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Postoperative Pain Facilitates Nonthermoregulatory Tremor

Ernst-Peter Horn, M.D.,* Frank Schroeder, M.D.,† Stefan Wilhelm, M.D.,† Daniel I. Sessler, M.D.,‡
Thomas Standl, M.D.,§ Katja von dem Busche, M.D.,|| Jochen Schulte am Esch, M.D.¶

Background: Spontaneous tremor is relatively common in normothermic patients after operation and has been attributed to many causes. The hypothesis that nonthermoregulatory shivering-like tremor is facilitated by postoperative pain was tested. In addition, the effects of intravenous lidocaine on nonthermoregulatory tremor were evaluated.

Methods: Patients undergoing knee surgery were anesthetized with 2 $\mu\text{g}/\text{kg}$ intravenous fentanyl and 0.2 mg/kg etomi-

date. Anesthesia was maintained with $1.7 \pm 0.8\%$ (mean \pm SD) isoflurane. Intraoperative forced-air heating maintained normothermia. The initial 44 patients were randomly allocated to receive an intra-articular injection of 20 ml saline ($n = 23$) or lidocaine, 1.5% ($n = 21$). The subsequent 30 patients were randomly allocated to receive an intravenous bolus of 250 $\mu\text{g}/\text{kg}$ lidocaine followed by an infusion of $13 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ lidocaine or an equivalent volume of saline when shivering was observed. Patient-controlled analgesia was provided for all patients: 3.5 mg piritramide, with a lockout interval of 5 min, for an unlimited total dose. Shivering was graded by a blinded investigator using a four-point scale. Pain was assessed by a 100-mm visual analog scale (0 = no pain and 100 = worst pain). The arteriovenous shunt status was evaluated with forearm-minus-fingertip skin-temperature gradients.

Results: Morphometric characteristics and hemodynamic responses were similar in the four groups. Core and mean skin temperature remained constant or increased slightly compared with preoperative values, and postoperative skin-temperature gradients were negative (indicating vasodilation) in nearly all patients. After intra-articular injection of saline, pain scores for the first postoperative hour averaged 46 ± 32 mm (mean \pm SD), and 10 of the 23 (43%) patients shivered. In contrast, the pain scores of patients who received intra-articular lidocaine were significantly reduced to 5 ± 9 mm and shivering was absent in this group ($P < 0.05$). In the second portion of the study, neither intravenous lidocaine nor saline reduced the magnitude or duration of nonthermoregulatory tremor or the patients' pain scores.

Conclusions: Intra-articular, but not intravenous, lidocaine reduced surgical pain and prevented nonthermoregulatory shivering. Therefore, these data indicate that postoperative pain facilitates nonthermoregulatory shivering. (Key words: Clonus; isoflurane; shivering; temperature; thermoregulation; volatile anesthetics.)

* Assistant Director, Outcomes Research™ Group; Assistant Professor, Department of Anesthesiology, University Hospital Eppendorf.

† Resident, Department of Anesthesiology, University Hospital Eppendorf.

‡ Professor, Department of Anesthesia and Perioperative Care, University of California–San Francisco; Professor, Ludwig Boltzmann Institute for Clinical Anesthesia and Intensive Care; Director, Outcomes Research™; Professor and Vice Chair, Department of Anesthesia and General Intensive Care, University of Vienna.

§ Associate Professor, Department of Anesthesiology, University Hospital Eppendorf.

|| Research Fellow, Department of Anesthesiology, University Hospital Eppendorf.

¶ Professor and Chair, Department of Anesthesiology, University Hospital Eppendorf.

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Address reprint requests to Dr. Horn: Department of Anesthesiology, University Hospital Eppendorf, Martinistreet 52, 20246 Hamburg, Germany. Address electronic mail to: EPHORN@compuserve.com. On the world-wide web: outcomes-research.org

MOST postanesthetic shivering-like tremor is presumably normal thermoregulatory shivering in response to core and skin hypothermia.¹ Nonetheless, shivering-like tremor reportedly occurs in normothermic rats,² patients,^{3–5} and cats⁶ after anesthesia. It has also been observed in normothermic patients during labor for childbirth, with and without epidural analgesia.⁷ Consistent with these observations, we recently showed that spontaneous tremor in normothermic patients after op-

eration is relatively common and that a considerable fraction is not thermoregulatory.⁸

We consider tremor to be nonthermoregulatory when it occurs in patients who are normothermic (core temperature equaling or exceeding individual initial values) and peripherally vasodilated. This is a strict criterion, because the shivering threshold (triggering core temperature) is typically 1°C less than normal body temperature and remains 1°C less than the vasoconstriction threshold even during anesthesia.⁹⁻¹¹

Nonthermoregulatory tremor has been attributed to many nonthermoregulatory causes, including decreased sympathetic nervous system activity,¹² pain,¹³ anesthetic drugs,¹⁴ loss of descending control,¹⁵ adrenal suppression,¹⁶ and respiratory alkalosis.¹⁷ None of these causes, however, has been proved or even systematically evaluated. In a previous study,⁸ we noted that the likelihood of postoperative nonthermoregulatory tremor seemed to increase when patients were in pain. Accordingly, we tested the hypothesis that nonthermoregulatory tremor is facilitated by postoperative pain. To eliminate a potential confounding factor, we separately evaluated the effects of intravenous lidocaine on nonthermoregulatory tremor.

Methods

With approval of the local review board and written informed patient consent, we studied 74 patients undergoing elective arthroscopic knee surgery. Patients were excluded when total knee arthroplasty was planned, they were younger than 18 yr, their American Society of Anesthesiologists physical status score exceeded 2, they required vasoconstrictor agents (*i.e.*, local administration of epinephrine) for surgery, or α_2 -agonists were administered on a long-term basis.

Protocol

All patients were premedicated with 7.5 mg oral midazolam. A venous catheter was inserted into the forearm and an infusion of lactated Ringer's solution was started. General anesthesia was induced by intravenous administration of 2 $\mu\text{g}/\text{kg}$ fentanyl, 0.2 mg/kg etomidate, and 0.5 mg/kg atracurium. Anesthesia was maintained with isoflurane, $1.7 \pm 0.8\%$, in 30% oxygen. Ventilation was adjusted to an end-tidal carbon dioxide tension of approximately 35 ± 3 mmHg.

Normothermia was maintained with forced air (Bair Hugger; Augustine Medical, Eden Prairie, MN). Active

upper-body warming was started when patients arrived in the operating room; it was continued throughout surgery and stopped when patients were transferred to the recovery unit. Because all surgeries began in the morning, patients were warmed to a target core temperature exceeding their preoperative temperatures by 0.1°C/h to compensate for the normal daily circadian increase in body temperature.¹⁸ During the initial part of surgery, boluses of 1 $\mu\text{g}/\text{kg}$ fentanyl were given as needed to control hemodynamic responses; however, fentanyl was not given during the last hour of surgery.

Postoperative pain was treated with patient-controlled analgesia using a Lifecare 4200 intravenous pump (Abbott, North Chicago, IL). When the pump was activated, a 3.5-mg bolus of the opioid piritramide was delivered. The lockout interval was 5 min, but there was no other limit to the number of boluses that could be administered.

Based on a sample-size estimate, the initial 44 patients (intra-articular lidocaine and saline) were randomly allocated to receive 20 ml saline, 0.9% ($n = 23$), or 20 ml lidocaine, 1.5%, without epinephrine ($n = 21$). Both solutions were injected intra-articularly *via* the wound drain; the drain was then clamped for 15 min.

Again, based on a sample-size estimate, the subsequent 30 patients (intravenous lidocaine and saline) were randomly allocated to receive an intravenous bolus of 250 $\mu\text{g}/\text{kg}$ lidocaine followed by an infusion of $13 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ lidocaine or an equivalent volume of saline when shivering was observed. In both portions of the study, randomization was accomplished using sealed envelopes containing computer-generated codes. The envelopes were opened when lidocaine or saline was injected.

Measurements

Throughout surgery and postanesthesia recovery, we recorded heart rate and mean arterial pressure (Dinamap; Critikon, Tampa, FL) in all patients. End-tidal anesthetic gas concentrations after extubation were measured from a sealed face mask (AirCare; Apotheus Laboratories, Lubbock, TX) connected to a Capnomac end-tidal gas monitor (Datex, Helsinki, Finland). Core temperatures were recorded from the tympanic membrane, and mean-skin temperatures were calculated from the weighted average of measurements at the chest, arm, thigh, and calf (Mon-a-Therm tympanic membrane and skin-surface thermocouples; Mallinckrodt Anesthesiology Products, St. Louis, MO).¹⁹ Arteriovenous shunt vasoconstriction was evaluated using forearm-minus-finger-tip skin-surface temperature gradients²⁰; gradients $<0^\circ\text{C}$

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identified vasodilation. The environmental temperature was also measured throughout the first hour of postanesthetic recovery.

Pain was assessed before and after operation by an investigator blinded to the group assignment using a visual analog scale on which 0 mm indicated no pain and 100 mm identified maximal pain. A new unmarked scale was used for each evaluation. Nonthermoregulatory shivering-like tremor was graded by the same single investigator using a four-point scale: 0 = no tremor, 1 = intermittent low-intensity tremor, 2 = moderate-intensity tremor, 3 = continuous intense tremor. A three-lead electrocardiographic recording with standard lead placement was adjusted so that 1 μ V equaled 40-mm amplitude to objectively document shivering activity. As in previous studies,^{8,21} shivering artifacts on the electrocardiographic recording were scored by another blinded investigator as no artifact, low-intensity tremor, moderate-intensity tremor, and continuous intense tremor. The visual shivering score was considered the reference technique to evaluate shivering.

Arousal state was assessed by patients' responses to the verbal command "Open your eyes and lift your arms." Absent or incomplete responses were graded as arousal state zero, and prompt and appropriate responses were graded as arousal state one.²² Data were recorded during operation at 15-min intervals and subsequently for 1 h after operation at 5-min intervals.

In the patients given intravenous lidocaine or saline, central-venous blood was sampled 15 and 30 min after patients arrived in the postanesthesia care unit. The samples were assayed for lidocaine by the hospital laboratory.

Data Analyses

Discontinuation of anesthesia was designated elapsed time zero. Postoperative pain scores, hemodynamic responses, isoflurane concentrations, and temperatures were averaged first for a period of 15–60 min of recovery in individual patients, and then they were averaged among the patients in each treatment group. Differences between the groups were compared using unpaired, two-tailed *t* tests or chi-square analysis, as appropriate. Data are expressed as means \pm SDs; *P* < 0.05 was considered significant.

Results

Morphometric characteristics, anesthetic management, and surgical factors were similar, and core and

Table 1. Morphometric and Demographic Characteristics, Temperatures, Surgical Factors, Time to Arousal State One, and Piritramide Requirement in the First Portion of the Study (Intraarticular Lidocaine/Saline)

	Saline (n = 23)	Lidocaine (n = 21)
Sex (male/female)	10/13	10/11
Age (yr)	47 \pm 19	52 \pm 15
Weight (kg)	76 \pm 17	75 \pm 14
Height (cm)	170 \pm 9	173 \pm 10
Preoperative core temperature ($^{\circ}$ C)	36.4 \pm 0.4	36.6 \pm 0.3
Preoperative mean skin temperature ($^{\circ}$ C)	33.8 \pm 0.6	33.6 \pm 0.5
Total intraoperative fentanyl (μ g)	307 \pm 19	298 \pm 31
Intraoperative mean end-tidal isoflurane (%)	1.20 \pm 0.31	1.15 \pm 0.47
Duration of surgery (min)	96 \pm 48	91 \pm 45
Postoperative end-tidal isoflurane (%)	0.20 \pm 0.06	0.24 \pm 0.13
Postoperative heart rate (beats/min)	81 \pm 10	80 \pm 15
Postoperative mean arterial blood pressure (mmHg)	100 \pm 17	91 \pm 15
Mean postoperative ambient temperature ($^{\circ}$ C)	24.0 \pm 1.1	24.8 \pm 1.1
Postoperative core temperature ($^{\circ}$ C)	36.7 \pm 0.4	36.8 \pm 0.6
Postoperative mean skin temperature ($^{\circ}$ C)	35.0 \pm 0.8	35.0 \pm 1.0
Postoperative skin-temperature gradient ($^{\circ}$ C)	-0.8 \pm 1.6	-0.6 \pm 1.2
Time to arousal score one (min)	23 \pm 20	29 \pm 16
Time to first piritramide dose (min)	20 \pm 19	133 \pm 59*
Piritramide during the first postanesthetic hour (mg)	8.8 \pm 8	0.6 \pm 1.5*

Data are presented as mean \pm SD. Hemodynamic responses, isoflurane concentrations, and temperatures were averaged over a period 15–60 min of recovery in individual patients and then averaged among the patients in each treatment group.

* *P* < 0.05.

mean skin temperature remained constant or increased slightly compared with preoperative values in each of the four groups. Postoperative skin-temperature gradients were negative (indicating vasodilation) in nearly all patients and were comparable in the four groups.

In the first portion of the study (intra-articular lidocaine and saline), patients given intra-articular saline instead of lidocaine required 10 times as much piritramide during the first postoperative hour; furthermore, the time until piritramide was required was significantly shorter in saline-treated patients. The times required to reach an arousal score of one were similar in each group (table 1).

Preoperative pain scores were comparable in the patients given intra-articular lidocaine or saline. However,

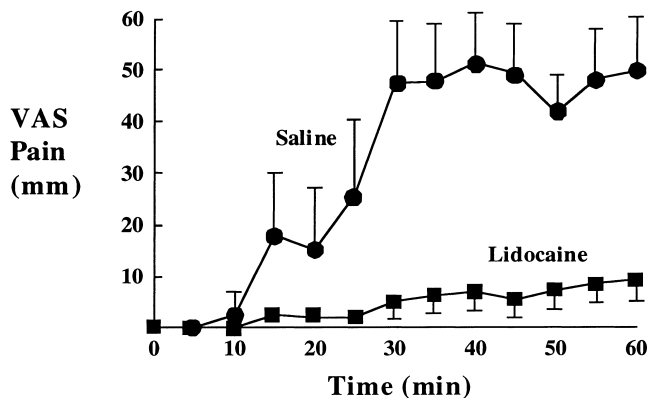


Fig. 1. Visual analog pain scores (VAS) in the patients given intra-articular lidocaine or saline. Pain was assessed after operation by an investigator blinded to group assignment. Time zero indicates discontinuation of anesthesia. Data are presented as the mean \pm SD. Patients receiving a local anesthetic block (lidocaine) had significantly less postoperative pain than did those given saline; all values after 10 elapsed min differed significantly in the two groups.

average postoperative pain scores were significantly higher after operation in the patients given intra-articular saline (46 ± 32 mm) than intra-articular lidocaine (5 ± 9 mm) (fig. 1). Nonthermoregulatory shivering-like tremor was comparably identified by visual inspection and electrocardiographic analysis (table 2). Among the patients given saline, 43% shivered. In contrast, no shivering was detected in patients given lidocaine ($P < 0.05$). Grade 1 shivering was observed in 43% of the patients given saline during 35 measurement epochs; grade 2 shivering was observed in 17% of these patients during 14 epochs. Onset of tremor was 21 ± 11 min after isoflurane was discontinued, and spontaneous muscular activity lasted an average of 23 ± 12 min. All four patients with grade

Table 2. Nonthermoregulatory Shivering After Intraarticular Saline or Lidocaine

	Saline	Lidocaine
Visual tremor		
No (grade 0)	13	21
Yes (grades 1–3)	10	0*
Low-intensive (grade 1)	6	0
Moderate-intensive (grade 2)	4	0
Continuous, intense (grade 3)	0	0
ECG shiver waves		
No (grade 0)	13	21
Yes (grades 1–3)	10	0*
Low-intensive (grade 1)	6	0
Moderate-intensive (grade 2)	3	0
Continuous, intense (grade 3)	1	0

ECG = electrocardiogram.

* $P < 0.05$ vs. saline.

Table 3. Morphometric and Demographic Characteristics, Temperatures, Surgical Factors, Pain Scores, and Piritramide Requirement in the Second Portion of the Study (Intravenous Lidocaine/Saline)

	Saline (n = 15)	Lidocaine (n = 15)
Sex (male/female)	7/8	6/9
Age (yr)	49 ± 15	45 ± 13
Weight (kg)	79 ± 15	76 ± 13
Height (cm)	173 ± 9	173 ± 10
Preoperative core temperature ($^{\circ}\text{C}$)	36.7 ± 0.4	36.5 ± 0.3
Total intraoperative fentanyl (μg)	291 ± 21	296 ± 27
Intraoperative mean end-tidal isoflurane (%)	1.23 ± 0.50	1.26 ± 0.38
Duration of surgery (min)	99 ± 37	89 ± 45
Postoperative end-tidal isoflurane (%)	0.22 ± 0.12	0.26 ± 0.17
Postoperative core temperature ($^{\circ}\text{C}$)	36.8 ± 0.4	36.6 ± 0.3
Postoperative pain scores (mm)	46 ± 27	51 ± 39
Piritramide during the first postanesthetic hour (mg)	8.6 ± 7	8.4 ± 7

Data are presented as mean \pm SD. Postoperative pain scores, isoflurane concentrations, and core temperature were averaged over a period 15–60 min of recovery in individual patients and then averaged among the patients in each treatment group.

2 tremor were given clonidine^{23,24} after the study period, as were four additional patients in whom grade 1 tremor proved bothersome.

Postoperative pain scores and the piritramide requirements were comparable in the patients given intravenous lidocaine or saline in the second part of the study (intravenous lidocaine/saline, table 3). Nonthermoregulatory tremor was observed in 14 of the 30 patients, with seven patients affected in each group. In the lidocaine-treated patients, central-venous plasma lidocaine concentrations were 0.5 ± 0.3 $\mu\text{g}/\text{ml}$ and 0.4 ± 0.3 $\mu\text{g}/\text{ml}$ 15 and 30 min, respectively, after lidocaine administration. Neither intravenous lidocaine nor saline reduced the magnitude or duration of nonthermoregulatory tremor or the patients' visual analog pain scores.

Discussion

The routine treatment for pain after knee surgery at the University Hospital Eppendorf is patient-controlled administration of opioids. However, to test our hypothesis that postoperative pain facilitates nonthermoregulatory tremor, we needed a group of patients who were receiving especially effective pain treatment. The administration of supplemental systemic analgesics was not possible, because opioids¹¹ and sedatives^{9,25,26} signifi-

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cantly reduce the shivering threshold. Therefore, we ameliorated postoperative knee pain by injecting local anesthetic into the knee capsule.

As expected based on previous research,²⁷ local anesthesia was effective and significantly reduced postoperative pain scores from 46 ± 32 to 5 ± 9 mm. The incidence of nonthermoregulatory tremor in the patients given patient-controlled opioids was 43%, whereas none was observed in those given intra-articular local anesthesia ($P < 0.05$). We can assume that all this tremor was nonthermoregulatory, because the patients were uniformly normothermic and vasodilated. (Fever causes shivering at normal or elevated body temperatures. However, shivering resulting from fever is preceded by vasoconstriction.²⁸)

Our data therefore indicate that nonthermoregulatory shivering is facilitated by postoperative pain. That the incidence of shivering was high in the patients not given intra-articular lidocaine further suggests that pain is an important stimulus for this muscular activity. This result is consistent with our recent observations in patients during labor of childbirth.⁷ Therefore, it is likely that sufficient postoperative pain treatment largely prevents grade 1 and 2 nonthermoregulatory tremors. This is clinically important, because reducing the incidence of nonthermoregulatory tremor increases patient comfort and decreases physiologic derangements associated with this activity.

Many drugs have proved effective for the treatment of postanesthetic shivering. Effective medications include meperidine,^{22,29} nefopam,³⁰ clonidine,^{23,31,32} ketanserin,³³ physostigmine,²² and magnesium sulfate.³⁴ None of these studies, however, distinguished thermoregulatory shivering from nonthermoregulatory tremor. It is likely, however, that the mechanism in most cases was inhibition of central thermoregulatory control, because most postoperative shivering is presumably thermoregulatory. Indeed, most of these drugs have been shown to reduce the shivering threshold.^{11,24,35,36} Which drugs might prevent or treat nonthermoregulatory tremor remains unknown. However, our data suggest that analgesics, even ones lacking thermoregulatory actions, are likely to prove effective. Inhibition of tremor by analgesics is presumably dose dependent, although we did not evaluate the effects of graded inhibition of pain on nonthermoregulatory tremor in this protocol.

A limitation of our study is that we detected nonthermoregulatory tremor qualitatively. Therefore, we could not evaluate tremor patterns and determine whether nonthermoregulatory shivering-like tremor has the wax-

ing-and-waning characteristics of thermoregulatory shivering,³⁷ the clonic activity that often follows volatile anesthesia,³⁸ or an entirely different pattern. Intra-articular lidocaine is slowly absorbed into the systemic circulation.³⁹ However, even substantial intravenous doses of lidocaine do not facilitate tremor or alter the shivering threshold.⁴⁰ Therefore, it is unlikely that the systemic actions of lidocaine contributed to our results.

A potential confounding factor in our initial study was that lidocaine injected into the intra-articular space eventually reaches the systemic circulation. Because only a small amount is injected and the space is poorly perfused, the systemic concentration after intra-articular injection³⁹ is much smaller (*i.e.*, $0.3 \mu\text{g/ml}$) than that observed after epidural anesthesia.⁴¹ It is already established that even relatively high plasma concentrations of lidocaine (*i.e.*, $3.5 \mu\text{g/ml}$) do not reduce the shivering threshold.⁴⁰ In the second portion of our study, we nonetheless evaluated the effects of intravenous lidocaine on nonthermoregulatory shivering. The dose of intravenous lidocaine was chosen to produce plasma concentrations similar to those resulting from intra-articular injection of the drug. Neither intravenous lidocaine nor saline had any influence on tremor activity, indicating that the results in our initial portion of the study were not confounded by systemic absorption of intrarticularly administered lidocaine.

In conclusion, we evaluated normothermic, vasodilated patients. Nonthermoregulatory shivering was common in those with substantial postoperative pain, but otherwise was absent. Surgical pain thus facilitates nonthermoregulatory shivering.

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