Effects of Preincisional Ketamine Treatment on Natural Killer Cell Activity and Postoperative Pain Management After Oral Maxillofacial Surgery

CPT Michael W. Bentley, CRNA, MSN, AN, USA
Fort Carson, Colorado
CPT John M. Stas, CRNA, MSN, AN, USA
Fort Jackson, South Carolina
CPT Jimmie M. Johnson, CRNA, MSN, AN, USA
Fort Hood, Texas
Bruce C. Viet, PhD
El Paso, Texas
COL Normalynn Garrett, CRNA, PhD, AN, USA
Fort Sam Houston, Texas

Hundreds of thousands of people die of cancer in the United States yearly, and most of the deaths are due to metastatic spread of the disease. Natural killer (NK) cells are one of the body’s first defenses against the metastatic spread of cancer; however, the activity of these cells is suppressed by a major treatment modality for cancer—surgery. Currently, the mechanism or mechanisms by which surgery suppresses NK cell activity have not been fully elucidated. One hypothesis is that pain related to surgery can suppress NK cell activity and thereby increase the risk of tumor metastasis. Therefore, the adequate treatment of postoperative pain, which continues to be inadequately managed, is more than just a humane or ethical matter, but one that may prolong life.

Classically, postoperative pain has been treated with opioid analgesics, but these drugs have important limitations. Opioid-related side effects, such as respiratory depression, have been cited as reasons that healthcare professionals are reluctant to treat pain. Second, tolerance limits the usefulness of opioids. Tolerance is characterized by resistance to the analgesic effects of an opioid. Morphine tolerance has been shown extensively in animals. Furthermore, acute tolerance may develop with a single bolus dose of an opioid, such as occurs in high-dose opioid anesthetic techniques. Although human studies regarding opioid tolerance have shown conflicting results, acute and chronic opioid tolerance clearly can develop in surgical and cancer patients.

If the pain of undergoing and recovering from surgery indeed increases the risk of metastatic sequelae through suppression of NK cell activity, and opioids have limitations, then other pharmacological agents must be explored as potential supplements to opioids. This study was designed to investigate the effects of ketamine, a noncompetitive N-methyl-D-
aspartate (NMDA) receptor antagonist, administered preincisioanlly to patients having oral maxillofacial surgery. Two research questions directed this study: (1) Does the preincisional administration of ketamine improve postoperative pain perception? (2) What are the effects of a preincisional dose of ketamine on NK cell activity?

By using an experimental metastasis model in adult male and female rats, Page and colleagues suggested that the metastatic-enhancing effects of surgery were ameliorated by the preoperative administration of opioid and/or the local anesthetic, bupivacaine. Whereas untreated rodents showed a 3- to 4-fold increase in retention of cancerous cells, rodents treated with subcutaneous fentanyl preoperatively and postoperatively and those treated with intrathecal bupivacaine and morphine had 65% and 45% reductions in tumor retention, respectively. However, neither opioids nor local anesthetic completely reversed this life-threatening consequence of surgery, suggesting that other pharmacological agents should be explored as potential adjuncts to opioids. One class of agents that may mitigate the undesirable effects of opioids and provide benefit with regard to NK cell activity is the NMDA receptor antagonists.

The NMDA antagonist compounds have 2 particularly desirable qualities: (1) inhibition of central sensitization, a hyperexcitable state within the central nervous system that can be initiated by surgery and has profound effects on pain transmission such that the intensity and duration of painful stimuli are enhanced and (2) prevention of the development of opioid tolerance, the phenomenon whereby a patient is less susceptible to the effect of an opioid as a consequence of its prior administration. Findings from studies suggest that NMDA receptor antagonists are effective as preemptive analgesics and potentiate the effect of analgesics such as morphine, local anesthetics, and nonsteroidal anti-inflammatory drugs. Combining an NMDA antagonist with an opioid provides a synergistic effect that offers greater pain control while minimizing the amount of each agent used. Only a few NMDA antagonists are clinically available. These include ketamine and dextromethorphan. These drugs are being used increasingly for chronic pain, including cancer pain, and acute perioperative pain. Yet NMDA receptor antagonists may have one serious side effect that has not been studied in humans. This class of drug may suppress NK cell activity.

Findings from early studies suggest that ketamine suppresses NK cell activity in mice. In addition, outcomes from a more recent study suggest that the competitive and noncompetitive NMDA antagonists LY235959 and MK-801, respectively, increase tumor metastasis via suppression of NK cell activity in adult male and female Fischer 344 rats. To our knowledge, no study has investigated the effects of ketamine on human NK cell activity or subsequent metastasis, nor have there been studies exploring additive or synergistic effects of ketamine plus opioid administration on NK cell activity. This study examined whether a preincisional dose of ketamine provides preemptive analgesia that decreases postoperative pain perception as measured by a visual analog scale (VAS) and 24-hour postoperative opioid consumption and assayed the effect of ketamine on NK cell activity.

**Materials and methods**

A randomized, double-blind, placebo-controlled clinical trial was used for this study. The inclusion of male and female subjects was intentional; therefore, the design was factorial so that men and women were compared regarding each outcome variable. The study was approved through the Medical Center Institutional Review Board at William Beaumont Army Medical Center, Fort Bliss, Tex, and the University of Texas Health Science Center, Houston, Tex.

The a priori sample size calculation suggested that 90 subjects would be required to demonstrate a significant difference; however, exigencies of military deployments forced the investigators to end the study without the intended 90 participants. The study used a convenience sample of 59 patients scheduled for elective oral maxillofacial surgery at a Texas medical center. The data from 9 participants were excluded due to protocol violations; therefore, the data from 50 participants, 26 men and 24 women, were evaluated. All participants were 18 to 65 years old, able to communicate in spoken or written English, and ASA physical status I or II.

After obtaining written informed consent, we randomly assigned participants to 1 of 3 groups: (1) those who received an induction dose of propofol, 200 mg, mixed with 2 mL of saline; (2) those who received an induction dose of propofol, 200 mg, mixed with 0.5 mg/kg of ketamine; or (3) those who received an induction dose of propofol, 200 mg, mixed with 1.2 mg/kg of ketamine. A standard anesthesia protocol was followed such that all patients received intravenous midazolam, 1 to 3 mg, in the preoperative holding area and fentanyl, 100 to 250 µg, with rocuronium, 0.5 to 0.7 mg/kg; lidocaine, 50 mg; and 200 mg of the propofol–additive solution intravenously at induction. General anesthesia was maintained with fentanyl, 3 to 6 µg/kg per hour (not to exceed a total perioperative dose of 6 µg/kg per hour, including the induction
dose), isoflurane, nitrous oxide, and rocuronium titrated to effect.

The VAS (anchored at one end by the label “No Pain” and at the other end by “Worst Possible Pain”) measured participants’ perception of pain at 1 hour postoperatively. Prolonged pain perception was derived from participants’ 24-hour opioid (or its equivalent) consumption (Table 1). The NK cell activity was measured before and 24 hours after ketamine administration using the chromium ⁵¹(Cr) release assay and flow cytometric analysis.

- Measurement of NK cell cytotoxic activity and NK cell numbers. Peripheral blood mononuclear cells (effector cells) obtained from study subjects were prepared by Ficoll-Hypaque density gradient separation and cocultured with ⁵¹Cr-labeled K562 cells (target cells), an established human NK-sensitive chronic myelogenous leukemia cell line. Cell mixtures were incubated in effector/target cell ratios of 100:1, 50:1, 20:1, 10:1, 5:1, and 2.5:1 for 4 hours followed by quantitation of ⁵¹Cr released from target cells as a function of NK-mediated target cell cytotoxicity. The percentage of specific cytolyis of K562 cells was calculated as follows:

\[
\% \text{ specific K562 cytosis} = \frac{\text{Experimental } ⁵¹\text{Cr cpm} - \text{Spontaneous } ⁵¹\text{Cr cpm}}{\text{Maximum } ⁵¹\text{Cr cpm} - \text{Spontaneous } ⁵¹\text{Cr cpm}} \times 100
\]

Flow cytometric analysis was used to quantitate the numbers of NK (CD56⁺) cells in the effector cell populations. Peripheral blood mononuclear cells were incubated with phycoerythrin (PE)-labeled anti-CD56 (Becton Dickinson, San Jose, Calif) or PE-labeled mouse IgG₁ as an isotype control. Labeled cells were then analyzed in a FACS Vantage flow cytometer (Becton Dickinson, San Jose, Calif). Lymphocytes were gated with forward angle vs 90° light scatter and numbers of fluorescent- (PE-) positive lymphocytes determined within the gated region. Ten thousand gated events were collected, and the percentage of specific CD56⁺ cells was calculated as follows:

\[
\% \text{ Specific CD56⁺ cells} = \frac{\text{number of PE-anti-CD56⁺ cells}}{\text{number of PE-mouse IgG₁⁺ cells}}
\]

**Results**

All parametric data met the assumptions for the statistical analysis used; however, not all of these assumptions are equally important. Whereas violation of the assumption that samples are randomly and independently assigned may not be violated, the analysis of variance (ANOVA) is a robust statistic and a moderate deviation of normality in each sample is tolerated without significantly affecting the integrity of the test. The assumption of equal variance is more sensitive; however, if groups are of equal or almost equal size, the concern about this assumption is minimal for factorial ANOVA. Groups in this study were near equal in size and met the assumption of homogeneity of variance as measured by the Levene test. The \( \chi^2 \) statistic was used for analysis of the demographic data regarding gender and physical status category. A multivariate ANOVA was used to examine the remaining demographics for the sample (eg, age, height, and weight). Table 2 shows the descriptive statistics for these covariates. There were no statistically significant differences by group or gender except height and weight by gender, which was expected. This was controlled for in the study design by administering all drugs on a kilogram basis.

The Kruskal-Wallis nonparametric statistic was used to analyze VAS scores (ordinal data) among groups by gender at 1 hour into their postanesthesia recovery. The decision was made a priori to compare the pain scores of men and women separately. Post hoc comparisons were performed with a Mann-Whitney U test when the Kruskal-Wallis demonstrated a significant difference among groups.

Women in the 0.5-mg/kg ketamine group showed a statistical difference \( (\chi^2, 6.128; P < .05) \) in their VAS scores compared with the control (saline) and 1.2 mg/kg of ketamine groups. However, this finding was not evident in men \( (P > .05) \). Thus, women receiving a 0.5-mg/kg bolus of ketamine before incision reported significantly less pain (VAS mean score, 1.96) during the immediate postoperative recovery period compared with women in the control group (VAS mean score, 4.1) and women in the 1.2 mg/kg of ketamine group (VAS mean score, 6.01). This is rep-

<table>
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<th>Drug</th>
<th>Dose</th>
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<tr>
<td>Acetaminophen</td>
<td>1 tablet</td>
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</tr>
<tr>
<td>Acetaminophen</td>
<td>1 tablet</td>
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</tr>
<tr>
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<tr>
<td>Hydromorphone</td>
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<tr>
<td>Ketorolac</td>
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<td>9</td>
</tr>
<tr>
<td>Tramadol</td>
<td>100 mg</td>
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**Table 1. Drugs calculated to 10 mg of parental morphine sulfate**
presented graphically in Figure 1. The SD and SEM were not calculated because this was a nonparametric statistic. The VAS scores for men are not shown.

A $2 \times 3$ ANOVA comparing 24-hour opioid consumption among the 3 groups by gender revealed a drug-gender interaction ($P < .05$), such that a 0.5-mg/kg ketamine bolus decreased postoperative opioid consumption for women more than for men. Whereas women receiving the 0.5-mg/kg bolus of ketamine on induction had a mean 24-hour morphine equivalent consumption of 4.04 mg, the mean opioid consumption for men receiving 0.5 mg/kg of ketamine was 17.54 mg. This interaction is illustrated in Figure 2.

Finally, postoperative NK cell activity was sup-

<table>
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<tr>
<th>Group</th>
<th>Sex</th>
<th>Mean</th>
<th>SD</th>
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<td></td>
<td></td>
<td>F</td>
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<td>Placebo</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>F</td>
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* There were no significant differences found among the groups except for height and weight by gender.
pressed in men and women and in all groups compared with preoperative values (2 × 3 RANOVA, \( P < .05 \)); however, there was no significant main effect or interaction when comparing attenuation of NK cell suppression among groups or by gender.

To present the data in more clinically relevant terms, we reanalyzed and graphed the data using the change scores (delta) method. Whereas male and female subjects who did not receive ketamine demonstrated 65% and 44% suppression of NK cell activity, respectively, compared with preoperative values, and men and women who received 1.2 mg/kg of ketamine demonstrated 51% and 60% suppression, and men who received 0.5 mg/kg of ketamine demonstrated a 49% suppression of NK cell activity, women who received 0.5 mg/kg of ketamine demonstrated 35% suppression of NK cell activity compared with preoperative values.

Although there was not a statistically significant attenuation of NK cell suppression identified among the groups or by gender, there are 2 factors that are important to discuss with regard to these data. First, we performed a sample size calculation a priori based on our previous animal research regarding NMDA antagonists administered before surgery. These previous studies suggested a medium effect size (0.25) for the ANOVA statistic. The post hoc observed effect size for the present study sample size was 0.1, which suggests a small effect size for the ANOVA statistic. Second, unlike our prior animal research, which suggested that NMDA antagonists suppress NK cell activity in a dose-dependent manner after surgery, in the present study, ketamine did not suppress NK cell activity in this manner (Figure 3).

There were no statistically significant differences (RANOVA; \( P > .05 \)) in preoperative and postoperative percentages of CD56+ peripheral blood lymphocytes among groups or by gender, which suggests that changes in NK cell activity are due to lytic activity and not to changes in the number of NK cells.

**Discussion**

The overall purpose of this study was to explore the effects of preincisional ketamine on postoperative pain perception and attenuating surgery-induced suppression of NK cell activity. It has been suggested that pain is a stimulator of surgery-induced NK cell suppression and that adequate pain management ameliorates this phenomenon; however, to our knowledge, no anesthetic regimen has been shown to completely reverse surgical suppression of NK cell activity. This study was designed to examine the effects of preincisional ketamine on postoperative pain perceptions and NK cell activity when used with an opioid–inhalation agent anesthetic protocol.
Most clinical trials of ketamine have centered on its analgesic efficacy during the perioperative period. Low dose (10-20 µg/kg per minute) infusions of ketamine intraoperatively have been suggested to decrease surgical wound hyperalgesia as measured by algometer and to decrease postoperative pain measured by VAS and morphine consumption. Administered as a single small intravenous dose (75-100 µg/kg) postoperatively, ketamine was shown to decrease morphine consumption in patients undergoing outpatient surgery.

Studies showing the effectiveness of preincisional ketamine have yielded mixed results. Compared with control and postincisional administration, a moderate (100 mg) single bolus of intravenous ketamine produced significantly lower VAS scores in patients undergoing abdominal hysterectomies with no increase in the incidence of side effects. Similarly, low-dose preincisional ketamine was shown to be an effective analgesic as measured by morphine consumption in patients undergoing anterior cruciate ligament repair and in children undergoing tonsillectomy. On the other hand, 2 studies examining the preincisional analgesic effects of small-dose intravenous ketamine (0.15-0.4 mg/kg) in patients undergoing abdominal hysterectomy or total mastectomy showed no significant effect on postoperative analgesia.

In the present study, women given a 0.5-mg/kg bolus of ketamine before surgical incision had significantly lower VAS scores 1 hour postoperatively compared with women in other groups and men in all groups. They also had significantly lower 24-hour morphine (or equivalent) use postoperatively compared with men in the same group, suggesting a benefit of low-dose ketamine in women. The U shape of the VAS graph and the morphine equivalent graph for women suggest a ceiling effect associated with ketamine, indicating that the higher dose of ketamine (1.2 mg/kg) has no greater efficacy with regard to analgesia and may, in fact, promote the well-known psychotomimetic effects. Similarly, a ceiling effect for ketamine and other NMDA receptor antagonists has been described for the neuroprotective effect of NMDA antagonists.

Furthermore, the U shape of the NK cell suppression graph for women mirrored the female VAS and 24-hour morphine equivalent graphs. Women given a 0.5-mg/kg bolus of ketamine exhibited the least suppression of NK cell activity compared with the other female groups, suggesting that the preservation of NK cell activity may be related to the analgesic effect of ketamine. Women given a 0.5-mg/kg bolus of ketamine had only a 35% suppression of NK cell activity compared with preoperative values, whereas women given no ketamine and those given a 1.2-mg/kg bolus of ketamine had 44% and 60% suppression of NK cell activity, respectively. It is interesting that all of the outcome measures suggest that the 0.5-mg/kg dose of ketamine was the most efficacious for women.

These findings may be explained by the unique pharmacological properties of ketamine. Ketamine is a nonselective noncompetitive NMDA receptor antagonist that is metabolized by the cytochrome P-450 system of the liver with minimal unchanged urinary excretion. Of the known primary NMDA receptor antagonists, ketamine alone has analgesic properties. These analgesic properties may be explained by evidence showing ketamine activity at all 3 opioid receptors (µ, κ, and δ). Because ketamine is an NMDA receptor antagonist and an agonist at the opioid receptors, we speculate that activity at one, some, or all of these receptors may contribute to the findings of this research.

The κ agonists have been suggested to be more efficacious in women than in men. For example, Gear and associates explored the efficacy of pentazocine, a κ-opioid agonist, as a postoperative analgesic, in male and female participants undergoing dental surgery. Their findings suggested that women receiving pentazocine experienced greater postoperative analgesia than did men. Further studies comparing the
efficacy of nalbuphine and butorphanol (κ opioids) as postoperative analgesics for dental surgery supported the previous study such that nalbuphine and butorphanol provided women greater postoperative analgesia compared with men. Finally, low-dose (5 mg) nalbuphine produced antianalgesia in men but not women, further supporting gender differences in the efficacy of κ opioids.33 Our findings suggest a similar gender-sex–related difference in the response to ketamine such that women but not men were provided analgesic benefit with a 0.5-mg bolus of ketamine administered preoperatively. Furthermore, the interaction effect in this study was such that men who received 0.5 mg/kg of ketamine consumed more morphine equivalent (17.5 mg) postoperatively than men who received placebo (7.5 mg) or 1.2 mg/kg (10.5 mg) of ketamine, whereas women who received 0.5 mg/kg of ketamine consumed less morphine equivalent (4.04 mg) than did women who received placebo (17.54 mg) or 1.2 mg/kg (24.53 mg) of ketamine. There is also evidence supporting sex-related differences in responses to pure NMDA antagonists.34,35 Non–opioid mediated swim stress-induced analgesia has been shown to be blocked by the preadministration of MK-801, an NMDA antagonist, in male mice only.35 Furthermore, NMDA receptor antagonism also may influence κ opioid analgesia in a sex-dependent way. Whereas, male mice exhibit a reduced analgesic response to κ opioids when pretreated with the competitive NMDA antagonist, NPC 12626, no such effects were observed in females.34 Moreover, high serum levels of progesterone have been examined as a mechanism by which NMDA-mediated hyperalgesia may be ameliorated in the rodent suggesting a sex-dependent characteristic to NMDA-mediated hyperalgesia. When hyperalgesia is produced in female Sprague-Dawley rats through intrathecal injection of NMDA, nociceptive activity is attenuated significantly in lactating females with high plasma levels of progesterone compared with normal cycling female rats.36

Finally, NMDA receptor antagonists have been shown to enhance µ receptor–induced antinociception in rodents in a sex-related manner. For example, NMDA competitive and noncompetitive receptor antagonists, including ketamine, enhance the peak effect of morphine (µ agonist) in female but not male rats and have been shown to increase the magnitude and duration of opioid analgesia in female rats more than in male rats.21,37

Together, this evidence suggests that a drug such as ketamine, with both opioid agonist and NMDA antagonist properties, may demonstrate sex-related differences that favor a more beneficial effect in females. Thus, as our findings suggest, ketamine may be a more efficacious analgesic for women than for men.

In addition to the effects of ketamine on opioid and NMDA receptors, ketamine also has been shown to increase monoamine levels within the brain.30 All NMDA antagonists increase monoamine and other neurotransmitter levels in the prefrontal cortex, amygdala, nucleus accumbens, and other areas of the brain.39,40 Increases in monoamines such as dopamine, serotonin, and norepinephrine are associated with the psychotomimetic effects of ketamine. Dopamine, glutamate, and serotonin exquisitely regulate cortical function. Changes within these neurotransmitter systems due to the administration of ketamine may contribute to a patient’s altered sensory perception. For example, increased dopamine and serotonin levels in the frontal cortex appear to contribute to the symptoms of schizophrenia, such as anhedonia (an inability to feel well) and restriction of range and intensity of emotion.31 In our study, neither women nor men received an analgesic benefit from the 1.2-mg/kg bolus of preincisional ketamine compared with placebo. Although monoamine levels in the brain were not measured, extensive research suggests that ketamine potentiates monoaminergic neurotransmission. Therefore, we speculate that the higher dose of ketamine may have been associated with changes in monoamine systems, resulting in the promotion of psychotomimetic side effects, thus blunting the analgesic benefit of high-dose ketamine.

Women in the 0.5-mg/kg ketamine bolus group had significantly lower VAS scores and less 24-hour morphine equivalent use than men in the same group, whereas men and women in the 1.2-mg/kg ketamine bolus group experienced no such effect. This finding suggests that there may be dose-related and gender-related differences in the response to ketamine. In a rodent model, Sershen et al38 suggested that the resulting neuronal dopamine increase secondary to NMDA receptor antagonist activity is significantly less in female rodents than in male rodents. If this phenomenon is true in humans as well, this may account, in part, for the beneficial effects of the 0.5-mg/kg ketamine bolus demonstrated in women compared with men but no beneficial effects for either group at the higher dose.

A relatively reduced dopamine milieu after NMDA antagonist administration in women compared with men also may account for the findings regarding NK cell activity in women in the 0.5-mg/kg ketamine bolus group. NMDA antagonists have been shown to
increase dopamine levels (noncompetitive > competitive) in the nucleus accumbens and prefrontal cortex of the brain in mice and rats. Stress also has been shown to increase dopamine levels in these same areas of the brain and suppress NK cell activity in rodents. Furthermore, dopamine levels in the prefrontal cortex and nucleus accumbens have been shown to be increased in female rats exposed to water-immersion stress with concomitant suppression of NK cell activity, suggesting an association between increased dopamine levels in these brain areas and NK cell suppression. Stress-induced activation of the prefrontal cortex also is associated with NK cell suppression in humans. Stress-induced decreases in NK cell activity due to dopamine release in the prefrontal cortex and nucleus accumbens have not been fully established; however, several reports indicate that brain dopamine levels influence NK cell activity in rodents and humans.

One explanation of our findings may be that at the 0.5-mg/kg ketamine dose, women experienced lower dopamine levels secondary to ketamine administration compared with men in either group and, therefore, were able to benefit from the analgesic effects of ketamine. Thus, pain perception and 24-hour postoperative opioid consumption were decreased significantly in women receiving 0.5 mg/kg of ketamine compared with men and other groups. Furthermore, women who received a 0.5-mg/kg bolus of ketamine had only a 35% suppression of NK cell activity.

Further research is warranted to investigate the effects of preemptive ketamine and its modulation of analgesia and NK cell activity. The interaction of NMDA antagonists, dopamine, serotonin, and NK cell activity is not fully elucidated. The addition of a dopamine antagonist within the structure of this protocol may further clarify the contribution of neuronal dopamine release to NK cell activity. The addition of a dopamine antagonist may be beneficial such that NK cell activity is conserved and the psychotomimetic side effects of ketamine are mitigated. In addition, the interaction of sex hormones on NMDA antagonists and pain perception has not been explained fully. Therefore, to explore this interaction, we are conducting a follow-up study using the same protocol in which female participants are assigned to menstrual phase through assay of serum progesterone levels.

Women who were given a 0.5-mg/kg bolus of ketamine on induction of anesthesia perceived less pain postoperatively as measured by the VAS and consumed less opioid or its equivalent within the 24-hour postoperative period. Moreover, although statistical significance was not reached, women who were given a 0.5-mg/kg bolus of ketamine demonstrated the least suppression of NK cell activity compared with baseline. These findings, if corroborated with further studies, may have significant impact on the anesthetic care of surgical patients undergoing solid tumor excision. For the millions of individuals who undergo surgery each year, any intervention that may reduce a risk such as immune suppression potentially would impact a large portion of the general population. If NK cell activity has a role in inhibiting spontaneous metastasis in humans and surgery suppresses NK cell activity, then any intervention shown to ameliorate surgery-induced decreases in host resistance to metastasis, even if that effect is small, potentially may decrease the risk of spontaneous metastasis and increase long-term survival. Finally, the findings of this research have the potential to support and extend findings implicating pain in the negative immune and metastatic consequences of undergoing and recovering from surgery.

REFERENCES

13. Page GG, Blakeley W, Ben-Eliyahu S. Evidence that postoperative


49. CPT Michael W. Bentley, CRNA, MSN, AN, USA, is a staff nurse anesthetist at Evans Army Community Hospital, Fort Carson, Colo. He was a graduate student in the US Army Graduate Program in Anesthesia
Nursing at William Beaumont Army Medical Center, El Paso, Tex, at the time of this study.

CPT John M. Stas, CRNA, MSN, AN, USA, is a staff nurse anesthetist at Moncrief Army Community Hospital, Fort Jackson, SC. He was a graduate student in the US Army Graduate Program in Anesthesia Nursing at William Beaumont Army Medical Center, El Paso, Tex, at the time of this study.

CPT Jimmie M. Johnson, CRNA, MSN, AN, USA, is a staff nurse anesthetist at Darnall Army Community Hospital, Fort Hood, Tex. He was a graduate student in the US Army Graduate Program in Anesthesia Nursing at William Beaumont Army Medical Center, El Paso, Tex, at the time of this study.

Bruce C. Viet, PhD, is chief, Immunology Section, Department of Clinical Investigation, William Beaumont Army Medical Center, El Paso, Tex.

COL Normalynn Garrett, CRNA, PhD, AN, USA, is the director of the US Army Graduate Program in Anesthesia Nursing, Fort Sam Houston, Tex. At the time of the study she was chief, Anesthesia Nursing Section, William Beaumont Army Medical Center, El Paso, Tex. Email: norma.garrett@cen.amedd.army.mil

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