphine requirements in the PACU (12 mg [8–20] *vs.* 18 mg [12–20]; $P = 0.32$), cumulative morphine consumption over the first postoperative 24 h (17 mg [9–28] *vs.* 15 mg [8–23]; $P = 0.54$), and cumulative morphine consumption over the first postoperative 48 h (43 mg [28–63] *vs.* 46 mg [32–57]; $P = 0.97$) (table 2). The 95% CI for morphine consumption over 24 postoperative hours was 11–26 mg for the lidocaine group and 9–22 mg for the placebo group. There were no statistically significant differences between both groups for the

Table 1. Patient's Characteristics

	Lidocaine Group	Placebo Group
Age, yr	64 ± 9	62 ± 13
Males of total patients	13 of 28	10 of 30
Weight, kg	73 ± 18	70 ± 13
Duration of preoperative pain, months	31 ± 28	33 ± 28
Preoperative pain intensity at rest, VAS	41 ± 13	37 ± 17
Preoperative pain intensity when moving, VAS	67 ± 20	66 ± 16
Preoperative hip flexion, degrees	103 ± 14	93 ± 19

Values are presented as mean ± SD, or number of patients.

VAS = visual analog scale.

Table 2. Perioperative Opioid Consumption

	Lidocaine	Placebo
Perioperative sufentanil dose, μg	50 [40–66]	45 [35–54]
Morphine given in PACU, mg	12 [8–20]	18 [12–20]
0–24 h cumulative postoperative morphine consumption without PACU, mg	17 [9–28]	15 [8–23]
0–48 h cumulative postoperative morphine consumption including PACU, mg	43 [28–63]	46 [32–57]

Data are presented as median [25–75% interquartile range].
PACU = postanesthesia care unit.

visual analog scale pain score at rest and when moving at the 24th and 48th hours and 3 months after the surgery. Preoperative hip flexion was comparable in the two groups; active hip flexion also was similar after 48 h (control group: 83 ± 13°; lidocaine group: 81 ± 12°) and 3 months (control group: 111 ± 14°; lidocaine group: 116 ± 11°). Duration of hospital stay was similar in both groups (table 3).

One hour after skin closure corresponding to the end of IV lidocaine infusion, mean lidocaine plasma and mean monoethylglycinexylidide plasma levels were 2.1 ± 0.4 μg/ml [1.5–3.2] and 0.3 ± 0.2 μg/ml [0.05–0.64], respectively, and none approached a toxic level (*i.e.*, plasma level > 4 μg/ml). No patient reported lidocaine toxicity side effects and no adverse events were reported in this group.

Both groups of patient experienced hyperalgesia to von Frey hair and algometer stimulation around the surgical wound at 24 and 48 h after the operation. However, punctuate and pressure pain threshold at 2–3 cm from the incision did not differ between groups (fig. 1). Hyperalgesia to von Frey hair stimulation proximal to the surgical incision was detected in all patients. Extent of hyperalgesia was similar in the placebo and lidocaine group at 24 h and 48 h (table 4). The 95% CI for extent

Table 3. Visual Analog Scale Pain Scores, Functional Recovery, and Duration of Hospitalization

	Lidocaine	Placebo
Mean VAS pain score at rest at 24 h, mm	27 ± 16	28 ± 21
Mean VAS pain score at rest at 48 h, mm	18 ± 13	18 ± 18
Mean VAS pain score at rest at 3 months, mm	6 ± 12	5 ± 8
Mean VAS pain score when moving at 24 h, mm	56 ± 21	53 ± 23
Mean VAS pain score when moving at 48 h, mm	45 ± 19	42 ± 20
Mean VAS pain score when moving at 3 months, mm	12 ± 11	21 ± 25
Operative hip flexion at 48 h, degrees	81 ± 12	83 ± 13
Operative hip flexion at 3 months, degrees	116 ± 11	112 ± 14
Hospital stay, days	5.4 ± 1.3	5.5 ± 1.1

Values are expressed as mean ± SD. No significant difference between groups.
VAS = visual analog scale.

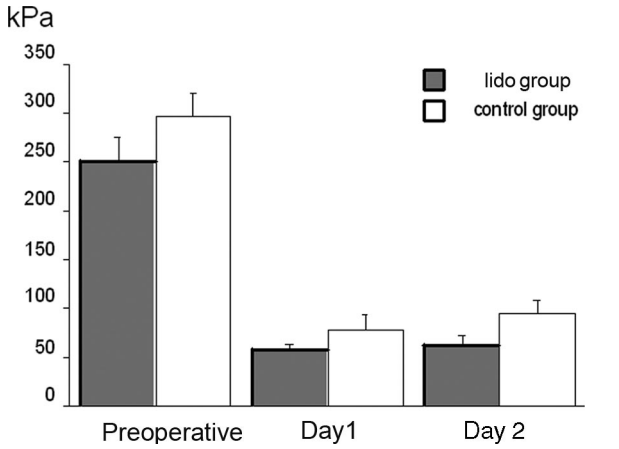

Fig. 1. Evolution of pressure pain threshold (kPa) determined with an algometer the day before surgery and at 24 and 48 h after surgery. The kPa was measured with an algometer at 2–3 cm from the incision before surgery (preoperative), then at 1 and 2 days after surgery. Results are expressed as mean ± SD. No significant difference was found between groups. lido = lidocaine.

of hyperalgesia at 24 h was 10–17 cm for the lidocaine group and 5–11 cm for the placebo group, and at 48 h 9–16 cm for the lidocaine group and 5–11 cm for the placebo group.

Punctuate and pressure pain thresholds measured on the opposite leg did not differ preoperatively *versus* postoperatively in any group.

Discussion

We did not find any significant impact of IV lidocaine on postoperative analgesia or wound hyperalgesia after total hip arthroplasty.

It is unlikely that the present negative results were due to a methodologic bias. A sample-size estimate indicated that 25 patients per group would give a power of 80% at an α level of 0.05 for detecting a clinically significant morphine-sparing effect of 15 mg over 24 h. For this type of surgery, leading to only moderate morphine consumption and possibly limited central sensitization, a larger sample size could point out significant morphine sparing of systemic lidocaine. However, the 95% CI for morphine consumption over the first postoperative 24 h suggests that the largest detectable difference lies within bounds that are not clinically relevant.

Table 4. Effects of Lidocaine and Placebo on the Extent of Hyperalgesia Induced by Von Frey Hair Stimulation Proximal to the Surgical Wound (Sum of Distance in cm from Wound)

	Lidocaine	Placebo
24 h after surgery	12 [7–18]	7 [5–11]
48 h after surgery	11 [9–17]	8 [3–12]

Data are presented as median [25–75% interquartile range]. No significant difference between groups.

Our results on analgesia may of course have differed if the infusion had been prolonged. We chose a short perioperative protocol because this administration period had been used in most previous studies evaluating intravenous lidocaine, and for safety reasons to avoid prolonged continuous IV lidocaine infusion with possible related inappropriate administration. Mean plasma lidocaine concentration of 2.1 μg/ml, 60 min after skin closure when lidocaine infusion was discontinued, are similar to lidocaine concentration in previous studies demonstrating beneficial effect of lidocaine.[3,13] However, although lidocaine concentrations lie between adequate bounds, lidocaine's analgesic properties also may depend on lidocaine dose infused, as demonstrated in an animal study.[16] It was shown that small doses suppress ectopic impulse generation in chronically injured peripheral nerves, whereas moderate doses suppress central sensitization and central neuronal hyperexcitability. However, large doses have general analgesic effect but induce systemic toxicity.[16]

Various lidocaine infusion protocols have been used only during surgery,[4,12,17,18] intraoperatively and for 24 h postoperatively,[11,13,19–21] or exclusively after surgery with patient-controlled analgesia.[22] Only two trials using patient-controlled analgesia associating morphine plus lidocaine[21] and perioperative[22] lidocaine administration failed to demonstrate opioid-sparing effect. The other studies reported various impacts on analgesia associated with a reduction of postoperative morphine requirement but opioid consumption was generally only secondary endpoints (except in three studies).[3,18,21] Thus, whereas patients who received intravenous lidocaine needed less morphine from the 36th to the 72nd hours after surgery in one study,[3] other reports noticed a 50% reduction in the demand for morphine just in the PACU[4] or during the first 24 h.[13]

This is the first report of the effects of intravenous lidocaine on nociceptive processing after orthopedic surgery. Most of the previously published studies[4,13] have been performed during abdominal surgery using as primary criterion the accelerated postoperative recovery of bowel function. Despite a larger number of patients and an adequate lidocaine plasma levels, we did not observe an opioid-sparing effect at any point of the perioperative period. The discrepancies with previous published studies may be explained by the type of surgery we used. Indeed, several animal reports have shown an excitatory effect of local anesthetics on intestinal smooth muscle both *in vitro*[23] and after systemic administration *in vivo*.[24] These hypotheses have been confirmed in human radiologic experimentation.[11] Moreover, a recent animal study showed that intravenous lidocaine had inhibitory effects on visceromotor and cardiovascular reflexes and on the evoked and spontaneous activity of neurons excited by colorectal distension, suggesting that sodium channel blockers may have a role in the treatment of visceral pain.[25] Thus, it is plausible that part of lidocaine's analgesic properties reported during digestive surgery was in fact indirect and related to an improvement in bowel function inducing a diminution of visceral pain.

For the first time, we studied the effect of lidocaine on punctuate and pressure pain detection threshold and on the extent of hyperalgesia surrounding surgical incision. This methodology already has been used in pharmacologic studies in humans to investigate the analgesic and antihyperalgesic effects of different drugs.[1,15,26] This mechanical hyperalgesia seems to share the same central neuronal mechanism as heat-induced secondary hyperalgesia, confirming a degree of central sensitization.[27] In our study, we were not able to demonstrate a reduction of secondary hyperalgesia around the surgical wound in the lidocaine group, whereas in recent human volunteer trials using intradermal capsaicin or incision-induced pain to produce cutaneous secondary hyperalgesia, authors found a reduction of secondary hyperalgesia to von Frey hair stimulation.[28–30] The 95% CI suggests significant variability of the extent of hyperalgesia at 24 h and 48 h. In addition, our study was not powered for comparison of secondary hyperalgesia, which limits interpretation of these results.

In summary, in contrast with previous published studies, our study did not show any benefit of the perioperative administration of low doses of IV lidocaine in terms of postoperative analgesia and functional recovery after total hip arthroplasty. Furthermore, these data suggest that systemic lidocaine has no effect on punctuate and pressure pain threshold as on secondary periincisional hyperalgesia.

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