Anesthesiology
1999; 91:639–47

Effects of Morphine and Tramadol on Somatic and Visceral Sensory Function and Gastrointestinal Motility after Abdominal Surgery

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Background: **Chronic nociceptive input induces sensitization and changes in regulatory reflexes in animal models. In humans, postoperative somatic and visceral sensitization and the secondary effects on reflex gut motility are unclear.**

Methods: **Somatic and visceral sensation and gastrointestinal motility were evaluated after abdominal hysterectomies in 50 patients who were randomized to receive double-blinded postoperative 48-h infusions of morphine or tramadol. Pain scores, rectal distension, skin electric sensation and pain tolerance thresholds, and gastrointestinal transit were assessed before and after operation, during and after analgesic infusions.**

Results: **Pain intensity scores decreased similarly with morphine and tramadol infusions (total doses, 66.8 ± 20 mg and 732.4 ± 152 mg [mean ± SD], respectively). Skin pain tolerance thresholds in the incisional dermatome remained similar with morphine and tramadol throughout the study. During morphine infusions, pain tolerance thresholds on the shoulder increased ($P < 0.05$) and then decreased after discontinuation on day 4 ($P < 0.02$) compared with before operation. Rectal distension pain tolerance pressure thresholds increased after operation during morphine infusions ($P < 0.05$). Similar but nonsignificant trends occurred with tramadol. Orocecal and colonic transit times increased after operation with both morphine and tramadol ($P < 0.005$), but gastric emptying was prolonged only with morphine ($P = 0.03$). All motility and sensory parameters had returned to preoperative levels by 1 month after operation.**

Conclusions: **Pain control was equally effective with morphine and tramadol infusions. No somatic or visceral sensitization was evident during morphine and tramadol infusions, but pain tolerance thresholds as markers of antinociception were increased more during morphine infusions. The significant sensitization seen only after morphine discontinuation may be due to convergent visceral input. Gut motility was prolonged significantly by visceral surgery itself and also by morphine. (Key words: Hyperalgesia; nociception; pain; sensitization; transit.)**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

POSTOPERATIVE analgesics are given to prevent pain and to inhibit the transmission of nociceptive stimuli with resulting stress reactions and long-term changes in sensory function. Prolonged or repetitive nociceptive input has resulted in sensitization and hyperalgesia in different experimental models.[1–3] Most clinical studies of sensitization have used global measures of pain sensation, such as visual analog or verbal rating scales, which may not reflect changes in the sensory system. A few studies in humans have measured superficial sensory and pain thresholds after operation to assess somatic sensitization.[4–9] It is unclear whether visceral sensitization occurs after visceral surgery in humans, if it is accompanied by changes in gut reflex activity and in converging somatic dermatomes, and whether it predisposes patients to later visceral hyperalgesic syndromes. Visceral hyperalgesia is considered a primary underlying cause of functional abdominal and pelvic pain syndromes, including irritable bowel syndrome, functional dyspepsia, and chronic pelvic pain.[1,10]

Prevention of postoperative sensitization has been attempted with many drugs, including opioids, nonsteroidal anti-inflammatory agents, local anesthetic blocks, and *N*-

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Received from the Visceral Physiology Institute, Department of Pharmacology, and the Department of Obstetrics and Gynaecology, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa. Submitted for publication December 28, 1998. Accepted for publication April 12, 1999. Supported by a research grant from Grünenthal AG, Mitlödi, Switzerland (manufacturers of tramadol). Presented in part as an abstract at the annual meeting of the American Society of Anesthesiologists, Orlando, Florida, October 17–21, 1998, and at the Digestive Disease Week of the American Gastroenterological Association, New Orleans, Louisiana, May 16–22, 1998.

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methyl D-aspartate antagonists with varying efficacy.[11,12] Tramadol is an analgesic combining mainly μ-opioid and monoaminergic actions with good clinical efficacy in treating visceral pain.[13–15] Because both of these mechanisms are important in analgesia, tramadol may be useful in preventing sensitization.

The aim of this study was to evaluate the effects of protracted infusions of morphine and tramadol on somatic and visceral sensation and nociception, on gastrointestinal motility, and on postoperative pain after visceral surgery.

Materials and Methods

Patients

Fifty successive patients scheduled for elective simple abdominal hysterectomy were included in this randomized, double-blinded, prospective study. Surgery was performed by the same two surgeons according to a standardized technique.[16] The University of Cape Town Medical School Ethics Committee approved the study, and all patients gave their written informed consent. Exclusion criteria were irritable bowel syndrome, as defined by Rome criteria[17]; previous major intra-abdominal or resective bowel surgery; intraoperative complications; gastrointestinal motility disorders; chronic pain syndromes; clinically relevant liver or renal compromise; a history of opioid use in the last 7 days before operation; severe obstructive airways disease; and inadequate communication abilities. All patients were classified as American Society of Anesthesiologists physical status grades 1 to 3. Patient demographics were recorded on a specific data sheet at a visit 2 weeks before surgery. During the same visit, the preoperative sensory and gastrointestinal motility tests were performed (see Physiological Tests section).

The anesthetic regimen was standardized for all patients: premedication with 10 mg diazepam given orally 2 h before surgery, induction of anesthesia with 3–5 mg/kg thiopentone and 3 μg/kg fentanyl, muscular relaxation with 0.08–0.1 mg/kg vecuronium, and inhalational anesthesia with halothane or isoflurane dosed to maintain a clinically adequate depth of anesthesia. The surgical incision was infiltrated with 20 ml bupivacaine, 0.25%.

Eligible patients were randomized to receive continuous tramadol or morphine infusions for postoperative analgesia. The dosing regimen for tramadol was as follows: At wound closure, a loading bolus of 2 mg/kg was given by slow intravenous injection and at the start of an intravenous infusion by pump of 0.5 $mg \cdot kg^{-1} \cdot h^{-1}$ for the first 24 h and 0.25 $mg \cdot kg^{-1} \cdot h^{-1}$ for the next 24 h. Rescue doses of 25 mg tramadol given intramuscularly were available on request, maximally once every 30 min. In case of more than three rescue doses per 12 h or the occurrence of marked side effects, the infusion rate was increased or decreased by 50%. After 48 h, the tramadol infusion was discontinued and all patients received 400 mg ibuprofen four times a day by mouth for analgesia. Intramuscular meperidine (100 mg) was available for rescue analgesia as much as once per hour in both groups. The dosing regimen for morphine was as with tramadol, but it included a loading bolus of 0.1 mg/kg given intravenously and continuous intravenous infusions of 0.05 $mg \cdot kg^{-1} \cdot h^{-1}$ in the first 24 h and 0.025 $mg \cdot kg^{-1} \cdot h^{-1}$ in the next 24 h. The rescue dose of morphine was 2.5 mg given intramuscularly. All study drugs were provided for blinded use in coded ampules and infusion bags by the hospital pharmacy according to their computer-generated randomization list. Antiemetic prophylaxis was provided for all patients in the form of 10 mg metoclopramide given three times a day by mouth for the first 2 days. Sensory and motility testing was again performed on the second postoperative day and 1 month later (see the Physiologic Tests section).

Symptom Documentation

After surgery, pain intensity at rest and during leg raising was recorded every 6 h on a verbal rating scale of 0 to 4 (0 = none, 1 = slight, 2 = moderate, 3 = severe, and 4 = unbearable pain). Side effects, bowel function, and requests for rescue analgesics were recorded by the patients on a standardized questionnaire every evening. Administration of all study medication, test procedures, and documentation were performed by the same three members of the research staff.

Physiologic Tests

The following procedures were performed for all patients 2 weeks before surgery, in the ward on the second postoperative day during analgesic infusions, and at a postoperative visit 1 month after surgery. On the morning of physiologic testing, patients had fasted since midnight. A practice run was performed before each physiologic test to familiarize patients with the procedure. The somatic sensation tests were followed by the rectal distension thresholds. The transit tests were performed subsequently.

Skin Sensory Thresholds. Electric sensory thresholds (first sensation, pain tolerance, stimulation with 100 ms, 1 Hz) were tested 5 cm from the incision wound (the same dermatome as the incision) and on the right shoulder (dermatome C5) and the threshold currents were noted. The current was increased at 1 mA/s until 5 mA and then 5 mA/s up to a maximal current of 50 mA. An additional threshold measurement was performed on postoperative day 4, 2 days after the analgesic infusions were discontinued.

Rectal Distension Thresholds. A standardized latex balloon catheter was introduced 5 cm into the rectum while patients rested in the left lateral position and inflated at 10 ml/s until the patient felt slight distension (first sensation threshold), the urge to defecate (urge threshold), and until distension just became intolerable (pain tolerance threshold).[18,19] Volumes and pressures were noted at these thresholds using a six-channel, solid-state datalogger (Gastroscan 6020, Medical Instruments Corp., Solothurn, Switzerland). A cutoff pressure of 80 mmHg and volume of 600 ml was defined. The compliance of the rectal wall was calculated (1/slope of Δpressure/Δvolume) from three points along the volume–pressure graph to ensure that threshold changes were not caused by changes in compliance.

Orocecal Transit Time. Orocecal transit time was determined using a standardized hydrogen breath test incorporating a meal (400 ml cream of chicken soup) with 26.4 g lactulose.[20,21] This test is based on the rapid metabolism of lactulose in the cecum with a resultant increase in hydrogen production, which can be measured in the expired breath. Breath samples were collected every 30 min until 4 h after the meal.

Gastric Emptying. Paracetamol (1.5 g) was ingested to measure gastric emptying. Because paracetamol is absorbed largely in the proximal small intestine, a distinct increase in serum paracetamol concentrations is indicative of the arrival of paracetamol in the duodenum, and thus gastric emptying can be approximated. Blood samples were taken every 15 min for 120 min to determine serum paracetamol levels (TDx-FLx acetaminophen assay; Abbott Laboratories, Sandton, South Africa).[22,23]

Colonic Transit Times. To assess colonic transit times, patients swallowed a capsule containing 10 small radiopaque marker particles on three consecutive mornings, and a supine abdominal radiograph was taken on day 4, from which transit times were calculated.[24,25]

Statistical Analyses

Normally distributed and continuous data were analyzed using analysis of variance, analysis of covariance, and multivariate analysis of variance, as appropriate, with *post hoc* Tukey honest significant difference testing. Non-normally distributed or discontinuous data were analyzed using the Kruskall–Wallis test, followed by the Mann–Whitney U test with Bonferroni correction. Intergroup comparisons of percentages were by the Fisher exact test (two tailed). Correlations between variables were evaluated with multiple linear regression testing. A significance level of $P < 0.05$ was applied.

Colonic transit times were analyzed according to the literature.[24,25] Briefly, the numbers of markers in the total colon and in each colonic segment were counted and multiplied by 2.4 to calculate the transit time in hours. Orocecal transit times were evaluated as the time taken for the hydrogen concentration in parts per million to increase by 100% over baseline values. Gastric emptying was compared using the area under the curve (0–2 h), which was calculated using the trapezoidal rule of paracetamol concentrations.

A 15% increase in rectal distension pain tolerance pressure thresholds, a 20% increase in skin electric pain tolerance thresholds, and a 15% delay in colonic transit times would have been detected as significant with the sample size of 25 patients based on the study data, using a two-tailed test, an alpha error of 0.05, and a beta error of 0.1.

Results

Fifty patients completed all study days, with 25 patients each in the morphine and tramadol groups (table 1). Seventy-eight patients were initially eligible for participation. Sixteen patients were excluded before the start of the study: Ten refused participation, four declined surgery, one had ulcerative colitis, and one was discovered belatedly to be severely constipated. Ten additional patients were not eligible for evaluation for the following reasons: eight failed to complete the physiologic tests, one had a vaginal hysterectomy, and one had a serious side effect (temporary respiratory arrest resulting from incorrect morphine dosing).

Indications (some were multiple indications) for hysterectomy were multifibroid uterus (n = 33), meno- or metrorrhagia (n = 11), dysmenorrhea (n = 4), pelvic inflammatory disease (n = 3), dysfunctional uterine bleeding (n = 3), endometrial carcinoma (n = 1), and cervical carcinoma (n = 1).

Table 1. Patient Characteristics

	Morphine (n = 25)	Tramadol (n = 25)
Age (yr)	45 ± 8	46 ± 9
Weight (kg)	74 ± 15	78 ± 20
Height (cm)	160 ± 6	162 ± 6
Race		
White	3	3
Black	1	4
Mixed-race Asian	20	18
Indian	1	0
Number of children	2.6 ± 2	1.9 ± 2
Smokers	9	9
Diabetics: type 1/type 2	0/4	0/6

Values are mean group values ± SD or patient numbers.

Pain Intensity

Pain intensity at rest decreased significantly to a median of 0, or no pain, within both treatment groups on the evening of surgery and remained this low until the third postoperative day ($P < 0.05$) (fig. 1A). Pain intensity during movement did not change significantly in either group over time (fig. 1B). There were no significant differences in pain intensity scores at rest or during movement between the treatment groups.

Drug Doses

Mean doses (±SD) of morphine and tramadol infused over 48 h were 60.7 ± 18 mg and 644.9 ± 133 mg, and mean rescue bolus doses were 6.1 ± 5 mg (2.4 boluses) and 87.5 ± 55 mg (3.5 boluses), respectively (no significant differences). No rescue doses of meperidine were given in either group.

Electric Skin Thresholds

Shoulder. Analyses were performed by analysis of covariance, because prestudy thresholds were greater in the morphine group. Significant time effects occurred in the first sensation and pain tolerance thresholds ($P = 0.04$ and $P = 0.0002$, respectively), and a drug effect was evident on the pain tolerance thresholds ($P = 0.05$). Figure 2A shows the group sensory thresholds at the different testing times.

Incisional Dermatome. Analysis by covariance showed no time or drug effects for the first sensation thresholds, but a time effect was apparent for the pain tolerance thresholds ($P = 0.02$). Figure 2B illustrates the course of the sensory thresholds. No patients reached the predefined maximum cutoff thresholds during sensory testing.

Rectal Distension Thresholds. Analysis of distension pressure thresholds by analysis of covariance showed significant time effects for defecatory urge ($P = 0.008$) and pain tolerance ($P = 0.01$) as well as significant drug effects for first sensation ($P = 0.04$) and defecatory urge ($P = 0.02$). *Post hoc* testing showed significant differences in postoperative pressure distension thresholds with morphine compared with tramadol, and they are summarized in table 2. Rectal distension threshold volumes were similar for the two treatment groups. There was a significant time effect for all three thresholds within the groups by analysis of covariance ($P < 0.001$). On *post hoc* testing, no significant differences within or between groups were seen. Rectal compliance remained similar throughout the study in both treatment groups.

Bowel Questionnaire

The median times to first flatus and to first bowel motion were 2 and 3 days with morphine and 1 and 2 days with tramadol, respectively (both $P < 0.05$). Nausea and vomiting occurred during the postoperative course in 50% and 37% of patients with morphine and in 71% and 24% of patients with tramadol, respectively (differences not significant).

Gastric Emptying

The area under the curve of paracetamol concentrations decreased significantly after operation compared with before operation and during follow-up with morphine treatment ($P = 0.03$) but not with tramadol (table 2).

Orocecal Transit Times

Orocecal transit time increased significantly after operation compared with before operation and during follow-up in both the morphine and the tramadol groups (table 2). By the time of follow-up, values had returned to preoperative levels.

Colonic Transit

In both treatment groups, total and right-sided colonic transit times were longer after operation than before operation or at follow-up, as shown in table 2. Left-sided and pelvic transit times did not change significantly over time. Median transit times were similar in the treatment groups, but the percentage of patients with abnormally prolonged transit (>66 h)[25] was greater with morphine (48%) than with tramadol (28%) in the postoperative measurement period ($P = 0.05$). Colonic transit time was prolonged (>66 h) before operation in 8% of pa-

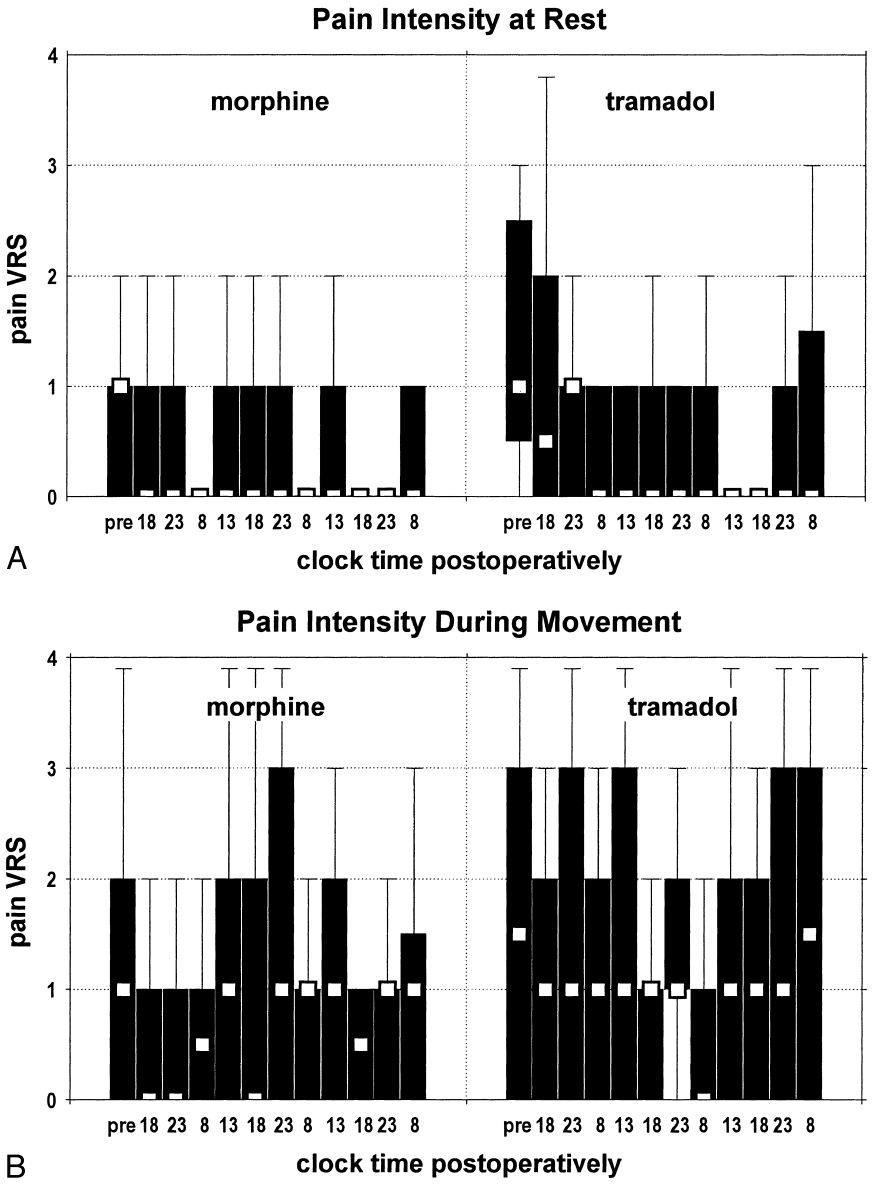

Fig. 1. (*A*) Pain intensity scores at rest (verbal rating scale: 0 = none, 4 = unbearable) before (pre) and after abdominal hysterectomy in 50 patients who received morphine or tramadol infusions for 48 h. Box whisker plots are shown (median = point; box = interquartile range; whiskers = range), with no significant differences. (*B*) Pain intensity scores during movement (verbal rating scale: 0 = none, 4 = unbearable) before (pre) and after abdominal hysterectomy in 50 patients who received morphine or tramadol infusions for 48 h. Box whisker plots are shown (median = point; box = interquartile range; whiskers = range), with no significant differences.

tients in the morphine and tramadol treatment groups each and at follow-up in 16% and 4.5%, respectively (morphine *vs.* tramadol, $P = 0.01$).

Early Postoperative Side Effects

In the morphine group, the following side effects, besides isolated nausea or vomiting, were reported in the first 3 postoperative days: none (50%), dizziness (17%), drowsiness (11%), dizziness with nausea and emesis (6%), nightmares (6%), and heartburn and nausea (6%). During tramadol treatment, the side effects reported were none (45%), dizziness (18%), dizziness with nausea and emesis (14%), and allergy (5%).

Discussion

This study was designed to evaluate pain control, sensory sensitization, and changes in gastrointestinal motility with morphine and tramadol infusions given for analgesia after major visceral surgery. Pain control after abdominal hysterectomy was similarly effective and well tolerated with both analgesics. Morphine and tramadol

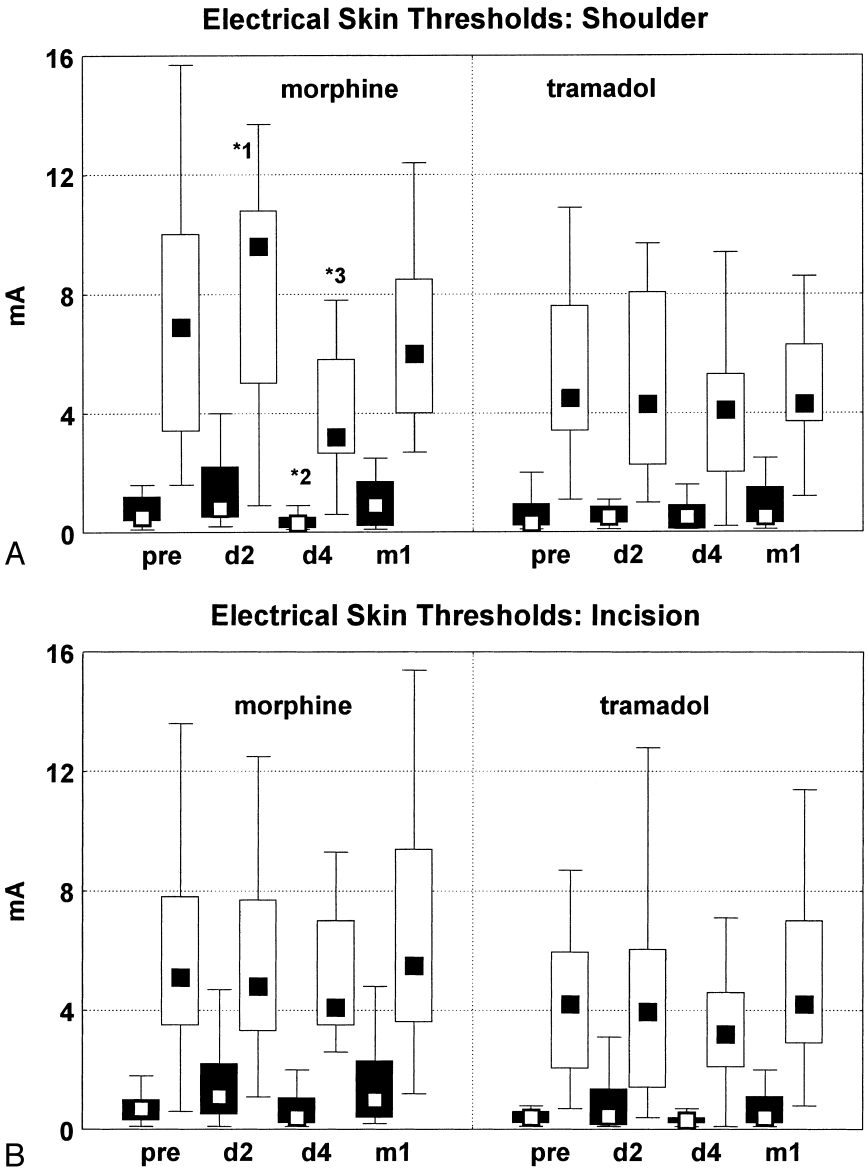

Fig. 2. (*A*) Electric sensation (open symbols, filled boxes) and pain tolerance (filled symbols, open boxes) thresholds on the shoulder before (pre), 2 and 4 days (d2, d4) after, and 1 month (m1) after abdominal hysterectomy. Morphine or tramadol infusions were given 48 h after operation. Box whisker plots are shown (median = point; box = interquartile range; whiskers = range).*1, $P = 0.04$ for pain tolerance thresholds with morphine *versus* tramadol on postoperative day 2. *2, $P < 0.05$ for sensation thresholds in the morphine group on postoperative day 4 *versus* day 2 and at the 1-month follow-up evaluation. *3, $P < 0.02$ for pain tolerance thresholds in the morphine group on postoperative day 4 *versus* before operation and on postoperative day 2. (*B*) Electric sensation (open symbols, filled boxes) and pain tolerance (filled symbols, open boxes) thresholds in the dermatome of surgical incision before (pre), 2 and 4 days (d2, d4) after, and 1 month (m1) after abdominal hysterectomy. Morphine or tramadol infusions were given 48 h after operation. Box whisker plots are shown (median = point; box = interquartile range; whiskers = range), with no significant differences.

had a relative potency of 11:1, which corresponds well with previously determined ratios.[26,27]

Sensory thresholds were measured at different perioperative times to assess effects on visceral and somatic sensory mechanisms. No significant hyperesthesia or hyperalgesia were evident in the incisional dermatome during the second day of infusions with morphine or tramadol, although there was a nonsignificant trend to lower first sensation and pain tolerance thresholds 2 days after discontinuation of both analgesic infusions. First sensation and pain tolerance thresholds measured on the shoulder, distant from the surgical site, increased markedly during morphine infusions and were significantly decreased 2 days after infusions were stopped. These changes were much less marked and nonsignificant with tramadol. By the 1 month follow-up evaluation, all thresholds had reverted to preoperative levels. Consequently, postoperative analgesia with wound infiltration with local anesthetic and protracted infusions of morphine or tramadol effectively suppressed sensitization temporarily. After the infusions were discontinued, sensitization became evident, which was significant after morphine and only a minor trend after tramadol. Sensitization was most prominent in the shoulder dermatome,

Table 2. Gastrointestinal Motor and Sensory Function Preoperatively and Postoperatively on Day 2 and at 1-Month Follow-up

	Morphine			Tramadol		
	Preoperative	Postoperative	1-mo Follow-up	Preoperative	Postoperative	1-mo Follow-up
Gastric emptying: paracetamol AUC_{0-2h} (μg/ml $\times$ 2 h)						
Median	1,533	846	1,176	1,340	1,154	1,499
IQR	974–2,305	172–1,365*	1,013–1,942	998–1,830	462–1,630	1,122–1,962
Orocecal transit (min)						
Median	60	180	60	60	120	60
IQR	30–60	120–240†	30–90	45–90	90–240†	30–60
Colonic transit (h)						
Median	34	68	31	32	65	29
IQR	14–41	58–72‡	22–58	19–50	58–72‡	22–41
Rectal distension pressure thresholds (mmHg, mean $\pm$ SD)						
First sensation	34 $\pm$ 10	42 $\pm$ 12*§	36 $\pm$ 12	32 $\pm$ 9	33 $\pm$ 10	32 $\pm$ 11
Defecatory urge	47 $\pm$ 10	55 $\pm$ 13*§	47 $\pm$ 9	41 $\pm$ 9	47 $\pm$ 9	43 $\pm$ 11
Pain tolerance	56 $\pm$ 14	63 $\pm$ 17*	54 $\pm$ 12	51 $\pm$ 13	55 $\pm$ 9	50 $\pm$ 10

AUC_{0-2h} = area under the curve (0–2 h); IQR = interquartile range.

* $P < 0.05$ *versus* preoperative and follow-up.

† $P < 0.01$ *versus* preoperative and follow-up.

‡ $P < 0.0001$ *versus* preoperative and follow-up.

§ $P < 0.05$ morphine *versus* tramadol.

which also receives visceral input from the C5 spinal segment. Convergent excitatory input from the diaphragm or viscera therefore could contribute to the observed hyperalgesia and hyperesthesia. Because morphine does not directly modulate sensation (*i.e.*, nonnociceptive thresholds), the postoperative effects on these thresholds suggest convergence of non-nociceptive and nociceptive input or a descending supraspinal action.[28,29] The reduced sensitization after tramadol compared with morphine is probably caused by its additional, prolonged monoaminergic modulation of inhibitory spinal or supraspinal pathways or by a selective blockade of the convergent visceral input.[30] Alternatively, morphine, as a more potent opioid than tramadol, might induce a greater withdrawal reaction and excitability, because opioid tolerance occurs after infusions of less than 48 h with potent opioids.[31] The postoperative sensitization was not accompanied by increased pain ratings or greater use of analgesic rescue medications.

Electric stimuli were used for somatic threshold testing in this study because of the multimodal stimulation characteristics compared with thermal and mechanical stimulation. Electric stimulation pain thresholds, although not a natural stimulus, have been validated and used in many experimental surgical and nonsurgical pain investigations, including a meta-analysis of sex differences in pain perception.[32] Opioids have also been shown to modulate electric pain tolerance thresholds in healthy volunteers and in patients.[4,9,33,34] Lund *et al.*[6] used electric pain thresholds to assess postsurgical sensitization and showed elevated sensory thresholds after 48 h. Wilder-Smith *et al.*[4] also demonstrated increased dermal electric sensory thresholds at different anatomical sites after abdominal hysterectomy during 24-h morphine infusions and no sensitization on the fifth postoperative day. Dahl *et al.*[7] showed decreased cutaneous electric pain thresholds and increased pain to suprathreshold stimulation 68 h after laparotomy. Epidural morphine increased the pain tolerance thresholds to electric, thermal, and mechanical stimulation.[34] The time courses of these results with electric stimulation correspond well with the results in the morphine arm of the current study. Postsurgical local sensitization also has been described using pressure sensory thresholds.[35]

Rectal distension sensation and pain thresholds were increased significantly more with morphine than with tramadol. No sensitization was evident during both analgesic infusions, despite the prolonged and intense surgical stimulation. However, no visceral threshold data from 2 days after discontinuation of analgesic infusions were available for comparison with this period of somatic sensitization. As noted before, it can be speculated that convergent input from sensitized visceral afferents with cranial extension could yield the dermal sensitiza-

tion shown in the C5 dermatome. If this were the case, tramadol had a prolonged inhibitory effect on the visceral afferents compared with morphine. No visceral sensitization was seen at the 1-month follow-up evaluation. Tramadol in high doses was shown previously to increase rectal distension pain tolerance threshold pressures.[14] Morphine, dihydrocodeine, and high-dose tramadol also increased the non-nociceptive first sensation and defecatory urge pressure thresholds.[14,36] This was as expected, because most of the colonic afferent input is from low-threshold mechanoreceptors encoding a wide continuous range of low, subnociceptive to high, nociceptive pressures.[37] The rapid phasic rectal distension rate of 600 ml/min used in the current study is mainly thought to activate mesenteric or serosal receptors with thoracolumbar, splanchnic and sacral, parasympathetic afferents, rather than the mucosal afferents, which respond more to tonic or shearing stimuli.[37,38] Sensitization of the afferents responding to rapid, phasic distension has been shown in patients with irritable bowel syndrome.[38] Various rectal and intestinal distension protocols have been validated in the study of a wide range of analgesic substances (for a review, see Lembo *et al.*[39]).

The postoperative return of gastrointestinal function was more rapid with tramadol, with first flatus and bowel motions occurring a day earlier than with morphine. This clinical difference was reflected in the gastrointestinal transit measures. Morphine, but not tramadol, significantly delayed gastric emptying. Morphine is known to markedly prolong transit in both the upper and lower gut.[14,40–43] Orocecal and colonic transit times were significantly prolonged in both groups, but more patients who received morphine had colonic transit times that were longer than the upper limit of normal. The pronounced effects on orocecal and colonic transit seen in the tramadol group can be attributed to a direct inhibition of propulsive motility by visceral surgery, because in previous studies tramadol did not significantly delay gastric emptying and orocecal transit times, even in very high doses, and it had only a minor prolonging effect on colonic transit.[14,19,41,42] Motility had returned to preoperative values by the 1 month follow-up evaluation. The methods used to determine gastrointestinal motility are well validated. Assessment of gastric emptying by paracetamol serum concentrations primarily reflects liquid rather than solid emptying, which may be affected differently by drugs and therapeutic interventions.

In conclusion, pain control with morphine and tramadol infusions was very effective. During morphine and tramadol infusions, pain tolerance thresholds as markers of antinociception were increased. The significant sensitization seen only after morphine discontinuation may be due to convergent visceral input. Gut motility was prolonged significantly by visceral surgery itself and also by morphine.

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