Anesthesiology
2000; 93:141-7

Attenuation of the Preoperative Stress Response with Midazolam

Effects on Postoperative Outcomes

Zeev N. Kain, M.D., Ferne Sevarino, M.D.,† Sharon Pincus, M.A.,‡ Gerianne M. Alexander, Ph.D.,§ Shu Ming Wang, M.D.,‖ Chakib Ayoub, M.D.,# Boonsri Kosarussavadi, M.D.‖*

Background. **Previously, effects of preoperative sedatives were assessed mainly with respect to preoperative outcomes such as anxiety and compliance. The purpose of this investigation was to evaluate the effects of preoperative sedatives on postoperative psychological and clinical recovery.**

Methods: **Patients undergoing general anesthesia and outpatient surgery were enrolled in a double-blind, randomized, placebo-controlled trial. Subjects (n = 55) were randomly assigned to receive either 5 mg intramuscular midazolam (n = 26) or a placebo injection (n = 29) at least 30 min before surgery. The anesthetic technique was controlled. Postoperative anxiety, pain, analgesic consumption, clinical recovery parameters, and global health (SF-36) were evaluated up to 1 month after surgery.**

Results: **Surgery length did not differ significantly between the treatment and placebo groups (118 ± 45 min *vs* 129 ± 53 min; *P* = NS). Throughout the first postoperative week, subjects in the treatment group reported a greater reduction in postoperative pain compared with subjects in the placebo group ($F_{1,50}$ = 3.5; *P* = 0.035). Moreover, at 1 week, ibuprofen use was reported by less subjects in the treatment group than in the placebo group (0% *vs* 17.2%; *P* = 0.026). Subjects in the treatment group also reported a greater reduction in postoperative anxiety throughout the follow-up period ($F_{1,53}$ = 9.2; *P* = 0.04). However, global health indexes (SF-36) did not detect any significant differences between the two experimental groups (multivariate $F_{1,45}$ = 0.44; *P* = 0.51).**

Conclusion: **Subjects treated with midazolam preoperatively self-report improved postoperative psychological and pain recovery. However, the clinical significance of these findings is unclear at the present time. (Key words: Anxiety; benzodiazepines; recovery; surgery.)**

A RECENT large-scale survey documented that up to 75% of anesthesiologists in the United States routinely administer sedative premedication to healthy adult patients who undergo surgery.[1] Previously, effects of sedatives such as midazolam were assessed mainly with respect to outcomes such as preoperative anxiety, amnesia, and compliance during induction of anesthesia.[2-5] However, it can be argued that these outcomes are, in fact, surrogate outcomes and that investigators should concentrate more on the impact of preoperative anxiety and preoperative sedatives on postoperative clinically relevant outcomes.[6] Indeed, several recent investigations have focused on the impact of preoperative sedatives and preoperative anxiety on outcomes such as intraoperative anesthetic requirements, postoperative patient satisfaction, postoperative nausea and vomiting, and postoperative behavioral recovery.[7-10]

Studies published in the Health-Psychology literature suggest that increased preoperative anxiety is associated with poor postoperative behavioral and clinical recovery.[11-14] Furthermore, multiple reports indicate that preoperative psychological interventions aimed at reduction of preoperative anxiety may also result in improved postoperative behavioral and clinical recovery.[12,14-17] Several behavioral and psychobiological mechanisms are proposed for these findings. First, patients who are less anxious preoperatively are also likely to be less anxious postoperatively and self-report a better postoperative recovery process.[12,15] Obviously, this mechanism may

* Associate Professor, Departments of Anesthesiology, Pediatrics, and Child and Adolescent Psychiatry.

† Associate Professor, Department of Anesthesiology.

‡ Research Assistant, Department of Anesthesiology.

§ Research Associate, Department of Anesthesiology.

‖ Assistant Professor, Department of Anesthesiology.

Resident, Department of Anesthesiology.

Received from the Departments of Anesthesiology, Pediatrics, and Child and Adolescent Psychiatry, Yale University School of Medicine, New Haven, Connecticut. Submitted for publication October 26, 1999. Accepted for publication February 25, 2000. Supported in part by grant no. NICHD R01HD37007-01 from the National Institutes of Health, Bethesda, Maryland, Roche Pharmaceuticals, Nutly, New Jersey, and the Patrick and Catherine Weldon Donaghue Medical Research Foundation, Hartford, CT (Dr. Kain).

Address reprint requests to Dr. Kain: Department of Anesthesiology, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510. Address electronic mail to: zeev.kain@yale.edu

explain the findings of cohort studies but not randomized controlled trials. Second, given that anxiety before surgery is associated with a stress hormone surge,[18–20] if we decrease this preoperative surge, we may change the set-point of the entire perioperative neuroendocrine stress response, which may, in turn, result in an overall decrease in the neuroendocrine response. Because a decrease in the perioperative hormonal response is likely to result in decreased catabolic response and improved wound healing,[21] one may expect an improved postoperative clinical course. Finally, it is possible that increased anxiety levels are associated with an increased risk for postoperative infections. This hypothesis is supported by previous data that indicates that factors such as anxiety and pain can stimulate sympathetic vasoconstriction[22,23] and therefore increase the risk for postoperative infection.[24] It is important to emphasize that none of the aforementioned explanations has been proven valid to date, and the mechanisms behind the studies published in the Health-Psychology literature remain unclear.

It is well established that patients treated preoperatively with midazolam exhibit lower levels of anxiety before surgery.[25] Based on the studies in the Health-Psychology literature, one can hypothesize that the use of preoperative midazolam may also be associated with improvements in the postoperative psychological and/or clinical recovery process. The mechanism behind this phenomena may be similar to that described with the use of psychological interventions directed at reduction of preoperative anxiety. To test this hypothesis, we conducted a randomized placebo-controlled trial that evaluated the effects of preoperative midazolam on the postoperative recovery of outpatients undergoing anesthesia and surgery.

Materials and Methods

Study Design and Interventions

The study population of this randomized, double-blind, placebo-controlled trial consisted of patients, men and women, aged 18–60 yr undergoing general anesthesia and outpatient surgical procedures such as tubal ligation, tonsillectomy, and adenoidectomy (table 1). To avoid potential confounding variables, patients with American Society of Anesthesiologists physical status higher than II, subjects with a history of an affective disorder, or patients taking any psychotropic medication were excluded from enrollment in this study. In addition, patients with any suspicion for malignancy or those undergoing plastic surgery procedures were not invited to participate in the study. The study protocol was approved by the institutional review board, and written informed consent was obtained from all subjects. Eligible patients (n = 55) were randomly assigned to one of two study groups: (1) treatment group (n = 26): patients in this group were premedicated with intramuscular midazolam (5 mg) at least 30 min before the surgical procedure; or (2) placebo group (n = 29): patients in this group were given an intramuscular injection of normal saline at least 30 min before the procedure. Randomization was performed according to a computer-generated list created from a random numbers table. Blinding and randomization were handled by Yale-New Haven Hospital's investigational pharmacy, and no other individuals (*e.g.*, anesthesiologists, surgeons, investigators) were informed of the particular treatment group to which a particular subject was assigned.

Table 1. Characteristics of the Two Study Groups

	Treatment Group (n = 26)	Placebo Group (n = 29)
Demographics		
Age (yr)*	34.6 ± 9.2	34.1 ± 6.8
Race†		
White	80.0	75.9
African American	8.0	6.9
Other	12.0	17.2
Gender†		
Male	20.0	10.3
Female	80.0	89.7
Previous surgery†	47.6	52.4
Medical procedures†		
Tubal ligation	23.1	24.1
Diagnostic laparscopy	26.9	13.8
ENT surgery	34.5	34.5
Minor gynecologic surgery	15.4	24.1
Other	0.0	3.4
Intraoperative data		
Length of surgery (min)	118.1 (±45.2)	129.5 (±53.5)
Anesthetic or surgical complications†	0	0
Fentanyl dose (mcg/kg)	3.0 ± 1.7	2.7 ± 1.9
PACU data		
Time to discharge (min)	140.3 ± 37.8	144.3 ± 42.2
Adverse effects†	27	23
Fentanyl (mcg)	58.3 ± 25.8	42.7 ± 24.7
Zofran (mg)	4.0 ± 0.0	4.0 ± 0.0
Percocet (mg)	1.5 ± .53	1.8 ± .40
Morphine (mg)	5.3 ± 1.9	1.8 ± 4.0

* Mean ± standard deviation.

† Percentage.

ENT = Ear, nose, and throat; PACU = postanesthesia care unit.

Outcome Measures

The main outcome of this study was the recovery of patients after surgery as assessed by behavioral and clinical measures. All perioperative data were obtained by a single blinded research assistant. Detailed psychometric data for measures used in this study were reported previously by our study group and are available in the references provided below.

Behavioral and Pain Domains.

1. State Trait Anxiety Inventory (STAI).[26] The 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.
2. McGill Pain Questionnaire.[27] Sensory and affective dimensions of pain were measured using the short-form McGill Pain Questionnaire, which consists of 15 pain descriptors that are rated on a four-point severity scale from 0 (none) to 3 (severe).
3. Visual Analogue Scale (VAS).[28] The VAS consisted of a horizontal 10-cm line between the phrases: "no pain at all" and "the worst pain I have ever felt" and required subjects to draw a mark anywhere on the line to indicate their current level of pain.
4. Analgesic consumption. Analgesic consumption was measured by recording the analgesics administered to the study subjects.

Clinical Recovery Domain.

1. Clinical recovery. Postoperative parameters recorded included time to clear fluid intake, voiding, and discharge from the hospital. The incidence of postoperative complications, such as postoperative nausea and vomiting and postoperative infections, was noted as well.
2. Global Health Questionnaire (GHQ).[29] The GHQ is used to assess postoperative recovery. Items include sleep, appetite, strength and energy, self assistance, and movement. The subject rated every item on a six-point Likert scale. The individual ratings were summed for a total recovery score.
3. SF-36.[30] The SF-36 global health index was used to measure quality of life in eight conceptual areas, document baseline status, and characterize changes in quality of life after surgery. The eight conceptual areas provide summary measurements for role physical, bodily pain, energy and vitality, role emotional, general health perceptions, physical functioning, social functioning, and mental health. Standardized scores between 0 (poorest health) and 100 (maximal health) are generated for each of the eight health domains. This instrument is used widely in the medical literature and is considered the gold standard for measurement quality of life.[31]

Study Protocol

The schedule of Yale-New Haven Hospital's ambulatory surgical facility was screened daily for potential subjects. Once identified, the research assistant interviewed patients for potential exclusion criteria. After recruitment, written consent, demographic data, and baseline data (STAI, GHQ, SF-36) were obtained. Subjects received the intervention, midazolam or saline from coded syringes provided by the investigational pharmacy, at least 30 min before surgery. Anesthesia was induced using 1–2 mg/kg propofol and 0.1 mg/kg vecuronium bromide or 2 mg/kg succinylcholine (if indicated). Isoflurane in N_2O 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. No other opioids were given, and regional anesthesia was not part of this study protocol. Reglan (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 agents such as droperidol, ketamine, benzodiazepines, or morphine was not allowed. Intraoperative variables, including 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. Incidence of adverse effects, analgesic requirements, pain scores (McGill Pain Questionnaire, VAS), and time to discharge were recorded in the postanesthesia care unit.

After discharge home, patients were contacted *via* telephone on postoperative days (PODs) 1, 2, 3, 7, and 30. This contact included administering the GHQ, anxiety questionnaire (STAI-state), pain analgesic consumption, and postoperative complications. On inquiring about pain, the patients were asked to rank the pain they felt over the past 24 h on a scale of 0 (no pain) to 10 (worse possible pain). The patients were asked to complete the SF-36 at 1 week and 1 month postoperatively.

Statistical Analyses

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

Demographic data were analyzed using Student *t* test and the Fisher exact test. Because the treatment group did not differ significantly from the control group at POD 1 with regard to self-reported pain (34.6 ± 23.4 *vs* 32.8 ± 20.1; $P = 0.70$) or anxiety (34 ± 10 *vs* 32 ± 8.9; $P = 0.31$), we opted to evaluate subsequent postoperative data as delta changes from POD 1. We calculated the delta pain and anxiety change for each individual subject 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. SF-36 data were compared between the two groups and across time using multivariable analysis of variance for repeated analyses. GHQ data were analyzed using repeated measures analysis of variance. Other measures of clinical recovery (*e.g.*, medication use) were compared using the Fisher exact test or Student *t* test as appropriate. Data were expressed as mean ± SD, and statistical significance was accepted at $P < 0.05$. Data were analyzed with the use of SPSS version 9.0 (SPSS, Chicago, IL).

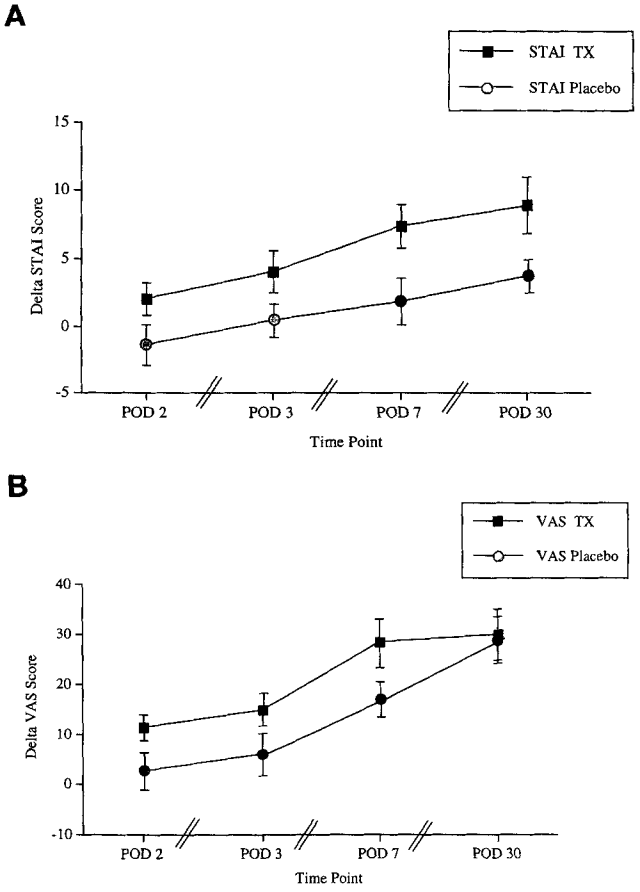

Fig. 1. (*A*) Anxiety scores across time (δ). The midazolam group reported a great reduction in anxiety throughout the postoperative period ($P = 0.04$). STAI = State Trait Anxiety Inventory. (*B*) Pain scores across time (δ). The midazolam group reported a greater reduction in pain throughout the postoperative period ($P = 0.035$). VAS = visual analog scale.

Results

Over a period of 14 months, 61 patients were randomized to one of the two groups. Patient characteristics and intraoperative parameters are summarized in table 1. Six subjects were excluded from the final sample because of noncompliance of the anesthesia staff to the study protocol. These subjects were excluded on the day of surgery, and no data were obtained regarding their postoperative course. Thus, a total of 55 subjects are included in this report.

Postoperative Pain and Anxiety

Pain. There were no effects of treatment on the percentage of subjects reporting significant postoperative pain (VAS > 30) on discharge from the postanesthesia care unit (61 % *vs* 56%; P = NS). Analysis of pain across time demonstrated a main effect of treatment group ($F_{1,50} = 3.5$; $P = 0.035$) and a main effect of time ($F_{1,50} = 4.7$; $P = 0.001$; fig. 1B). That is, throughout PODs 2–7, the treatment group reported a greater reduction in self-reported pain compared with the placebo group (fig. 1B). In addition, at POD 7, ibuprofen use was reported by more subjects in the placebo group than in the midazolam group (17.2% *vs* 0%; $P = 0.026$). There were no other differences in the medication required by the two groups across the various time points.

Anxiety. Analyses of anxiety across time showed a main effect of treatment group ($F_{1,53} = 9.2$; $P = 0.04$) and time ($F_{1,53} = 11.4$; $P = 0.0001$), but no group by time interaction. That is, throughout PODs 2–30, the

treatment group reported a greater reduction in anxiety compared with the placebo group (fig. 1A).

Postoperative Clinical Course

There were no significant differences between the two study groups with regard to any of the intraoperative or postanesthesia care unit variables recorded (table 1). Fewer patients in the midazolam group self-reported any postoperative infection at 1 week postoperatively (0% *vs* 16%; $P = 0.037$) compared with the placebo group. There were no significant differences in reports of infection at 1 month (0% *vs* 8.7%; P = NS), and comparable percentages of subjects in both groups reported taking antibiotics at 1 week (40% *vs* 37%; P = NS).

Multivariable analysis of variance showed no group differences on the SF-36 scores (multivariate $F_{1,45} = 0.44$; $P = 0.51$) and no group by time interactions (multivariate $F_{1,45} = 0.92$; $P = 0.34$). Regardless of group assignment, there was improved functioning at 1 month postoperatively compared with 1 week postoperatively on the various subscales of the SF-36 (multivariate $F_{7,49} = 8.8$; $P = 0.0001$). Similarly, analyses of self-report general health (GHQ) levels across time demonstrated a main effect of time ($F_{5,29} = 20.9$; $P = 0.0001$), but no effects of treatment group.

Discussion

Although there is a consensus in the literature about the usefulness of preoperative sedatives, there is a paucity of studies that evaluate the effects of preoperative sedatives on postoperative clinical outcomes. This study was designed to test the hypothesis that the use of sedatives before anesthesia and outpatient surgery contributes to improvements in the postoperative recovery process. We found that patients who were treated with midazolam 30 min before surgery reported a greater reduction in postoperative pain throughout the first postoperative week and a greater decrease of anxiety throughout the first postoperative month. Furthermore, patients treated with midazolam required less ibuprofen and reported less postoperative infection at 1 week postoperatively. However, we must emphasize that two global health indexes used in the study (SF-36, GHQ) did not detect any difference between the two groups. Thus, the clinical significance of our findings is not clear.

The finding of improved postoperative psychological recovery in this population of adult patients is similar to the finding reported previously for children undergoing surgery.[8] In the pediatric study, children who were premedicated with midazolam exhibited significantly less psychological distress during the first week after surgery, *i.e.*, children in the midazolam group had a lower incidence of new-onset negative behaviors such as general anxiety, nightmares, and apathy and withdrawal.[8] Similarly, adult subjects in the present study who were treated with midazolam preoperatively reported less postoperative psychological distress. The findings of reduced pain in the adult population may reflect improved psychological recovery as well because patients who are more anxious report more pain and *vice versa*.[32,33] Thus, it may be that because patients in the midazolam group had better emotional functioning at 1 week, they also reported less pain. Alternatively, it may be that these patients did, in fact, experience less pain. At the present time, we do not know why preoperative midazolam has postoperative effects, and because we did not measure the stress hormones of the two groups, it is unclear if the neuroendocrine system is involved in this phenomenon.

It is interesting that, although most of the improvements in patient recovery occurred within the psychological/pain domain, a reduced incidence of postoperative infection rate was also reported. One can postulate two mechanisms for these findings. First, it is important to realize that the diagnosis of postoperative infection was not established by examining the patient's wound directly, but rather by relying on patient self-report. Thus, it is possible that patients in the placebo group, who were more anxious at 1 week postoperatively, reported higher rates of infection as a result of heightened vigilance associated with anxiety. Alternatively, it is possible that the placebo group did indeed have a higher incidence of postoperative infection. It may very well be that patients in the placebo group had a higher incidence of postoperative infection and thus were in more pain and required more ibuprofen for fever control and pain control, all because of increased anxiety levels. This hypothesis is supported by previous reports that indicate that multiple perioperative factors, including anxiety, hypovolemia, pain, and cold, all stimulate sympathetic vasoconstriction[22,23] and therefore probably increase infection risk.[24] Of interest are also multiple studies in the psychosomatic field that have reported increased incidence of various infectious process in patients who were more anxious and felt more stress.[34,35] Carefully controlled trials in which the postoperative wound is directly evaluated by a blind surgeon are needed to clarify this issue.

We have demonstrated that, although postoperative

pain and anxiety were reduced by the use of preoperative midazolam, no group differences were noted with regard to the overall clinical recovery process as assessed by SF-36 and the GHQ. Thus, it may be that our findings are not clinically significant. There are several possible explanations for the lack of significant results as assessed by the SF-36 and GHQ. First, midazolam does not have the same effects as do preoperative preparation programs. Second, the preoperative anxiolytic response in this study was attenuated too late to achieve significant postoperative clinical improvement. Because it is well established that the preoperative anxiolytic response develops days and weeks before surgery, it may be that reducing the response 30 min before the procedure is simply "too late." 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 undergoing surgery several days before the procedure. This can explain why previous studies that used psychological interventions reported improvements in the clinical domain as well, whereas we have failed to demonstrate such differences. Finally, it may be that both the SF-36 and GHQ are not sensitive enough to detect small but significant differences between study groups.

We also must emphasize that the results of this study are relevant only to the patient population investigated, *i.e.*, we excluded from this investigation patients with American Society of Anesthesiologists status higher than II, patients with a history of an affective disorder, and patients taking any psychotropic medication. Furthermore, the patient population studied underwent minor outpatient surgery, and thus their level of preoperative anxiety was probably lower if compared with the anxiety of patients undergoing major inpatient surgery. This is an important point because it is possible that, although midazolam is effective in attenuating the preoperative stress response and improving the postoperative anxiety and pain response among patients undergoing minor surgery, this effect will not be observed in patients undergoing major inpatient surgery. We have selected midazolam as the intervention for this study because a previous survey indicated that midazolam is the most commonly used anxiolytic in the United States.[1] It may be that a different anxiolytic administrated in a different timing in relation to surgery will result in different findings.

Several methodologic issues related to the design of this study must be addressed. First, many previous studies that examined the effects of psychological interventions on postoperative outcomes were hindered by various methodologic flaws. For example, the patient population was not homogenous in terms of medical and psychological history, and the anesthetic management was not uniform. Some previous studies used nonvalidated outcome measurement scales and subjective rather than objective outcome variables. Moreover, almost all previous investigations were conducted by investigators from a single discipline. This is important because investigations like these require very close collaboration between disciplines such as psychology, anesthesiology, and surgery. The present multidisciplinary study was designed very carefully to minimize the aforementioned methodologic concerns.

Second, we report the VAS and the STAI as change scores from POD 1. This was done to control for individual patient variability. We suggest that because both the VAS and the STAI are self-reported measures, they will vary significantly based on individual personality characteristics. Two patients experiencing the exact same postoperative pain may give it significantly different ratings on the VAS. Thus, we decided to control for the individual variability by introducing the pain experienced on POD 1 as a baseline to which all subsequent pain ratings are compared. We believe that this approach better controls for personality-related variability in self-reported measures. A similar approach, for different reasons, is widely used in neuroendocrinologic and cardiovascular research areas. Finally, although a power analysis was performed at the onset, the study clearly would have benefitted from a larger sample size.

We conclude that adults who are premedicated 30 min before outpatient surgery with intramuscular midazolam demonstrate improved postoperative psychological and pain recovery process. Thus, in addition to its significant beneficial preoperative effects, midazolam has some beneficial postoperative effects on adults undergoing outpatient surgery. However, the clinical importance of these findings is unclear because global health measures failed to detect a difference between the two experimental groups. We believe that the results of this study should be encouraging for other investigators involved in this area of research. As a result of this investigation, we are in the process of designing a large-scale study that will block the preoperative stress response earlier (1 week) in the perioperative process. Because it is not feasible to achieve this solely with a pharmacologic intervention, a combination of psychological and pharmacologic interventions is planned.

The authors thank Paul G. Barash, M.D., for critical review of the manuscript.

References

1. Kain ZN, Mayes LC, Bell C, Weisman S, Hofstadter MB, Rimar S: Premedication in the United States: A status report. Anesth Analg 1997; 84:427-32

2. Virkkila ME, Ali-Melkkila TM, Kanto JH: Premedication for outpatient cataract surgery: A comparative study of intramuscular alfentanil, midazolam and placebo. Acta Anaesthesiol Scand 1992; 36:559-63

3. McMillan CO, Spahr-Schopfer IA, Sikich N, Hartley E, Lerman J: Premedication of children with oral midazolam. Can J Anaesth 1992; 39:545-50

4. Polster MR, McCarthy RA, O'Sullivan G, Gray PA, Park GR: Midazolam-induced amnesia: Implications for the implicit/explicit memory distinction. Brain Cogn 1993; 22:244-65

5. Twersky R, Hartung J, Berger B, McClain J, Beaton C: Midazolam enhances anterograde but not retrograde amnesia in pediatric patients. ANESTHESIOLOGY 1993; 78:51-5

6. Kain Z: Perioperative information and parental anxiety: The next generation. Anesth Analg 1999; 88:237-9

7. Maranets M, Kain Z: Preoperative anxiety and intraoperative anesthetic requirements. Anesth Analg 1999; 89:1346-51

8. Kain Z, Mayes L, Caramico L, Wang S, Hofstadter M: Postoperative behavioral outcomes in children: Effects of sedative premedication. ANESTHESIOLOGY 1999; 90:758-65

9. Kain Z, Mayes L, Wang S, Krivutza D, Hofstadter M: Parental presence and a sedative premedicant for children undergoing surgery: A hierarchical study. ANESTHESIOLOGY 2000; 92:939-46

10. Wang S, Kain Z: Preoperative anxiety and postoperative nausea and vomiting in children: Is there an association? Anesth Analg 2000; 90:571-5

11. Wallace LM: Pre-operative state anxiety as a mediator of psychological adjustment to and recovery from surgery. Br J Med Psychol 1986; 59:253-61

12. Johnston M: Pre-operative emotional states and post-operative recovery. Adv Psychosom Med 1986; 15:1-22

13. Johnson J, Dabbs J, Leventhal H: Psychological factors in the welfare of surgical patients. Nurs Res 1970; 19:18-28

14. Kiecolt-Glaser JK, Page G, Marucha P, MacCallum R, Glaser R: Psychological influences on surgical recovery. Am Psychologist 1998; 53:1209-18

15. Johnston M, Vogele C: Benefits of psychological preparation for surgery: A meta-analysis. Ann Behav Med 1993; 15:245-56

16. Johnston M: Impending surgery, Handbook of Life Stress. Edited by Fisher S, Reason J. New York, Wiley, 1988, pp 79-100

17. Johnston M: Anxiety in surgical patients. Psychol Med 1980; 10:145-52

18. Zhou D, Kusnecov AW, Shurin MR, DePaoli M, Rabin BS: Exposure to physical and psychological stressors elevates plasma interleukin 6: Relationship to the activation of hypothalamic-pituitary-adrenal axis. Endocrinology 1993; 133:2523-30

19. Price D: Preoperative emotional states and adrenal cortical activity: Studies on cardiac and pulmonary patients. Arch Neurol Psychiatr 1957; 77:646-56

20. Rogers M, Reich P: Psychological intervention with surgical patients: Evaluation outcome, Psychological Aspects of Surgery. Edited by Fava G, Guggenheim FG, Lipowski ZJ, Nemiah JC, Reich P, Engel GL, Levi L, Reichsmann F. Basel, Karger, 1986, pp 23-50

21. Weissman C: The metabolic response to stress: An overview and update. ANESTHESIOLOGY 1990; 73:308-27

22. Derbyshire D, Smith G: Sympathoadrenal responses to anaesthesia and surgery. Br J Anaesth 1984; 56:725-39

23. Halter J, Pflug A, Porte D: Mechanism of plasma catecholamine increases during surgical stress in man. J Clin Endocrinol Metab 1977; 45:936-44

24. Hopf HW, Hunt TK, West JM, Blomquist P, Goodson WH 3rd, Jensen JA, Jonsson K, Paty PB, Rabkin JM, Upton RA, von Smitten K, Whitney JD: Wound tissue oxygen tension predicts the risk of wound infection in surgical patients. Arch Surg 1997; 132:997-1004

25. Reves G, Glass P, Lubarsky D: Nonbarbiturate intravenous anesthetics, Anesthesia, 5th Edition. Edited by Miller R. Philadelphia, Churchill Livingstone, 2000, pp 228-72

26. Spielberger CD: Manual for the State-Trait Anxiety Inventory (STAI: Form Y). Palo Alto, Consulting Psychologists Press, 1983

27. Melzack R: The short-form McGill pain questionnaire. Pain 1987; 30:191-7

28. Wewers ME, Lowe NK: A critical review of visual analogue scales in the measurement of clinical phenomena. Res Nurs Health 1990; 13:227-36

29. Wilson JF: Behavioral preparation for surgery: Benefit or harm? J Behav Med 1981; 4:79-102

30. Ware J: SF-36 Health Survey: Manual and Interpretation Guide. Boston, Boston: The Health Institute, New England Medical Center, 1992

31. Anderson R, Aaronson N, Wilkin D: Critical review of the international assessments of health-related quality of life. Qual Life Res 1993; 2:369-95

32. Chapman CR: Psychological aspects of postoperative pain control. Acta Anaesthesiol Belg 1992; 43:41-52

33. Feinmann C, Ong M, Harvey W, Harris M: Psychological factors influencing post-operative pain and analgesic consumption. Br J Oral Maxillofac Surg 1987; 25:285-92

34. Biondi M, Zannino LG: Psychological stress, neuroimmunomodulation, and susceptibility to infectious diseases in animals and man: A review. Psychother Psychosom 1997; 66:3-26

35. Heninger GR: Neuroimmunology of stress, Neurobiological and Clinical Consequences of Stress: From Normal Adaptation to PTSD. Edited by Friedman MJ, Charney DS, Deutch AY. Philadelphia, Lippincott-Raven, 1995, pp 381-401