Prophylactic Use of Epidural Mepivacaine/ Morphine, Systemic Diclofenac, and Metamizole Reduces Postoperative Morphine Consumption after Major Abdominal Surgery

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Background: Surgical trauma induces nociceptive sensitization leading to amplification and prolongation of postoperative pain. While preemptive analgesic treatment with numerous agents has been successful in experimental animals, results of human studies remain conflicting. The authors used a multimodal approach for preemptive analgesia before abdominal surgery: diclofenac and metamizole inhibit prostaglandin synthesis, thus influencing peripheral sensitization; epidural local anesthetics induce conduction block, epidural opioids inhibit nociceptive synaptic transmission, and metamizole induces descending inhibition. The interaction of these drugs might suppress spinal nociceptive sensitization and postoperative analgesic demand.

Methods: One hundred forty-two patients scheduled for major abdominal surgery were randomly assigned to one of three groups and studied prospectively. Epidural catheters in groups 1 and 2 were placed at interspaces T8–T10, the position of the catheter was confirmed by epidurography, and sensory testing after administration of 5 ml mepivacaine 1%. Group 1 received 75 mg intramuscular diclofenac, 1000 mg intravenous metamizole, 5.3 ± 1 mg epidural morphine, and 15–20 ml mepivacaine 1% 85 ± 41 min before skin incision. Epidural analgesia was maintained by injections of $0.1 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ mepivacaine 1%. Group 2 patients received the balanced analgesia regimen before wound closure (221 ± 86 min after skin incision). Group 3 patients did not receive any study substances. General anesthesia was induced with 5 mg/kg thiopental and 2 µg/kg fentanyl and maintained with enflurane and nitrous oxide. Postoperative analgesia consisted of patient-controlled intravenous morphine over 5 days.

Results: Median visual analog scale pain intensities were <3 cm and did not differ among the groups. Morphine consumption per hour on postoperative day 2 was 0.8 ± 0.1 mg/h (group 1) < 1.2 ± 0.1 mg/h (group 2) = 1.1 ± 0.1 mg/h (group 3) and cumulative morphine consumption (in mg) on the morning of day 5 was 95 ± 9 (group 1) < 111 ± 11 (group 2) < 137 ± 10 (group 3).

Conclusions: A significant reduction of patient-controlled analgesia requirements could be achieved by our preincisional balanced analgesia regimen compared to application before wound closure. The more distinct difference between patients receiving balanced analgesia and those in the control group is based on the analgesic action of the study substances, which lasted about 14 h. (Key words: Analgesia: patient-controlled; postoperative; preemptive. Analgesics, opioid: diclofenac; metamizole; morphine. Anesthetics, local: mepivacaine. Anesthetic techniques: epidural; general.)

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UNDER light general anesthesia surgical trauma results in a barrage of nociceptive input to the dorsal horn neurons,[1] which causes prolonged reduction of thresholds, increase in duration of response to stimuli, and expansion of the size of receptive fields.[2] The prevention of spinal cord hyperexcitability after peripheral noxious stimulation using spinal local anesthetics[3] or opioids[4] is successful in rodents. In humans, the clinical usefulness of preemptive postoperative analgesia remains controversial: while regional nerve block seems to prevent postoperative pain, the preventive effect of neuraxial local anesthetics, opioids, or systemic nonsteroidal antiinflammatory drugs has been as well demonstrated[5–8] as rejected[9,10] in human studies. Reductions in postoperative analgesic consumption on

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the order of 25%[11,12] with preemptive treatment are of limited clinical relevance.

The facilitation of nociception after noxious stimuli is multimodal: primary hyperalgesia depends on an increase in the sensitivity of peripheral nociceptors, and secondary hyperalgesia is based on an increase in excitability of spinal cord neurons involved in nociceptive transmission.[13] To achieve a preemptive effect of clinically relevant magnitude we used a balanced analgesia regimen: Peripheral sensitization should be suppressed by intramuscular diclofenac and intravenous metamizole, which both inhibit prostaglandin synthesis[14]; central sensitization should be suppressed by afferent conduction block with epidural mepivacaine 1% and central effects of epidural morphine[15] and metamizole.[16]

We hypothesize that, in patients under general anesthesia, preventive application of the balanced analgesia regimen reduces postoperative pain intensity and/or patient-controlled intravenous morphine consumption compared to postoperative application of the same regimen and to the control group without additional medication.

Methods and Materials

One hundred forty-two patients scheduled for major elective abdominal surgery were included in the study. Exclusion criteria were age >65 years, creatinine level >140 μM/l, chronic treatment with analgesics or corticosteroids, allergy against one of the study substances, and contraindications against epidural puncture. Written informed consent was obtained from all patients and the study was approved by the Ethics Committee of the University. Patients were allocated to the three groups according to a prerandomized list unknown to the investigator recruiting the patients: group 1 (study drugs 60 min before start of the operation), group 2 (study drugs 60 min before the end of the operation), or group 3 (no study drugs). Patients and personnel involved in the postoperative care of the patients and data collection were blinded regarding the allocation of the patients to groups 1 and 2, respectively. Because we believe it is unethical to place an epidural catheter and not to use it at any time, group 3 patients did not receive a catheter and consequently could not be blinded.

On the day before surgery, patients in groups 1 and 2 received an epidural catheter inserted between T7 and T12 using the loss of resistance technique and a midline approach; the catheter was advanced approx-

imately 7 cm into the epidural space. Intervertebral level of catheter placement and symmetry of epidural distribution of 5 ml contrast medium (Iopamidol, Solustrast 250, Byk Gulden, Konstanz, Germany) was verified by epidurography. After this, the epidural catheter was tested with 5 ml mepivacaine 1% for symmetrical segmental spreading of epidural analgesia. Correct placement and segmental analgesia had to be confirmed the day before surgery, because we did not want to inject an epidural test dose of local anesthetic on the day of surgery to rule out any intraoperative residual analgesic effect in patients not receiving preemptive treatment. Patients were made familiar with the use of the visual analog scale (VAS, a 10-cm long vertical scale anchored at 0, "no pain at all," and 10"worst pain imaginable") and instructed in the use of the patient-controlled analgesia (PCA) device (Prominject, Pharmacia, Uppsala, Sweden).

On the day of surgery, group 1 patients received an epidural injection of 0.2 ml/kg mepivacaine 1% and 75 μg/kg morphine, an intravenous infusion of 1000 mg metamizole over 10 min and an intramuscular injection of 75 mg diclofenac about 60 min before dermal incision. Intraoperatively, group 1 patients received epidural injections of 0.1 ml/kg mepivacaine 1% every 60 min. About 1 h before the end of surgery, group 2 patients received an epidural injection of 0.2 ml/kg mepivacaine 1% and 75 μg/kg morphine, an intravenous infusion of 1000 mg metamizole over 10 min, and an intramuscular injection of 75 mg diclofenac. If the time to the end of surgery was longer than 1 h 0.1 ml/kg mepivacaine 1% was repeated. Group 3 patients did not receive any analgesic medication in addition to general anesthesia.

General anesthesia was induced in all three groups with 1 mg pancuronium, 2 μg/kg fentanyl, 5 mg/kg thiopental, and 2 mg/kg succinylcholine to facilitate tracheal intubation; it was maintained with oxygen:nitrous oxide 1:2, enflurane as necessary to maintain heart rate and blood pressure within ±20% of preinduction values; neuromuscular blockade was maintained with pancuronium. The maximum inspiratory concentration of enflurane that was used for longer than 30 min was recorded. Intraoperative fluid replacement consisted of 8 ml · kg^{-1} · h^{-1} lactated Ringer's solution and hydroxyethyl starch 6%, 0.5/200 and packed red cells as needed to keep central venous pressure >5 mmHg and hematocrit >26%. Special care was taken to keep central temperature above 35°C (heating blanket, prewarming of infusions).

All patients were tracheally extubated in the operating room after antagonism of residual neuromuscular blockade with 0.1 mg/kg pyridostigmine and 0.5 mg atropine.

When patients in the postanesthesia care unit reported pain of >4 cm on the VAS they received intravenous boluses of 2 mg morphine (loading dose) until they were comfortable and/or alert enough to use the PCA pump (bolus: 2 mg morphine, lockout interval 10 min). If pain intensities of more than 5 cm on the VAS occurred at two consecutive time points, epidural bupivacaine 0.25% was started at 0.1 ml $\cdot$ kg$^{-1} \cdot$ h^{-1} as rescue medication; this led to study drop-out.

Time of the first request of analgesia relative to the end of the operation and to the time of epidural morphine injection was noted. At 8 AM, noon, 4 PM, and 8 PM on postoperative days 1–4 and at 8 AM on postoperative day 5 the following parameters were registered: PCA cumulative morphine consumption (including the loading dose), VAS pain intensity, heart rate, and systolic and diastolic arterial pressure measured by Riva Rocci method, and respiratory frequency measured by counting thoracic excursions during 60 s. After tracheal extubation in the recovery room and at 8 AM on days 1–5 an arterial blood gas analysis (Stat Profile 5, Nova, Waltham, Massachusetts) was done and serum creatinine level (Jaffe's reaction) was determined.

Data Analysis

Morphine consumption per hour was calculated as follows:

$$\frac{\begin{array}{c}cumulative\ morphine\ consumption \\ (8\ \text{AM},\ day\ x + 1) - cumulative\ morphine \\ consumption\ (8\ \text{AM},\ day\ x)\end{array}}{24}$$

Nominal data are reported as frequencies, ordinal data are reported as median (1. and 3. quartile) and continuous data are reported as mean ± standard error of

Table 1. Patient Demographics

	Group 1	Group 2	Group 3	P
Patients (n)	48	48	46	
Age (yr)	53 ± 12	52 ± 10	50 ± 12	0.440
Height (cm)	169 ± 9	170 ± 10	172 ± 10	0.309
Weight (kg)	71 ± 13	71 ± 13	68 ± 13	0.369
Sex male (n)	26	33	29	0.333

Values are counts or mean ± SD.

Table 2. Operations

	Group 1	Group 2	Group 3
Pancreatic resection (n)	27	23	18
Gastric resection (n)	4	5	7
Hepatic resection (n)	0	1	3
Colonic resection (n)	7	6	4
Proctectomy (n)	7	9	10
Adrenalectomy (n)	1	2	0
Palliative bypass (n)	2	2	4

Values are counts.

the mean (SEM). Statistical analysis was performed using chi-square analysis on nominal data, Mann-Whitney U test on ordinal data and two-way analysis of variance for repeated measures and Student-Newman-Keuls test on continuous data. The Kolmogorov-Smirnov test was used to verify Gaussian distribution of variables and Sen & Puri's nonparametric test was used to verify homogeneity of variances. Continuous data not fulfilling analysis of variance assumptions were analyzed by the Kruskal-Wallis test. A P value ≤ 0.05 was considered significant.

Results

Groups 1, 2, and 3 were not significantly different with regard to age, height, weight, sex (table 1), type of operation (table 2), and duration of the operation (table 3). Groups 1 and 2 did not differ with regard to the intervertebral location of the epidural puncture site (T9) and dermatomal spread of analgesia after 5 ml mepivacaine 1% (T4–T12). Group 1 patients needed a significantly lower maximum inspiratory concentration of enflurane than those in groups 2 and 3, respectively ($P < 0.001$). They received more epidural mepivacaine 1% than group 2 patients ($P < 0.001$). Group 1 patients received their study drugs 85 min before the start of surgery and group 2 patients received their study drugs 221 min after the start of surgery (table 3). There was no difference between the groups with regard to the duration of time between extubation and 8 AM the morning of postoperative day (time = 0; 16 ± 0.2 h). Data analysis was performed in 139 patients: two group 1 patients and one group 2 patient had insufficient analgesia from intravenous morphine; they required epidural infusion of bupivacaine 0.25% as rescue medication and were consequently withdrawn from the trial.

Table 3. Anesthetic Procedures

	Group 1	Group 2	Group 3	P
ASA physical status	2 (2; 2)	2 (2; 2)	2 (2; 2)	0.883
Epidural catheter (segment)	T9 (T8; T10)	T9 (T8; T10)		0.569
Upper limit (segment)	T4 (T3; T6)	T4 (T3; T6)		0.278
Lower limit (segment)	T12 (T12; L2)	T12 (T12; L2)		0.495
Duration of operation (min)	294 ± 116	273 ± 93	262 ± 103	0.317
Fentanyl (µg)	134 ± 50	140 ± 45	140 ± 57	0.830
F_i enflurane	0.6 ± 0.2	1.8 ± 0.4	1.6 ± 0.4	<0.001
Temperature (°C)	35.8 ± 0.7	36.2 ± 0.9	36.0 ± 0.7	0.046
Time of extubation (min)	5 (0; 10)	10 (5; 15)	5 (5; 10)	<0.001
Morphine (mg) ep	5.3 ± 1	5.4 ± 1		1
Diclofenac (mg) im	75	75		1
Metamizole (mg) iv	1000	1000		1
Mepivacaine 1% (ml) ep	63 ± 23	21 ± 8		<0.001
Time of medication (min)	−(85 ± 41)	221 ± 86		<0.001

Values are mean ± SD, median (lower quartile; upper quartile).

Upper/lower limit = upper/lower sensory level to pin prick after 5 ml of mepivacaine 1%; time of extubation = relative to the end of the operation; F_i enflurane = maximal inspiratory fraction of enflurane over >30 min; time of medication = application of study drugs relative to the beginning of the operation; ep = epidural; im = intramuscular; iv = intravenous.

Analgesia

Time from injection of epidural morphine to the first request of analgesia was comparable in groups 1 (875 ± 73 min) and 2 (852 ± 153 min), respectively (F(1; 91) = 0.018, P = 0.892). Time from the end of the operation to the first request of analgesia was significantly shorter in group 3 (40 ± 7 min) compared to groups 1 (531 ± 78 min) and 2 (758 ± 153 min), respectively (F(2; 136) = 14.6, P < 0.001).

Postoperative analgesia was comparable in groups 1–3 and adequate: median pain intensities were ≤3.0 cm

on the VAS in groups 1–3 (fig. 1). The only difference in pain intensities among the groups occurred at 8 AM on the first day, when VAS pain intensity in group 3 (median = 3, quartile range = 2) was significantly higher compared to group 2 (median = 1, quartile range = 3; P = 0.001).

Cumulative morphine consumption was comparable in the morning of the first postoperative day (16 ± 0.2 h after the end of anesthesia) in groups 1 (13 ± 4 mg) and 2 (8 ± 1.6 m), but it was significantly higher in group 3 (41 ± 3.6 mg). The difference between group
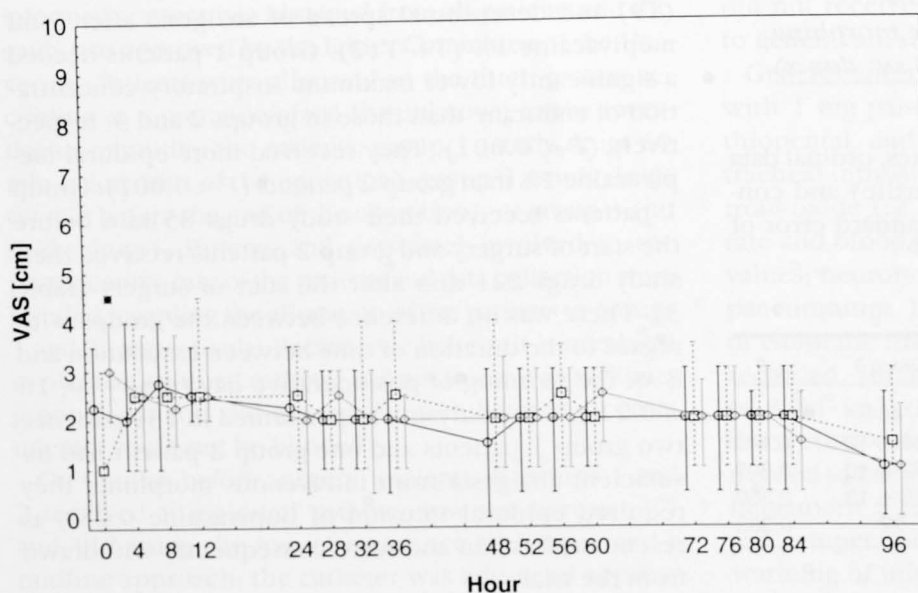

Fig. 1. Pain intensities on postoperative days 1–5. Time 0 = 8 AM in the morning of postoperative day 1. Group 1 (circles, solid line) = preincisional treatment; group 2 (square, interrupted line) = postincisional treatment; group 3 (diamonds, dotted line) = no perioperative treatment. Values are presented as median, lower, and upper quartile (whiskers). *P < 0.05 compared to group 2.

3 and groups 1/2 remained significant until the morning of the fifth postoperative day. Beginning the morning of the fourth postoperative day, cumulative morphine consumption was higher in group 2 (95 ± 8.7 mg) compared to group 1 (90 ± 7.8 mg). The difference increased during the next 24 h (111 ± 10.5 mg (2) *vs.* 95 ± 8.7 mg (1); $P = 0.002$; figure 2).

Patient-controlled morphine requirements per hour were significantly higher in group 3 (2.5 ± 0.2 mg/h) compared to groups 1 (0.9 ± 0.2 mg/h) and 2 (0.5 ± 0.1 mg/h) from the end of anesthesia until 8 AM on postoperative day 1. Group 1 showed a trend toward lower PCA morphine requirements per hour compared to groups 2 and 3 on postoperative days 1–4 (fig. 3). A significant difference could be observed on postoperative day 2, when hourly morphine consumption was 0.8 ± 0.1 mg/h in group 1 compared to 1.2 ± 0.1 mg/h in group 2 ($P = 0.03$).

Respiration

Respiratory frequencies observed ranged from 6 to 34 breaths/min with mean frequencies of 15–18 breaths/min. There was no difference in respiratory frequencies among the groups at any time.

Carbon dioxide in the arterial blood (Pa_{CO_2}) in the recovery room after extubation was significantly lower in group 3 patients (38.4 ± 0.6 mmHg) compared to group 1 patients (41 ± 0.7 mmHg; $P = 0.004$) and group 2 patients (41 ± 0.7 mmHg; $P = 0.004$). On postoperative days 1–4 no significant differences in Pa_2 (range 25–56 mmHg) could be observed.

Renal Function

Postoperative serum creatinine level was comparable in patients who were randomized to receive diclofenac (groups 1 and 2, respectively; creatinine 90 ± 2 $\mu M/$l). There was a significant difference in serum creatinine level on postoperative days 1 and 2 between patients receiving diclofenac compared with patients not having received the drug (fig. 4). This difference could no longer be observed on postoperative days 3 and 4. Mean creatinine values remained in the normal range at all times. There was a tendency of serum creatinine values to decline over the time both in patients who received diclofenac and those who did not, respectively.

Discussion

This study shows that preoperative application of a balanced analgesia regimen, consisting of systemic diclofenac, metamizole, and epidural mepivacaine and morphine, reduces postoperative consumption of analgesics compared to before wound closure or no utilization at all of the same regimen: morphine consumption per hour was approximately 40% higher in group 2 patients compared to group 1 patients on postoperative day 2. Cumulative morphine consumption over 112 h in the preemptive *group* (1) was 14% and 31% lower compared to the postoperative and control groups (2 and 3), respectively. However, the absolute difference was only 16 and 42 mg.

Because analgesia was comparable in the three groups at all times, morphine consumption is a valid measure

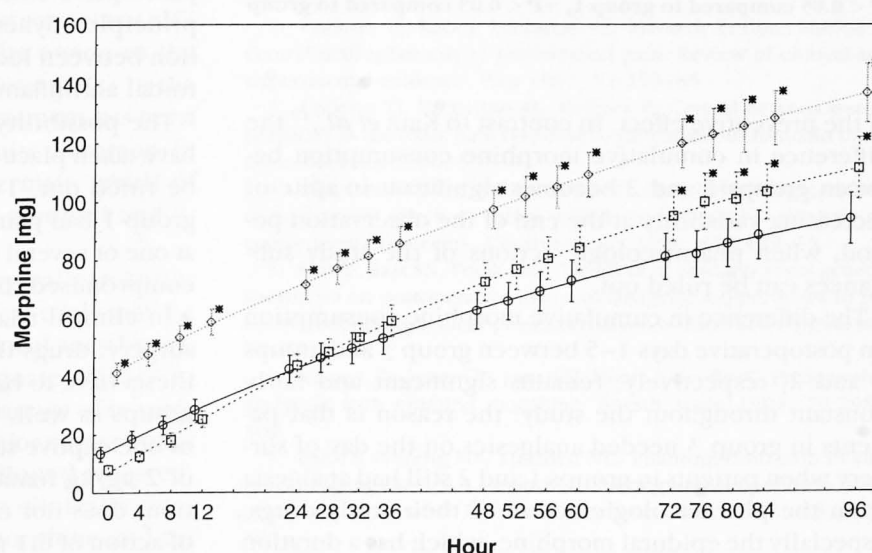Fig. 2. Cumulative morphine consumption on postoperative days 1–5. Time 0 = 8 AM the morning of postoperative day 1. Group 1 (circles, solid line) = preincisional treatment; group 2 (squares, interrupted line) = postincisional treatment; group 3 (diamonds, dotted line) = no perioperative treatment. Values are presented as mean and SEM (whiskers). The lines indicate the minimal squares regression. *$P < 0.05$ compared to group 1.

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Fig. 3. Morphine consumption per hour. Op = day of the operation until 8 AM on postoperative day 1; day 1 to 4 = 8 AM until 8 AM. Group 1 (circles, solid line) = preincisional treatment; group 2 (squares, interrupted line) = postincisional treatment; group 3 (diamonds, dotted line) = no perioperative treatment. Values are presented as mean and SEM (whiskers). *$P < 0.05$ compared to group 1, +$P < 0.05$ compared to group 2.

of the preventive effect. In contrast to Katz *et al.,*[12] the difference in cumulative morphine consumption between groups 1 and 2 becomes significant in spite of increasing variability at the end of the observation period, when pharmacologic actions of the study substances can be ruled out.

The difference in cumulative morphine consumption on postoperative days 1–5 between group 3 and groups 1 and 2, respectively, remains significant and fairly constant throughout the study: the reason is that patients in group 3 needed analgesics on the day of surgery when patients in groups 1 and 2 still had analgesia from the pharmacologic action of their study drugs, especially the epidural morphine, which has a duration

of action of approximately 12 h.[17] Consequently, the morphine consumption per hour on the day of the operation was significantly greater in group 3 patients (2.5 ± 0.2 ml/h) compared to those in groups 1 (0.9 ± 0.2 mg/h) and 2 (0.5 ± 0.1 mg/h), whereas later, no differences in morphine consumption per hour between group 3 and groups 1 and 2, respectively, could be observed.

In spite of a multimodal analgesic approach, the preemptive effect in our study is of no greater magnitude than that in other studies.[11,12]

Care was taken to match drug effects and anesthetic techniques with the operative procedures in this study. A duration of action of the study substances equivalent to the duration of the operation was achieved with metamizole (elimination half-life 7 h[18]), epidural morphine (duration of action 12.3 h[17]) and epidural mepivacaine (repetitive injections every 60 min), whereas the elimination half-life of diclofenac of approximately 1.1 h[19] is significantly shorter but was compensated by slow absorption after intramuscular injection. Mepivacaine 1% was chosen as a compromise between depth of neural block[20] and limitation of the cumulative amount of local anesthetic infused over time. Adequacy of the extension of the epidural block was confirmed by epidurography and application of a test dose on the day before the operation. A complete blockade of nociceptive input to the spinal cord with local anesthetic, as has been shown to be of preemptive effect,[5] is not clinically possible in upper abdominal surgery: the upper limit of the blocked area would have to be above C3 (phrenic nerve). However, we intend to show a preemptive effect of the interaction of four analgesic principles. Synergism has been shown for the interaction between local anesthetics, morphine, and nonsteroidal antiinflammatory drugs.[21,22]

The possibility that postoperative sensitization may have taken place in the preemptive group cannot totally be ruled out. Twenty-five percent of our patients in group 1 had pain intensities of 2.5–7.5 cm on the VAS at one or several time points. This mechanism may have compromised the preemptive effect.[23]

In clinical trials of preemptive analgesia and major surgery, drugs that induce and maintain general anesthesia have to be used in the preoperative and control groups as well. We believe that possible suppression of nociceptive sensitization by the initial systemic dose of 2 µg/kg fentanyl, given to reduce stress on intubation, does not compromise our results. The duration of action of 0.1 mg fentanyl (1–2 h[24]) is too short com-

Fig. 4. Serum creatinine level (μM/l) preoperatively and on postoperative days 1–4. Diclofenac (circles, solid line) = patients with perioperative intramuscular diclofenac 75 mg (groups 1 and 2); no diclofenac (squares, dotted line) = patients without perioperative diclofenac (group 3). Values are presented as mean and SEM (whiskers). *$P < 0.05$ compared to "no diclofenac."
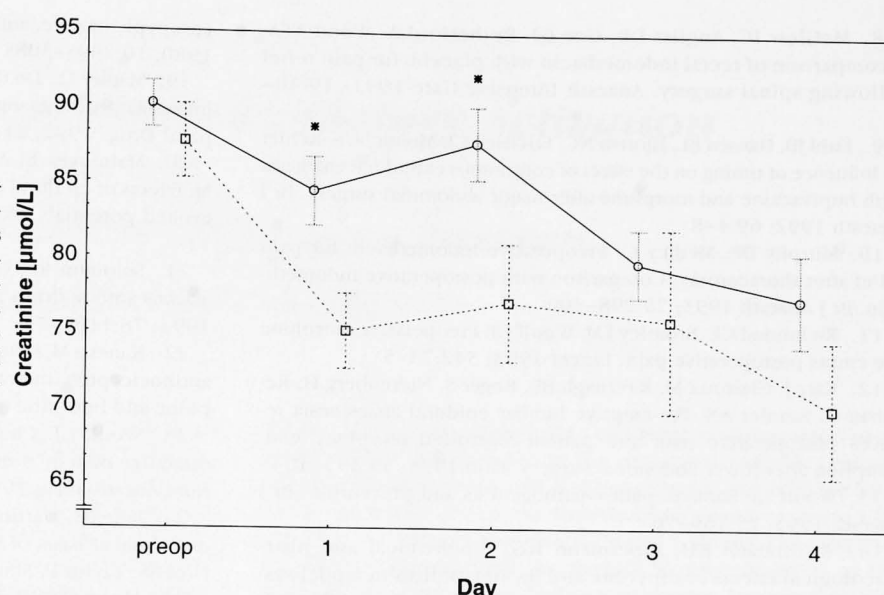
pared to the duration of the operation (4.5 h). The importance of a preventive effect of inhalational anesthetics is still a matter of debate[25–28] and may have influenced our result, as both the postoperative (2) and control groups (3) had higher inspiratory fractions of enflurane compared to the preemptive group (1).

The magnitude of the difference between groups 1 and 2 compared to group 3 may have been influenced by a placebo effect. Group 1 and 2 patients had an epidural catheter whereas group 2 patients did not have an epidural catheter. The more complex treatment with epidural anesthesia/analgesia may have reduced analgesic requirements in groups 1/2. However group 3 was only included in the study to show that the design "prophylactic treatment" *versus* "no treatment at all" always has to lead to significant results owing to the pharmacologic action of the study substance(s) in the postoperative period, if an effective treatment has been used. This study design has been quite common in studies on preemptive analgesia. The main result of this study refers to the comparison of groups 1 and 2, which were fully blinded.

The reason for unequivocal or marginally relevant results in adequately conducted clinical trials may be that except for complete blockade by local anesthetics, no single analgesic technique of adequate efficacy to protect the neuraxis from the afferent barrage of sensory and sensible pathways produced by major surgery over a multitude of segments has been developed or tested.

No severe side effects, especially no clinically relevant respiratory depression by PCA morphine and no

clinically relevant reduction in renal function by systemic diclofenac, were observed.

In conclusion, the preoperative application of a balanced analgesia regimen of epidural mepivacaine and morphine plus systemic diclofenac and metamizole leads to a opioid-sparing effect, which becomes significant in the later postoperative phase (after $\geq$40 h). This indicates a preemption of nociceptive sensitization even after abdominal surgery.

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