Multimodal Perioperative Management—Combining Thoracic Epidural Analgesia, Forced Mobilization, and Oral Nutrition—Reduces Hormonal and Metabolic Stress and Improves Convalescence After Major Urologic Surgery

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We sought in this prospective study to use a multimodal approach to reduce stress and improve recovery in patients undergoing major surgery. During an initial study period, 30 patients were randomly allocated to receive general anesthesia (GA; Group 1) or a combination of GA and intraoperative thoracic epidural analgesia (TEA; Group 2) when undergoing radical cystectomy. Parenteral nutrition was provided for 5 days after surgery. During the second period, 15 patients were treated with a multimodal approach (Group 3) consisting of intraoperative GA and TEA, postoperative patient-controlled TEA, early oral nutrition, and enforced mobilization. Data for plasma and urine catecholamines, plasma cortisol, the nitrogen balance, the postoperative inflammatory nutrition index, pain relief, fatigue, sleep, overnight recovery, recovery of bowel function, and mobilization were recorded up to the fifth postoperative day. Plasma concentrations of catecholamines and cortisol were comparable in all patients, but those in Group 3 had lower levels of urinary catecholamine excretion. Protein intake was more effective with parenteral nutrition. Nitrogen balances were less negative, and the postoperative inflammatory nutrition index score increased significantly in the traditional groups but not in Group 3. Multimodally treated patients reported less fatigue and better overnight recovery. Along with improved pain relief, recovery of bowel function, and ambulation, there were no differences in the postoperative complication rates among the three groups. The multimodal approach reduced stress and improved metabolism and recovery after radical cystectomy.

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Surgical stress evokes a complex response pattern, with an increase in catabolic hormones and a reduction in anabolic hormones, altered carbohydrate and protein homeostasis, and hypermetabolism (1,2). Secretion of cortisol and catecholamines, as well as the acute-phase response, are important markers of this surgical stress response (1,2).

Interrupting the nociceptive afferent input from the injured area and blocking the sympathetic efferents with epidural local anesthetics suppresses this response pattern and restores metabolic activity, with improved posttraumatic recovery (3). However, in view of the multiple factors influencing postoperative physiology, as well as the complexity of these physiological processes, a unimodal intervention of this type is not sufficient to improve postoperative convalescence. Tolerance of a regular diet and the ability to walk without assistance, which have been defined as criteria for fast-track hospital discharge after radical retropubic prostatectomy (4,5), return earlier if optimal pain relief and blockade of the perioperative stress response are combined with additional specific interventions such as physiotherapy or early enteral feeding. Epidural analgesia should therefore form part of a multimodal approach and should be integrated into a

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therapeutic program that includes early mobilization and oral nutrition (6–8).

As a consequence of these arguments, the perioperative regimen used at our urologic department was altered. An interdisciplinary multimodal regimen was developed that consists of effective thoracic epidural analgesia (TEA), i.e., establishing the epidural blockade before surgery; patient-controlled postoperative TEA (PCEA) and continuous evaluation and treatment of postoperative pain by an acute pain service; early tracheal extubation; enforced mobilization; and an early return to enteral nutrition without the use of gastric tubes.

The purpose of this study was to compare the traditional regimen, with or without epidural analgesia, and the multimodal approach with regard to their effects on the hormonal and metabolic stress response, pain relief, and recovery of vigilance, gastrointestinal function, and mobility after major urologic surgery.

Methods

After approval by the local ethics committee and after informed consent had been obtained, 45 patients undergoing radical cystectomy and formation of an ileal neobladder were included in this prospective clinical study.

During the first phase of the study, 30 patients were randomly allocated to receive either general anesthesia (GA; Group 1) or a combination of GA and TEA (Group 2) during surgery. TEA was restricted to the intraoperative period. After termination of this phase, the multimodal regimen was introduced and investigated in the 15 patients in Group 3.

In Group 1, GA was induced with propofol (2 mg/kg) and sufentanil (0.3–0.5 μg/kg). Rocuronium (0.6 mg/kg) was administered to facilitate tracheal intubation. The lungs were mechanically ventilated with P_{ETCO_2} maintained at 35–45 mm Hg. Maintenance of anesthesia was achieved by continuous administration of 6–10 $mg \cdot kg^{-1} \cdot h^{-1}$ IV propofol and 60% nitrous oxide in oxygen in a semiclosed circular system with intermittent positive-pressure ventilation. Supplemental bolus doses of IV sufentanil (0.1–0.15 μg/kg) were delivered if there were clinical signs of inadequate analgesia (e.g., sweating, lacrimation, increased heart rate, or arterial pressure more than 20% above baseline values). IV fluid therapy, transfusions, and other procedures followed the usual standards.

The patients in Groups 2 and 3 received a combination of GA and TEA. Thoracic epidural catheters were inserted at T9-11 before the induction of GA. After a test dose of 2 mL of ropivacaine 5 mg/mL, an initial dose of 10–15 mL of 10 mg/mL ropivacaine was administered epidurally to confirm a sensory block up to T4, and the block was tested before introduction of GA. The induction and maintenance of GA were similar to those in Group 1 patients, except that less sufentanil was used; sufentanil was administered only as a bolus of 0.3–0.5 μg/kg, to facilitate tracheal intubation. Epidural bolus doses of 5–10 mL ropivacaine 5 mg/mL were administered if there were clinical signs of inadequate intraoperative analgesia.

At the end of surgery, all patients were tracheally extubated and admitted to the perioperative anesthesia care unit (PACU). In the PACU, postoperative pain therapy in Group 1 patients was started with 7.5–15 mg piritramide (a μ-opioid agonist) IV. Group 2 received 10 mL epidural ropivacaine 2 mg/mL, and the epidural catheters were removed after normal postoperative coagulation had been confirmed: Quick $> 80\%$, partial thromboplastin time < 40 s, and platelets $> 90{,}000$/mL. For further analgesia, patients in Groups 1 and 2 received piritramide and dipyrone at the discretion of the managing physician. Postoperative treatment followed routine practice in the Department of Urology. Oral fluid intake was possible from the first postoperative day, and gastric tubes were removed after confirmation that gastric function had recovered: nasogastric tubes turned to "no suction," no self-reported nausea, reflux $<$1000 mL, and oral intake without emesis after removal of tubes. Patients received IV nutrition with 0.525 g/kg protein and 1.875 g/kg glucose on the first postoperative day, and 1.05 g/kg protein and 3.75 g/kg glucose from the second to fifth postoperative days. At the discretion of nursing staff, patients were asked to rest on the bedside or sit or stand beside their beds in the afternoon of the first postoperative day. However, mobilization was stopped if patients felt uncomfortable (pain, nausea, motor weakness).

Patients in Group 3 received an epidural bolus of 10 mL ropivacaine 2 mg/mL after arrival in the PACU. A PCEA pump was then started (5 mL/h), providing a continuous mixture of 2 mg/mL ropivacaine and 1 μg/mL sufentanil epidurally. During the postoperative course, physicians from the acute pain service adjusted the infusion rate twice a day to the individual patient's requirements. Additional bolus doses of 2 mL up to every 20 min for on-demand self-administration were set in the bedside pump's program. The aim was to achieve a dynamic pain score (i.e., for coughing, taking deep breaths, etc.) of 40 or less on a visual analog scale (0–100). The drug dosage was limited only by side effects such as sedation, respiratory depression, nausea, or pruritus. On the fourth postoperative day, the continuous infusion dose was reduced by 50%. On the fifth postoperative morning, the infusion was terminated, the epidural catheter was removed, and the patients were treated with IV dipyrone and piritramide, depending on the intensity of pain. During the first 72 postoperative hours, patients received only IV lactated Ringer's solution. Gastric tubes were removed immediately after surgery, and oral nutrition was started from the first postoperative day. The nursing staff discussed mobilization with the patients on the morning of the first postoperative day, and this was adjusted to the patients' recovery of motor power.

The patients in all three groups were visited by an independent investigator who was aware of the treatment group but was not involved in perioperative therapy. He recorded data on the quality of analgesia and side effects of pain management on the day before surgery and 3, 24, 48, 72, 96, and 120 h after surgery. Fatigue, recovery of bowel function, and mobilization were assessed daily from the first to the fifth postoperative day. Pain relief was judged according to the dynamic visual analog scale score. Patients rated their satisfaction with pain therapy on a five-point Likert scale (1 = excellent, 2 = good, 3 = moderate, 4 = insufficient, 5 = bad). The following side effects of epidural and IV analgesia were examined: motor block [Bromage (9) score = 0, normal motor function; score = 1 or greater, reduced motor function]; respiratory depression (1 = normal respiratory rate, 2 = respiratory rate of 8–12 breaths/min, 3 = respiratory rate < 8 breaths/min); sedation (1 = awake, patient looks around; 2 = tired, sleepy, patient easy to wake up when spoken to; 3 = asleep, can easily be woken with a light glabellar tap; 4 = coma, sedated, a sluggish response—too deep) (10); nausea (yes or no); emesis (yes or no); and pruritus (yes or no). Postoperative fatigue was registered by using psychological scales, which were constructed and tested in earlier studies (11). Fatigue was assessed by using expert ratings for exhaustion (a five-point rating scale with end points of 1 = not at all and 5 = bad); overnight recovery (a five-point rating scale with end points 1 = excellent and 5 = bad); and self-ratings of sleep during the day and during the night (hours of sleep). Recovery of bowel function was recorded on the day of first defecation. Postoperative mobilization was assessed by the distance (meters), as measured by the accompanying person, while patients walked during their rounds in the area outside their room. In addition, the time until discharge from the postoperative intermediate care unit and regular surgical ward was recorded.

Demographic variables, medical history, preoperative physical status, intraoperative medication, duration of GA, blood loss, volume replacement, fluid balance, and transfusions were recorded in a standardized protocol for further analysis.

Plasma samples were taken from a central venous catheter on the day before, immediately after, and 24, 72, and 120 h after surgery. Samples were centrifuged at 4000–5000 rpm and stored at −20°C until analysis. C-reactive protein (CRP), α_1-acid glycoprotein (α_1-AGP), albumin (ALB), and prealbumin (PALB) levels were assayed for prognostic inflammatory nutrition indices (PINI). Cortisol was measured with a chemiluminescence immunoassay by using the Centaur system (Bayer Diagnostics, Fernwald, Germany); catecholamines were measured by high-pressure liquid chromatography by using electrochemical detection and a kit from Chromsystems (Munich, Germany); proteins were analyzed by immune nephelometry (BN 100; Dade Behring, Liederbach, Germany); and PINI scores were calculated with the following formula (12):

$$(\text{CRP [mg/L]} \times \alpha_1 - \text{AGP [mg/L]})/(\text{ALB [g/L]} \times \text{PALB [mg/L]})$$

where CRP = C-reactive protein, α_1-AGP = α_1-acid glycoprotein, ALB = albumin, and PALB = prealbumin. Urine catecholamine excretion and nitrogen balances (measured by chemiluminescence; Antek, Dusseldorf, Germany) were recorded 24, 48, 72, 96, and 120 h after surgery. Urine was collected in plastic containers (with the addition of 10 mL 25% HCl) over periods of 24 h. Samples of 10 mL were drawn from these containers and stored at −20°C until analysis by high-pressure liquid chromatography.

Immobilization, delayed recovery of bowel function, and fatigue were regarded as important aspects of postoperative convalescence. The effects on these outcome variables should be clear and large, because arguments for implementing multimodal therapy are based on the clinical significance of these aspects. A total sample size of 45 patients would allow us to detect a significant effect of F = 0.5 with a statistical power of $1 - \beta = 0.8$ and a significance level of $\alpha < 0.05$ for postoperative ambulation (13).

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS 6.1) system (SPSS Inc., Chicago, IL). Nominal scale variables were described by using relative and absolute frequencies, and the χ^2 test was used to assess differences among groups. Fisher's exact test was used if matched cells were rare (expected frequencies <5). Variables with interval or rational scales were described as mean and SD. After logarithmic transformation, one-way analysis of variance or repeated-measures analysis of variance was used to compare groups. Following the design of the study, the initial comparison was between the two groups of patients who were randomly allocated to Groups 1 and 2 in the first study period. Because no differences were found, and to test the hypothesis that it is the multimodal intraoperative and postoperative approach that contributes to the outcome, these patients were therefore compared with Group 3. Covariation between variables was assessed with Pearson correlation analyses.

Table 1. Demographic Data, Preoperative Diagnoses, and Intraoperative Characteristics

Variable	Group 1 (n = 15) Mean	SD	Group 2 (n = 15) Mean	SD	Group 3 (n = 15) Mean	SD
Age (yr)	59	13.5	63	8.8	62	9.0
Weight (kg)	74	12.6	75	10.4	84	24.1
Height (cm)	169	9.6	170	4.2	175	6.5
Duration of anesthesia (min)	475	59.7	431	74.2	509	108.7
Duration of surgery (min)	392	52.1	366	70.0	423	101.5
Blood loss (mL)	1663	684.4	2369	1351.2	2086	995.0
Stay in the postanesthesia care unit (min)	219	276.5	188	190.6	109	36.5
Stay in the intermediate care unit (days)	1.4	0.9	0.9	0.1	1.2	0.9
Stay in the regular surgical ward (days)	17.9	4.4	19.5	5.7	16.0	3.0

	Group 1 Absolute frequency	Group 2 Absolute frequency	Group 3 Absolute frequency
Male sex	12	14	13
ASA physical status II/III/IV	4/6/5	7/5/3	4/6/5
Diabetes mellitus diet/oral antidiabetics/insulin	5/5/5	0/5/5	0/8/15
Chronic obstructive pulmonary disease (expert rating)	1	3	1
Coronary heart disease (history, electrocardiography)	3	2	1
Hypertension (anesthesiologist's rating)	5	2	7

Group 1 = general anesthesia; Group 2 = general anesthesia plus intraoperative thoracic epidural analgesia; Group 3 = general anesthesia plus intraoperative thoracic epidural analgesia plus postoperative patient-controlled epidural analgesia, early oral feeding, and forced mobilization. $P > 0.05$ among the groups.

Results

One male patient in Group 3 suffered from inadequate analgesia caused by catheter dislocation on the second postoperative day. This patient was withdrawn from the study, and another patient was included to provide a sample size of $n = 45$.

There were no significant differences among the groups in the demographic data, preoperative diagnoses, intraoperative characteristics, or stay on the postoperative wards (Table 1).

Plasma cortisol increased in all groups after surgery during the whole observation period, with no significant differences among the groups (Fig. 1). Plasma epinephrine was significantly increased 3 h after surgery, but not thereafter, and with no differences among the groups (Fig. 1). Plasma norepinephrine increased ($P < 0.05$) in all patients from the first postoperative day, with no differences among the groups. Cumulative urinary excretion of epinephrine and norepinephrine was significantly less in Group 3 than in Groups 1 and 2 ($P < 0.05$; Fig. 1).

There was no systematic covariation between plasma cortisol and catecholamine levels ($P > 0.05$).

The nitrogen balance was negative in all groups but significantly more negative in Group 3, in accordance with the lack of parenteral protein administration in this group. A protein intake similar to that in the other groups (combined IV and oral) was first achieved on postoperative Day 5 (Fig. 2). The PINI scores increased significantly in Groups 1 and 2 ($P < 0.05$), but not in Group 3. The increase in the PINI score was significantly less in Group 3 in comparison with the values for Groups 1 and 2 (Fig. 2).

Although the patients in Group 3 had less sleep during both the day and the night ($P < 0.05$), they were significantly less fatigued compared with Groups 1 and 2 ($P < 0.05$; Fig. 3).

Postoperative dynamic pain scores were significantly ($P < 0.05$) lower in Group 3 compared with Groups 1 and 2 (Fig. 4). The cumulative walking distance within the first 120 h was significantly longer in Group 3 than in Groups 1 and 2 ($P < 0.05$). The time to first defecation was significantly shorter in Group 3 compared with Groups 1 and 2 ($P < 0.05$; Fig. 4).

There were no differences in the data for nausea, vomiting, and pruritus among the three groups ($P > 0.05$), and the average Bromage score was 0 in Group 3 from 24 to 120 h after surgery.

Cumulative oral fluid intake (Days 1–5) was significantly more ($P < 0.05$) in Group 3 (5469 mL) compared with Group 1 (2329 mL) and Group 2 (2636 mL).

There were no differences among the groups with regard to postoperative complications. There was one case of delayed abdominal wound healing and one of wound dehiscence in Group 1; there were two cases of wound dehiscence and one of rebleeding with repeat surgery, as well as one case of pneumonia, in Group 2; and there was one case of delayed wound healing and one of pneumonia in Group 3. None of the patients suffered angina pectoris, myocardial infarction, arrhythmia, thromboembolism, anastomotic insufficiency, or

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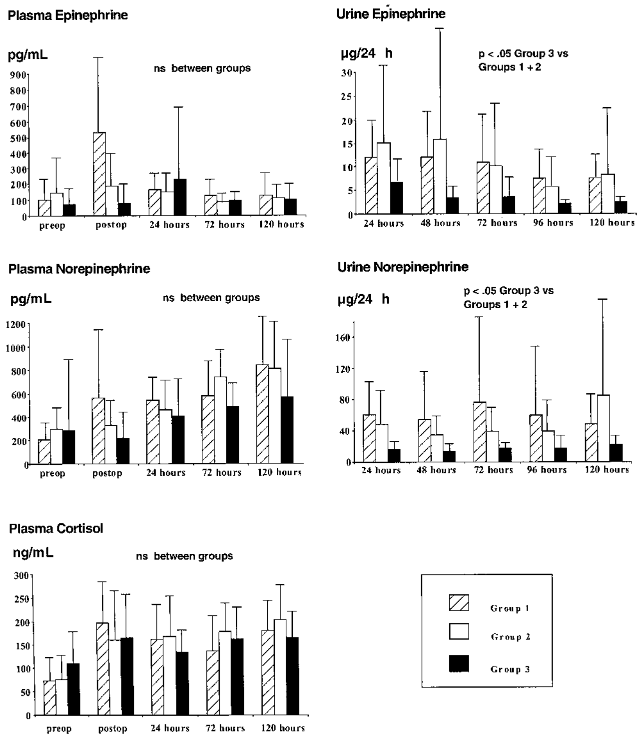

Figure 1. Changes in catabolic hormone responses in Groups 1, 2, and 3. Group 1 = general anesthesia; Group 2 = general anesthesia plus intraoperative thoracic epidural anesthesia; Group 3 = general anesthesia plus intraoperative thoracic epidural anesthesia plus postoperative patient-controlled epidural anesthesia, early oral feeding, and forced mobilization.

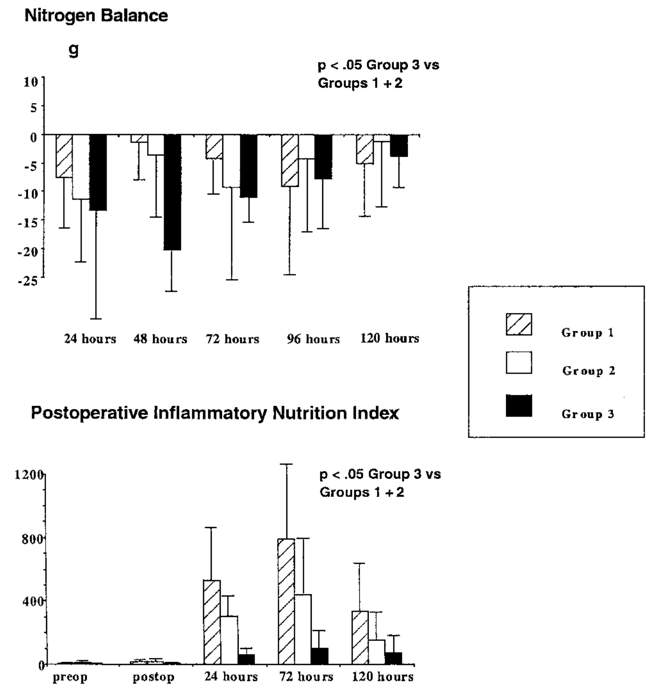

Figure 2. Nitrogen balance and postoperative inflammatory nutrition index (PINI) scores in Groups 1, 2, and 3. Group 1 = general anesthesia; Group 2 = general anesthesia plus intraoperative thoracic epidural anesthesia; Group 3 = general anesthesia plus intraoperative thoracic epidural anesthesia plus postoperative patient-controlled epidural anesthesia, early oral feeding, and forced mobilization. The cumulative nitrogen balances and PINI scores were significantly lower ($P < 0.05$) in Group 3 than in Groups 1 and 2.

respiratory insufficiency caused by atelectasis or dystelectasis. The lengths of the hospital stay were similar in the three groups (Table 1).

Discussion

The results of the study can be summarized as follows: intraoperative epidural local anesthetic blockade has no relevant effects on late postoperative responses in plasma and urinary catecholamines or on plasma cortisol or the nitrogen balance. Nor was any effect observed on sleep recovery scores, fatigue, pain, postoperative walking distance, or time of first defecation after major urologic surgery. In contrast, intraoperative and continuous postoperative epidural analgesia combined with enforced mobilization and oral fluid intake reduced urinary catecholamine excretion and improved mobility and subjective ratings of recovery, with the patients experiencing less fatigue even though they had less sleep during the day and night. Dynamic pain scores were also reduced, and the time of first defecation was earlier. The results with regard to pain relief and ambulation indicate that PCEA and early mobilization are essential components of the multimodal approach.

The finding that there were no significant late postoperative effects on plasma or urinary hormonal responses, or on the nitrogen balance because of intraoperative epidural local anesthetic blockade, is in accordance with the findings of previous reports (3,14). Thus, a more prolonged block and preferably at least a 24–48-hour epidural blockade are necessary to reduce the catabolic hormonal responses and improve protein economy (3,14).

As in other studies, no correlation was found between catecholamine and cortisol responses (15); the lack of a significant reduction in the cortisol response is probably related to difficulties in achieving a total afferent blockade during major abdominal surgery (3).

The more pronounced negative nitrogen balance in patients receiving multimodal rehabilitation in this study is probably related to the smaller nitrogen input, because this group was not given IV nutrition, in contrast to Groups 1 and 2. Thus, despite a significant larger oral fluid intake, a comparable protein intake was not achieved until Day 5. Because the time to first defecation was significantly shorter in Group 3 patients with the multimodal approach, a more aggressive oral protein feeding regimen may be possible, thereby improving postoperative protein economy.

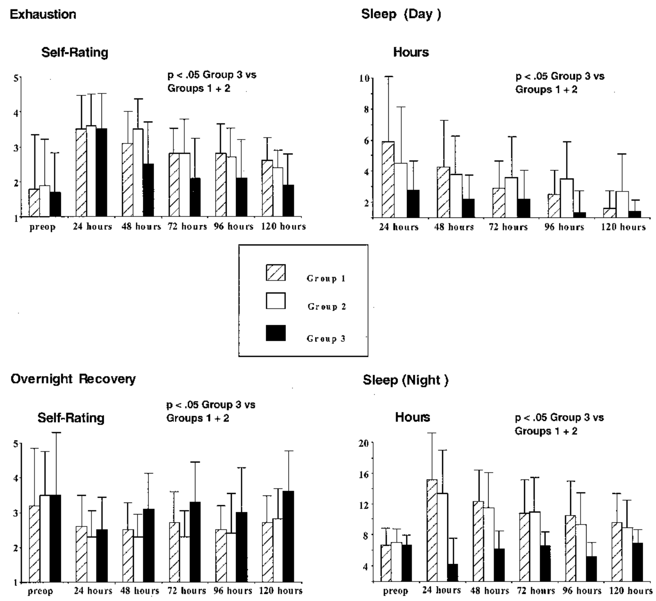

Figure 3. Fatigue, sleep, and recovery in Groups 1, 2, and 3. Group 1 = general anesthesia; Group 2 = general anesthesia plus intraoperative thoracic epidural anesthesia; Group 3 = general anesthesia plus intraoperative thoracic epidural anesthesia plus postoperative patient-controlled epidural anesthesia, early oral feeding, and forced mobilization. Group 3 had less sleep ($P < 0.05$) during both day and night compared with Groups 1 and 2, but the patients reported less fatigue ($P < 0.05$) and improved recovery ($P < 0.05$).

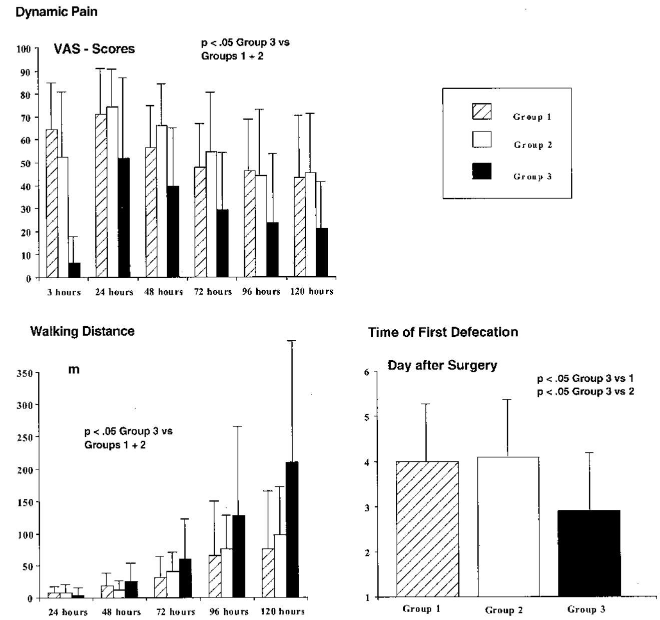

Figure 4. Postoperative recovery (pain, walking, and time to defecation) in Groups 1, 2, and 3. Group 1 = general anesthesia; Group 2 = general anesthesia plus intraoperative thoracic epidural anesthesia; Group 3 = general anesthesia plus intraoperative thoracic epidural anesthesia plus postoperative patient-controlled epidural anesthesia, early oral feeding, and forced mobilization. The pain scores, walking distance, and time to first defecation were significantly improved ($P < 0.05$) in Group 3 compared with Groups 1 and 2.

Patients undergoing GA (Group 1) or GA plus intraoperative epidural analgesia (Group 2) showed the usual increase in PINI. Group 3 patients, however, receiving continuous epidural analgesia and enforced mobilization and oral intake, showed a significantly reduced inflammatory response. The explanation for this is not known, although others have shown that early enteral nutrition reduces the catabolic and cytokine responses to surgery (16,17). However, oral protein intake was not clinically significant in Group 3 patients until Days 4 and 5.

It is most interesting to note that the effort to achieve multimodal rehabilitation led to increased postoperative mobilization and enhanced subjective reporting of recovery, with less fatigue—suggesting potentially important clinical implications of this approach. In contrast to these positive findings, however, the overall hospital stay was not reduced, indicating that other factors may influence hospital stay, and that further revision may be needed for the full benefits of a postoperative multimodal rehabilitation approach to be achieved. Physicians should increasingly be asked why any patient who is not critically ill needs to be in the hospital after surgery (18). One important strategy, for example, is to alter traditional practices: drains or catheters should be removed in patients who do not need these devices. Patients should be trained in the use of drains and discharged from the hospital if the wound healing is uncomplicated and if they are vigilant, can tolerate enteral nutrition, and are mobile (5).

It might be argued that comparisons between Groups 1 and 2 against Group 3 should have been performed with a randomized design. However, this is not possible within a single department. Because of the difficulties that staff (and other personnel) would have in treating patients in the same environment with different feeding and mobilization regimens, the settings for the Control and Treatment groups would inevitably become more and more similar. The treatment of the last patients in the Control group would differ from that of the first ones. However, the observation of similar preoperative and intraoperative demographic data in the three groups supports the validity of the present findings, although they will obviously need to be confirmed and extended in future large-scale studies, including studies focusing on morbidity and hospital stay.

In summary, the multimodal rehabilitation approach improved pain relief, reduced hormonal and metabolic stress, enhanced normalization of gastrointestinal function, and improved postoperative vigilance and mobilization. On the basis of these arguments, traditional practices in keeping noncritically ill patients in the hospital should be changed.

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