Preoperative Anxiolysis and Postoperative Recovery in Women Undergoing Abdominal Hysterectomy

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Background: Every year, millions of patients receive sedatives for reduction of anxiety before surgery, but there is little objective data on the effect of this treatment on postoperative outcomes. To address this issue, the effects of benzodiazepine administration were evaluated in women undergoing abdominal surgery.

Methods: Patients were randomized to receive 1 mg of oral lorazepam the night before surgery and 5 mg of intramuscular midazolam on the morning of surgery (n = 34), or to receive a placebo the night before surgery and on the morning of surgery (n = 36). Postoperative pain (Visual Analogue Scale for pain, McGill Pain Questionnaire) and analgesic consumption (patient-controlled analgesia), and clinical recovery parameters such as time to discharge from hospital were evaluated after surgery.

Results: Patient-controlled analgesia use showed a marginal main effect of treatment group (F(1,51) = 2.8, P = 0.07). Postoperative pain was lower in the treatment group only during the first 4 h of patient-controlled analgesia use after surgery (P = 0.027). There were no significant group differences at any later postoperative time points (P = not significant). No group differences were found in the cumulative Percocet (Pfizer, New York, NY) consumption in the postoperative period (P = not significant). Further, self-reported postoperative pain did not differ significantly between groups at any of the time points (P = not significant). There were also no group differences with regard to any postoperative clinical recovery parameters.

Conclusions: Benzodiazepines administered before surgery have minimal beneficial effects on the postoperative clinical course of women undergoing abdominal hysterectomy.

EVERY year, millions of patients receive sedatives for reduction of anxiety before surgery, but there is little objective data on the effects of this treatment on postoperative outcomes. Four decades ago, Janis' proposed that moderate levels of preoperative anxiety are associated with good postoperative behavioral recovery, whereas low and high levels of preoperative anxiety are associated with poor behavioral recovery. Although Janis' theory is intriguing, his studies were based on descriptive data from nonrandom, limited samples and retrospective reports. Subsequent studies have been critical of Janis' methodology and have reported a linear rather than a curvilinear relation. A far more important question, however, is the possible association between anxiety before surgery and postoperative clinical recovery.

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the night before surgery in addition to intramuscular midazolam 30 min before surgery.

The purpose of the present investigation is to examine the effects of preoperative benzodiazepines on the postoperative clinical recovery process as assessed by variables such as postoperative analgesic requirements.

Methods

Study Design and Patients

This randomized, double-blind, placebo-controlled trial was conducted between June 1997 and January 1999. The study population consisted of women aged 18–60 yr undergoing general anesthesia and elective abdominal hysterectomy for the treatment of fibroid uterus. Exclusion criteria included American Society of Anesthesiology physical status higher than II, a history of affective disorder, alcohol or drug abuse, psychotropic medication use, or suspicion of malignancy. Yale University’s Institutional Review Board (New Haven, Connecticut) approved the study protocol, and informed consent was obtained from all patients.

Outcomes and Study Interventions

The primary outcome of the study was the postoperative pain response as assessed by analgesic consumption and self-reported pain scores. Secondary outcome measures included variables such as postoperative complications and time to solid diet.

Patients were randomly assigned to one of two treatment groups; they received either 1 mg oral lorazepam the night before surgery and intramuscular midazolam (5 mg) 30 min before surgery or patients received oral placebo the night before surgery and an intramuscular injection of placebo 30 min before surgery. The randomization process was controlled by the investigational pharmacy and treatment assignment was concealed from investigators and patients.

Primary Outcome Assessment. Detailed psychometric data for measures used in this study were reported previously by our study group and are available in the references provided below.

McGill Pain Questionnaire. Sensory and affective dimensions of pain were measured using the short form of the McGill Pain Questionnaire, which consists of 15 pain descriptors that are rated on a 4-point severity scale from 0 (none) to 3 (severe).

Visual Analog Scale. The Visual Analog Scale (VAS) is widely used as a self-report measure of pain. The scale consists of a 100-mm line that pictorially represents two behavioral extremes at either end of a continuum: no pain (score of 0) and extreme pain (score of 100).

Analgesic Consumption. Analgesic consumption was measured by recording the amount and duration of intravenous patient-controlled analgesia (PCA) usage and by recording the amounts of oral analgesics administered to the patient by hospital staff.

Secondary Outcome Assessment. Clinical Recovery. Parameters recorded included: time to solid diet, time to start of ambulation after surgery, time to bowel sounds, time to flatus, time to clear fluid intake, time to emptied bladder by voiding, time to discontinuation of indwelling catheter, and time to discharge from the hospital. The incidence of postoperative complications, such as thromboembolic disease, was recorded. Wound inflammation and infection was assessed using ASEPSIS.

SF-36 Health Survey. We used the SF-36 Health Survey to measure quality of life at baseline and after surgery. The conceptual areas assessed by the SF-36 Health Survey include pain, energy and vitality, role functioning limitations—emotional and physical, general health perceptions, physical functioning, social functioning, and mental health.

Other Measures. State Trait Anxiety Inventory. The State Trait Anxiety Inventory (STAI) is a 40-item questionnaire that provides measures of trait (20 items) and state (20 items) anxiety, where higher scores indicate greater anxiety levels.

Observer’s Assessment of Alertness/Sedation. The Observer’s Assessment of Alertness/Sedation Scale was used to assess the level of sedation after administration of the intramuscular injection (midazolam and placebo). The scale has been validated specifically for use with midazolam as a sedative.

Interleukin 6 and Cortisol. Interleukin (IL) 6 was measured in plasma with the Quantikine-HS assay (R&D Systems, Minneapolis, MN). The assay uses a quantitative enzyme immunoassay technique. Cortisol analysis was performed with a radioimmune assay in a single large batch; duplicates agreed within 15%, and quality assessment samples were well within the manufacturer’s defined range.

Lymphocyte subsets. Blood was drawn into EDTA for complete blood count and leukocyte differential on an automated cell counter (STK-8; Coulter, Palo Alto, CA). Two milliliters of whole blood was lysed with ammonium chloride to prepare total leukocytes, which were washed in phosphate buffered saline containing 10% fetal calf serum and 0.1% sodium azide and resuspended at 3 × 10⁶ cells/ml. Two hundred-microliter aliquots of the cell suspension were incubated with the following combinations of monoclonal antibodies: (1) FITC-anti-CD45/PE-anti-CD14; (2) FITC-anti-CD3/PE-anti-CD4/PerCP-anti-CD8; (3) FITC-anti-CD5/PerCP-anti-CD19; (4) PE-anti-CD16/56/PerCP-anti-CD3; and (5) FITC-control/PE-control/PerCP-control (all antibodies from Becton Dickinson, San Jose, CA).
Determination of lymphocyte subset values. Mononuclear cells were acquired on a FACScan flow cytometer (Becton-Dickinson, Mountain View, CA) as previously described. Lymphocyte and monocyte subsets were differentiated using side scatter and CD14 fluorescence.

Study Protocol

Preadmission Testing Facility (Approximately 10 Days before Surgery). After recruitment and written consent, demographic, baseline behavioral (STAI-trait, SF 36), and baseline pain data (VAS) were obtained. To assure blindness of the primary research assistant involved in the study, a second research assistant scored the STAI-trait and called the pharmacy with the result. This was needed for randomization purposes (see Statistical Analysis). Beyond the telephone call to the pharmacy, the second research assistant was not involved with the study protocol. A blood sample was also obtained, and a capsule was given to the patient to take at home on the night before surgery.

Night before Surgery. All patients and anesthesia personnel were called by the principal investigator to assure adherence to the study protocol. The oral medication (lorazepam vs. placebo) was self-administered by patients.

Day of Surgery, Express Admission Area. State anxiety was assessed (STAI) and a blood sample was obtained before administration of the intramuscular injection. Then, patients received the intramuscular injection (midazolam or placebo) at least 30 min before surgery. Then, sedation (Observer’s Assessment of Alertness/Sedation Scale) and anxiety (STAI) were assessed just before separation to the operating room.

Day of Surgery, Operating Room. Anesthesia was induced using 3–5 mg/kg sodium thiopental and 0.1 mg/kg vecuronium bromide or 2 mg/kg succinylcholine (if indicated). Isoflurane in nitrogen oxide and oxygen was used for maintenance of general anesthesia. Additional vecuronium bromide was titrated to maintain an adequate level of muscle relaxation. Fentanyl was used up to 4 μg/kg during the induction phase of anesthesia. If the procedure lasted more than 1.5 hr, additional fentanyl doses of up to 2 μg · kg⁻¹ · hr⁻¹ were used. No other opioids were given to study patients, and regional anesthesia was not part of this study protocol. Metoclopramide (5 mg) was given to prevent postoperative nausea and vomiting, and if needed, ondansetron was given as well (4 mg). No other anesthetic agents were used with this protocol. The use of other agents, such as droperidol, benzodiazepines, or morphine, was not allowed. Blood samples were obtained at the conclusion of the surgery, on closure of the fascial layer, from all patients. Intraoperative variables, such as length of surgery, blood loss, anesthetic and surgical complications, blood transfusions, and intravenous fluids, were noted.

At the conclusion of surgery, the isoflurane was discontinued, neuromuscular blockade was reversed, and the patient was extubated on satisfactory emergence from general anesthesia.

Day of Surgery, Postanesthesia Care Unit. Patients received morphine 1 or 2 mg intravenously as required for pain relief and ondansetron 4 mg intravenously for treatment of nausea and vomiting. Incidence of adverse effects, analgesic requirements, pain scores (VAS), and time to transfer to the surgical ward were recorded.

Hospital, Postoperative Days 1–3. After being transferred to their rooms, patients were connected to a morphine PCA with 1-mg dose, 6-min lockout, and a maximum 4-h dose of 30 mg. If pain was unrelieved by PCA, the patients were given a bolus of 3 mg morphine from the PCA pump, and the dose increased by 10%. As soon as the patient tolerated oral liquids and the PCA was discontinued, oral Percocet (Pfizer, New York, NY) was given every 4 h for pain control. No other pain medications were allowed. If required, metoclopramide (10 mg) was given for nausea, and if not effective, it was supplemented with ondansetron (4 mg). To standardize therapy and avoid mood-altering drugs, no other medications, such as droperidol, benzodiazepines, hydroxyzine, or ketamine, were allowed.

At 2 h after surgery, the patient’s pain was assessed using the VAS. At 12 h, 24 h, and 48 h after surgery, pain scores (McGill Pain Questionnaire, VAS) and anxiety scores (STAI) were assessed while the patient was at rest. Blood samples were obtained at 1 h, 2 h, and 24 h after surgery. Analgesic use was recorded as well. Milestones, including start of patient ambulation, time to clear liquids and solid food, bowel sounds, time to first flatus, and time to voiding, were recorded. Chart review, nursing and medical staff interview, and patient interview identified postoperative complications, such as wound infection and fever. To assure adherence to the study protocol, the research assistant and a physician-investigator reviewed all medications that the patient received. Using the ASEPSIS system, surgical wounds of patients were evaluated daily by a surgeon who was blind to group assignment.

Home, Day 1, Day 2, 1 Week, and 1 Month. Patients who had completed the hospital-based portion of the study were contacted by telephone. Inquires were made about pain (VAS), anxiety (STAI), analgesics consumption (type and frequency), and postoperative complications. Patients were also asked about their quality of life at 1 week and 1 month after surgery (SF-36).

Statistical Data Analysis

The number of patients in each group was determined by using a power analysis based on earlier studies involving the effects of psychological interventions on postoperative outcomes. The particular postoperative outcome chosen for the purpose of power analysis was postoper-
ative pain (VAS). The analysis indicated that a study with two groups of 30 participants would detect a difference of 30% between groups with a probability of 0.80, at a significance level of 0.05 (a).

Block randomization based on a random number table was used to assign patients to the two treatment groups. Specifically, we stratified the level of trait anxiety (STAI) of all patients into three groups: high, medium, and low. The cut off for this stratification was taken from the STAI manual. We chose this randomization protocol to allow examination of any interaction between trait anxiety level and treatment group with regard to the postoperative outcomes. As would be expected, the mean STAI scores were significantly different for the high, medium, and low anxiety groups (52 ± 9.4 vs. 39 ± 9.5 vs. 32 ± 6.9, respectively; P = 0.001). Within each trait anxiety group, we randomly assigned patients to the two treatment groups. We chose matched randomization that assured an equal number of control and intervention patients.

Demographic data were analyzed using a Student t test, Kruskal–Wallis test of variance by rank, and the Fisher exact test. Perioperative cortisol and IL-6 values were normalized to reflect changes from the baseline obtained during preadmission testing. Cortisol and IL-6 levels, immunologic parameters, PCA requirements, and STAI scores were analyzed using two-way repeated-measures analysis of variance with baseline measures of trait anxiety and quality of life (SF-36) as covariates. The percentages of CD3+ T cells, CD3+CD4+ helper T cells, CD3+CD8+ suppressor T cells, CD19+ B cells, and CD16/56+CD3-NK cells were expressed as a percentage of the total lymphocyte population. We evaluated postoperative pain as δ changes from pain at 1 h after surgery, because pain that time point did not differ between the two groups. Thus, we calculated δ pain and anxiety change for each patient and compared the two experimental groups by repeated measures analysis of variance, with treatment group as the grouping factor and time as the repeated measure. For all analysis, statistical significance was accepted at P < 0.05, two-tailed. Post hoc tests were performed using the least significant difference test. Data were analyzed using SPSS version 9.0 (SPSS, Chicago, IL).

Results

Figure 1 is a flow diagram of the 70 women eligible to participate in the trial. As can be seen in table 1, the groups were comparable on baseline demographic and behavioral characteristics, as well as intraoperative clinical parameters such as intraoperative fentanyl and postoperative morphine used. Behavioral assessment performed on the morning of surgery, after they received the oral medication the night before and before receiving the intramuscular medication, indicated that the intervention group had lower STAI scores, but this finding was not statistically significant (41 ± 10 vs. 44 ± 11; P = 0.16). After administration of the intramuscular medication, however, women in the intervention group were rated by an observer blind to group assignment as being significantly more sedated than those in the control group (Observer’s Assessment of Alertness/Sedation Scale composite score, 1.4 ± 0.5 vs. 1.0 ± 0.18; P = 0.001; Observer’s Assessment of Alertness/Sedation Scale sum score, 6.8 ± 2.2 vs. 4.3 ± 0.9; P = 0.001).

Primary Outcome

Analysis of PCA use across time showed a marginal main effect of treatment group (F(1,51) = 2.8; P = 0.047) and a significant effect of time (F(9,43) = 54.6; P = 0.001) (fig. 2). Post hoc analysis demonstrated that PCA consumption was significantly lower in the intervention group only during the first 4 h of PCA use after surgery (P = 0.027). There were no significant group differences at any of the other postoperative time points assessed (P = not significant). Overall, patients required significantly less PCA as a function of time from surgery (P = 0.001).

There were no group differences in the cumulative Percocet consumption in the perioperative period at 24 h (intervention, 8.3 ± 3.3 mg vs. placebo, 8.2 ± 3.2 mg; P = not significant) and at 48 h (intervention, 2.7 ± 3.1 mg vs. placebo 2.8 ± 4.4 mg; P = not significant). Similarly, there were no differences in the amount of Percocet required at home at 1 day, 2 days, and 1 week after surgery (P = not significant).

Finally, self-reported postoperative pain as assessed by VAS, δ VAS, and the McGill Pain Questionnaire did not differ significantly between the two groups at any of the time points assessed (P = not significant; fig. 3A). Further, no interaction with trait anxiety group was found. That is, the trait anxiety group of the patient did not affect the response of the patient to the experimental intervention.

Secondary Outcomes

There were no group differences in parameters such as time to first ambulation, first bowel sounds, first flatus, clear fluid intake, time to solid diet, and discharge from hospital (table 2). There were also no differences in the percentage of women in each group in whom complications developed during hospitalization (intervention, 0% vs. placebo, 3.3%; P = not significant). Postoperative SF-36 scores in all subdomains (role limitation–physical, bodily pain, energy and vitality, role limitation–emotional, general health perceptions, physical functioning, social functioning, and mental health) did not differ significantly between the two groups (P = not significant). There were no significant group differences in the ASEPSIS scores and between antibiotics used by patients.
During hospitalization and at 1 week and 1 month after surgery (P ≠ not significant). Also, the frequency of use of drugs such as metoclopramide and ondansetron did not differ between the two study groups (P ≠ not significant).

**Other Outcomes**

**IL-6 and Cortisol.** Interleukin 6 levels showed a main effect of treatment (F(1,41) = 4.6; P = 0.04) and time (F(1,41) = 28.3; P = 0.0001) (fig. 4A). Post hoc analysis did not localize the effect to a particular time point. Analysis of cortisol levels across time showed a marginal main effect of treatment group (F(1,41) = 2.78; P = 0.44) and time (F(1,41) = 35.9; P = 0.0001) (fig. 4B). Post hoc analysis demonstrated a significant difference only in the holding area before surgery (P = 0.001).

**Natural Killer, T, and B Lymphocytes.** The percentage of CD16/56^+^CD3-NK cells in placebo-treated patients rose simultaneously with a decrease in the percentage of CD3^+^T cells (P < 0.001). The proportion of T cells that were CD4^+^ decreased relative to the CD8^+^T cells, producing a decrease in the CD4:CD8 ratio (table 3). CD19^+^B cells exhibited a biphasic increase, peaking first on the morning of surgery and then again on the first postoperative day. Patients in the intervention group demonstrated a significantly blunted natural killer cell increase (P = 0.05; fig. 5). There were no group differences with respect to the changes in these T cell subsets; however, the increase in CD19^+^B cells was also significantly blunted in intervention group patients (P < 0.01; table 4).

**Discussion**

This study was undertaken to assess postoperative outcomes of sedatives administered before surgery. We found that reducing the behavioral stress response the night before surgery and at the morning of surgery had a minimal impact on postoperative analgesic requirements and the clinical recovery process.

The protocol for this study was designed to test the hypothesis that the use of sedatives before surgery would contribute to meaningful improvements in the

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**Table 1. Characteristics of the Study Sample**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group</th>
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<tr>
<td></td>
<td>Intervention (n = 25)</td>
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<tr>
<td>Demographics</td>
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<tr>
<td>Age (yr)</td>
<td>47 ± 6.6</td>
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<tr>
<td>Weight (kg)</td>
<td>78 ± 17</td>
</tr>
<tr>
<td>Previous surgery (%)</td>
<td>45</td>
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<tr>
<td>Race (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>65.2</td>
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<tr>
<td>African American</td>
<td>21.7</td>
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<tr>
<td>Other</td>
<td>13.0</td>
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<tr>
<td>Coping style (MBSS)</td>
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<tr>
<td>Monitor coping style</td>
<td>8.0 ± 3.2</td>
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<tr>
<td>Blunter coping style</td>
<td>3.9 ± 2.2</td>
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<td>Trait anxiety (STAI-T)</td>
<td>38 ± 11</td>
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<tr>
<td>Intraoperative parameters</td>
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<tr>
<td>Intraoperative fentanyl (µg/kg)</td>
<td>4.9 ± 1.9</td>
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<tr>
<td>Fluid use, crystalloid (l)</td>
<td>2.2 ± 1.4</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>340 ± 352</td>
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<tr>
<td>Urine output (ml)</td>
<td>181 ± 87</td>
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<tr>
<td>Surgery duration (min)</td>
<td>180 ± 48</td>
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* Data are mean ± SD.

MBSS = Miller Behavioral Style Scale; STAI-T = State Trait Anxiety Inventory trait.
postoperative pain response and clinical recovery process. It was hypothesized that this effect is modulated via a reduction in the preoperative anxiety response, similar to the mechanism that is described with psychological preoperative interventions. To gain external validity for the series of studies we undertook, it was necessary to use treatment regimens that are widely used in clinical settings, for example, administering 5 mg of midazolam intramuscularly approximately 30 min before surgery. After analysis of the earlier study,26 we decided to intensify the intervention and to introduce a pharmacologic intervention the night before surgery as well as at the morning of surgery. The combination of lorazepam the night before with midazolam on the morning of surgery is again a practice that is used in clinical settings.

We found that reducing the preoperative stress response had a minimal impact on postoperative analgesic requirements and the clinical recovery process. There are several possible explanations for the lack of significant results in this study. First, the anxiolytic pharmacologic regimen used in this study differs significantly from a behavioral preoperative preparation program. Although benzodiazepines are effective in reducing anxiety before surgery, they are not a substitute for enhancement of coping skills and increased knowledge with regard to the perioperative course. These latter factors may be the ones responsible for the improvement in the postoperative course that is reported with the use of

Table 2. Clinical Milestones

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<th>Clinical Milestone</th>
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<tr>
<td></td>
<td>Intervention</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>First movement from bed*</td>
<td>8.5 ± 3.4</td>
<td>11 ± 5.7</td>
<td>NS</td>
</tr>
<tr>
<td>First bowel sounds*</td>
<td>19.9 ± 8.9</td>
<td>19.7 ± 6.4</td>
<td>NS</td>
</tr>
<tr>
<td>First flatus*</td>
<td>53.6 ± 14.9</td>
<td>51.9 ± 14.8</td>
<td>NS</td>
</tr>
<tr>
<td>Clear fluid intake*</td>
<td>25.6 ± 12</td>
<td>24.1 ± 9.6</td>
<td>NS</td>
</tr>
<tr>
<td>Time to solid diet*</td>
<td>59.8 ± 15.6</td>
<td>53.8 ± 15.3</td>
<td>NS</td>
</tr>
<tr>
<td>Discharge*</td>
<td>74.9 ± 12.9</td>
<td>75.3 ± 15.2</td>
<td>NS</td>
</tr>
<tr>
<td>Calls for assistance (n/24 h)</td>
<td>4.0 ± 2.5</td>
<td>4.7 ± 3.1</td>
<td>NS</td>
</tr>
<tr>
<td>Number of lines nurse recorded (n)</td>
<td>17.3 ± 9.6</td>
<td>17.5 ± 11.1</td>
<td>NS</td>
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Data are presented as mean ± SD.
* Hours to clinical milestone.
NS = not significant.

Fig. 2. Patient-controlled analgesia (PCA) morphine consumption across time. Each time block represents total morphine consumption across 4 h.

Fig. 3. Self-report δ pain scores. See Methods for δ calculations. Hr = hours after surgery; Home = day at home after discharge from hospital; VAS = Visual Analog Scale, pain assessment.

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Fig. 4. (A,B) Neuroendocrinologic and immunologic markers across time. IL-6 = interleukin 6; am = morning of surgery before intervention; closure = wound closure in the operating room; hr = hour after patient arrived in the recovery room.
needed to clarify this issue.

In contrast, patients in the present study had a minor operative pain response only if the postoperative pain reduction in postoperative pain and state anxiety.23 In that patients treated with midazolam demonstrated a minimal effect on postoperative analgesic requirements. An important difference is that preoperative benzodiazepine administration in the present study had a minimal effect on postoperative psychological preparation programs. Second, it is important to realize that a major difference between psychological interventions and use of sedatives is timing in relation to surgery. Typically, psychological preparation programs are administered to patients days to weeks before the surgical procedure. This timing issue may have an influence on the effectiveness of the intervention with regard to the postoperative course. We do not believe that the absence of significant effects was caused by insensitive outcome measures. A careful examination shows that we have a variety of validated outcome measures from multiple domains.

In our previous investigation assessing the effects of midazolam before outpatient minor surgery, we found that patients treated with midazolam demonstrated a reduction in postoperative pain and state anxiety.23 In contrast, preoperative benzodiazepine administration in the present study had a minimal effect on postoperative analgesic requirements. An important difference is that all patients in the earlier study underwent minor outpatient surgery, and as result, their postoperative behavioral and physiological stress response was also relatively minor. In contrast, patients in the present study had a significant stress response. Thus, it may be that reducing anxiety before surgery has an impact on the postoperative pain response only if the postoperative pain response is not profound. Further investigations are needed to clarify this issue.

Some of the findings in this manuscript may be explained by the pharmacokinetics of lorazepam and midazolam. Although the half life of lorazepam (10–20 h) as well as midazolam (1–4 h) is relatively short,34 there may be a synergy with benzodiazepines even at very low serum concentrations in the presence of opioids. Thus, the analgesic effects observed may have been influenced by the pharmacology of benzodiazepines.

There may be additional mechanisms for our neuroendocrine/psychologic findings. One mechanism may be similar to the one responsible for the findings reported in studies involving preoperative psychological interventions. Given that preoperative anxiety is associated with a surge of stress hormones,35 if we are able to prevent or decrease this preoperative surge, we may in fact change the set point of the entire perioperative neuroendocrine stress response. This in turn may result in an overall decrease in the global hormonal stress response. Additional research will be needed to determine the actual mechanism supporting our results.

The ability of intense psychological stress to induce increases in the percentage of natural killer cells is well recognized.36,37 The stress of anesthesia and surgery causes perioperative decreases in natural killer cell function together with decreases in the natural killer cell population occurring on postoperative days 1–3.38,39 Our data suggest that the stress of surgical anticipation may be a major contributor to changes in immune cell populations associated with surgery, most notably a premature mobilization of natural killer cells before surgery. Natural killer cells are capable of synthesizing IL-6,40 and the greater number of natural killer cells in placebo-treated patients may have contributed to subsequent increased IL-6 levels noted in these patients. Similarly, placebo-treated patients exhibited a greater postoperative B cell response, suggesting that preoperative anxiety may influence immune cells in the postoperative period. Further studies are needed to assess whether these changes in circulating immune cells as a result of preoperative anxiety are associated with functional alterations, with special relevance for tumor surveillance in cancer surgery patients and postoperative wound infections.41

Finally, at the onset of this study, we noted that much of the previous research that examined the effects of

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Table 3. T- and B-cell Percentages and CD4/CD8 T-cell Ratios for Each Sample

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<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
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<tr>
<td></td>
<td>PAT Holding</td>
<td>Intraoperatively</td>
</tr>
<tr>
<td>T cells*</td>
<td>100</td>
<td>99 ± 1.7</td>
</tr>
<tr>
<td>CD4/CD8</td>
<td>2.7 ± 0.2</td>
<td>2.4 ± 0.21</td>
</tr>
<tr>
<td>B cells*</td>
<td>100</td>
<td>116 ± 14.4</td>
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* Percentage of baseline. † P < 0.01 compared with placebo patients, repeated-measures analysis of variance. ‡ P < 0.001 compared with placebo patients, repeated-measures analysis of variance.

PAT = preadmission testing; POD = postoperative day.

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Fig. 5. Change in natural killer cells across time. NK = natural killer; PAT = preadmission testing, baseline blood draw; am = morning of surgery before intervention; closure = wound closure in the operating room; POD#1 = first postoperative day after surgery.

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psychological interventions on postoperative outcomes may have been hindered by methodologic issues such as nonhomogenous patient populations in terms of past medical history, uncontrolled surgical procedure variables, and uncontrolled anesthetic management. The study presented in this report was designed to minimize the above methodologic concerns. The patient population, indication for surgery, and surgical procedure were homogenous. Further, because anesthetic management can influence many outcome variables, the anesthetic management was carefully controlled.

In conclusion, benzodiazepines administered before surgery have minimal beneficial effects on the postoperative clinical course of women undergoing abdominal hysterectomy. The results of this study are in contrast to the results of previous studies involving psychological preparation programs. Further research is needed to identify the reasons behind these differential findings.

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