Morphine Inhibits Spontaneous and Cytokine-enhanced Natural Killer Cell Cytotoxicity in Volunteers

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Background: Opioids are used by patients who have conditions ranging from the acute pain of surgery and chronic cancer pain to substance abuse. Despite their widespread use and considerable experimental data about them, little is known about how opioids may alter the immune system in humans. This study was designed to evaluate the in vitro effect of morphine on human peripheral blood immune functions.

Methods: Healthy volunteers underwent continuous exposure to morphine for 24 h including a 24-h intravenous infusion in the hospital. Peripheral blood was drawn for immune function studies at five measurement times before, during, and after morphine exposure. Peripheral blood mononuclear cells were tested for acute and chronic interferon-stimulated natural killer cell cytotoxicity (NKCC), antibody-dependent cell cytotoxicity (ADCC), antibody Fc receptor expression, and human immunodeficiency virus infectivity.

Results: Significant suppression of NKCC was observed at 2 and 24 h after the onset of intravenous morphine exposure. Suppression of NKCC persisted for 24 h after termination of morphine infusion. In a "high-dose" study group, interferon-stimulated NKCC and antibody-dependent cell cytotoxicity were also decreased after 24 h of intravenous morphine exposure. No effect on Fc receptor expression was observed. Mean virus antigen production after lymphocyte infection with human immunodeficiency virus was not increased (p = 0.17).

Conclusions: These results suggest that morphine administration, at doses within the range of analgesic use, can cause significant suppression of some components of the human cellular immune system. (Key words: Analgesics, opioid; morphine; immunity; human immunodeficiency virus infection; natural killer cells.)

Materials and Methods

This study was approved by the Medical Center Human Research Committee and Institutional Animal Care and Use Committee.

Participants

Participants were paid, $50, of either sex; were healthy volunteers, and had no history of substance abuse, or immunodeficiency.

Study Design

Participants served as their own controls in a randomized, single blind study in two groups of subjects, each of 6. Each group was further divided into two subgroups of 3 each. The first group was the control group, which received no morphine. The second group was the morphine group, which received 10 mg of morphine intravenously over a 24-h period. The study was conducted in two phases: Phase I, during which the baseline anesthetic response was evaluated, and Phase II, during which the effect of morphine on the anesthetic response was evaluated.
MORPHINE AND IMMUNE FUNCTION

Morphine and immune function have been studied extensively, and it appears to have an important role in immune defense against viral infections. NK cells also mediate antibody-dependent cell cytotoxicity (ADCC) by means of antibody Fc receptors on their surface. Rats exposed to morphine after laparotomy with injection of syngeneic NK-sensitive colon cancer cells show increased growth of inoculated tumor cells compared with control animals not exposed to morphine. In this study, administration of an immune stimulating cytokine, interleukin-2, decreased tumor growth after inoculation. Finally, there is evidence that lymphocytes cultured in vitro in the presence of morphine are more susceptible to infection with human immunodeficiency virus (HIV). Despite these data implicating opioids as a cause of impaired immunity in animals and in vitro, there are few studies evaluating in vivo effects of opioids on human immunity. We conducted a clinical study to evaluate peripheral blood immune function in healthy volunteers before, during, and after they received a continuous intravenous exposure to morphine.

Materials and Methods

This study was approved by the Dartmouth-Hitchcock Medical Center Committee for Protection of Human Subjects and Institutional Animal Care and Use Committee.

Participants
Participants were paid, healthy volunteers, aged 24–45 yr. of either sex; were receiving no long-term medications; and had no history of opioid intolerance, substance abuse, or immunologic deficiency.

Study Design
Participants served as their own control for each immunologic assay and subsequent analysis. Preliminary data in six subjects who received oral morphine for 36–60 h showed an average (± SD) decrease in peripheral blood mononuclear cell (PBMC) ADCC of 9.5% (± 6.6) specific cytotoxicity. Although NKCC, not ADCC, was the primary outcome variable in this study, we calculated that, with ten subjects in the high-dose study group and assuming that NKCC would be comparably depressed, we would have 95% power to detect a significant decrease in NKCC with a two-sided 5% level test.

The study was conducted in two sequential phases. Peripheral blood NKCC was the primary study variable in both phases. During the first phase, participants received intravenous morphine at a dose of 0.025 mg/kg loading dose followed by 0.015 mg·kg⁻¹·h⁻¹ infusion (“low” dose) for 24 h. This phase of the study tested reproducibility of earlier experimental findings regarding morphine effects on ADCC and leukocyte antibody Fc receptor expression and provided experience with the study protocol before initiating a higher-dose morphine study. Intergroup comparisons of results were not planned because of the nonblinded, sequential nature of the study and insufficient power to detect significant intergroup differences. During the second phase of the study, participants received morphine at a dose of 0.05 mg/kg loading dose followed by 0.03 mg·kg⁻¹·h⁻¹ (“high” dose) designed to approximate more closely the analgesic doses administered to patients in pain. During the second phase, lymphocytes from participants were also tested for lymphocyte infectivity with HIV. The study protocol included one 30-mg oral dose of morphine (MS Contin, Purdue Frederick, Norwalk, CT) taken the night before intravenous morphine to test subjects for sensitivity to opioid side effects before initiation of intravenous morphine. On the following day, participants were admitted to the hospital, and a peripheral intravenous infusion of lactated Ringer’s solution was initiated at 50 ml/h. As soon as intravenous access was established, the morphine infusion was started at the doses described using a commercially available infusion device (PCA-plus, Abbott Lifecare) with a morphine concentration of 1 mg/ml. The morphine infusion was initiated between 9:00 and 10:00 AM. The study protocol allowed a one-time, 5% decrease in the morphine infusion rate as a treatment for morphine side effects. Continued side effects were treated by discontinuation of the morphine infusion, pharmacologic therapy if necessary, and withdrawal from the study. After initiation of the morphine infusion, participants remained in hospital for 24 h. At the end of 24 h the infusion was stopped and participants were discharged from the hospital. Peripheral blood for analysis was drawn during a baseline period the week before morphine exposure (baseline) 2 h after the initiation of intravenous morphine (2 h), at the end of the morphine infusion (24 h), 24 h after termination of the morphine infusion (48 h), and 7–10 days after termination of the morphine infusion (8 day).

Effector Cell Isolation
PBMCs were isolated as described and resuspended in RPMI-1640 supplemented with 10% fetal calf serum.
(‘serum-free’ medium to designate that it did not contain human autologous serum) at the cell concentration required for subsequent assays. After isolation, PBMCs used for NKCC assays were either suspended immediately in serum-free medium, or in medium containing 50% autologous serum, and used in the NKCC assay, or incubated overnight in serum-free medium at 37°C and 5% CO₂ with or without γ-interferon (IFN-γ) (Genentech, South San Francisco, CA) at a concentration of 10 U/ml. Serial dilutions achieved the final desired effector:target (E:T) ratios. Similar isolation and testing procedures were used for the ADCC assay.

**Effector Cell Assays**

The human myeloid cell line, K-562, was used as the target cell in the NKCC assay. Aliquots of K-562 cells containing 10⁶ cells were labeled with ⁴¹Cr, washed, and resuspended to a final concentration of 10⁶ cells/ml. Aliquots of 100 μl of the resulting suspension (10⁶ cells) were pipetted into 96-well round-bottom plates containing effector cells at the desired E:T ratio. After incubation at 37°C with 5% CO₂ for 4 h, 100 μl supernatant was removed from each well and counted for 1 min on a γ counter to quantify ⁴¹Cr release. The percentage of isotope released was used as a measure of cytotoxicity and was calculated as

\[
\text{Cytotoxicity (\%)} = \frac{\text{CPM(experimental)} - \text{CPM(control)}}{\text{CPM(maximum)} - \text{CPM(control)}} \times 100
\]

where CPM (experimental) = counts released after incubation of effector cells with target cells; CPM (maximum) = counts released by lysis of 1 × 10⁶ target cells with detergent; and CPM (control) = counts released after incubation of target cells in medium alone. Results are expressed as percent specific lysis at a single E:T ratio and as lytic units (20% specific lysis) per 10⁴ effector cells. Specific cytotoxicity results represent the mean of three determinations.

Chicken erythrocytes (CE) were used as target cells for the ADCC assay and were obtained fresh on the day of the experiment by venipuncture, washed, labeled with ⁴¹Cr in a mixture of 15 μl packed CE and 50 μl fetal calf serum. Labeled target cells were resuspended to a concentration of 0.5 × 10⁶ cells/ml. Washed packed ox cells were also added to the target cells to increase cell density and keep spontaneous lysis low. Rabbit anti-CE antibodies were diluted with medium to final antibody concentrations of 2, 1, 0.1, and 0.01 μg/ml. Fifty μl each of medium containing CE, effector cells, and rabbit anti-CE antibodies were added to 96-well round-bottom plates in triplicate at an E:T ratio of 20:1. After incubation in 5% CO₂ at 37°C, 75 μl of the supernatant was harvested into disposable culture tubes and counted for 1 min in a γ counter. The percentage of ADCC was determined using a calculation similar to that used for NKCC. Control conditions for antibody independent and antibody-only killing had 0% killing.

**Quantitation of Fc Receptors**

Quantitation of Fc receptors was performed by an indirect immunofluorescence procedure using the following monoclonal antibodies at saturating concentrations: 22 (Medarex, Annandale, NJ), which binds specifically to Fc receptor I; IV.3 (Medarex, Annandale, NJ), which binds specifically to Fc receptor II; and 3G8 (obtained from Dr. Jay Unkeless, Mt. Sinai Hospital School of Medicine, New York, NY), which binds specifically to Fc receptor III. The immunoglobulin G1 myeloma, P3 (a gift from Dr. Michael Fanger, Dartmouth Medical School), was used as an isotype control for nonspecific binding. Mean fluorescence intensity was quantified by flow-cytometric analysis using a fluorescence-activated cell sorter (Becton Dickinson, San Jose, CA). A standard curve was constructed with mean fluorescence intensities of six fluorescein-labeled latex beads and their respective fluorescein concentrations (Flow Cytometry Standards, Research Triangle Park, NC). The mean fluorescence intensity of the effector cells was translated to the number of antibodies bound per cell (fluorescein isothiocyanate-conjugated goat anti-mouse Fab₂ per cell) from a standard curve. The number of antibody molecules bound per cell in each of the control conditions (autofluorescence and second antibody only) was always less than the number of antibody molecules bound per cell with the isotype control. Antibody molecules bound per cell were corrected for nonspecific binding by subtracting the level of P3 binding from the binding of monoclonal antibodies 22, IV.3, and 3G8.

**Human Immunodeficiency Virus Infectivity Assay**

For analysis of morphine effects on HIV infectivity, PBMCs were isolated and stimulated in culture for 5 days in the presence of phytohemagglutinin, washed extensively, and infected with the HIV-1H9-FL strain. Cultures were maintained without phytohemagglutinin, but with exogenous interleukin-2 and interleukin-1β. Culture was assayed on day 7 for viral infectivity by HIV-1 p24 antigen, Abbott Laboratories, using a standard enzyme-linked immunosorbent assay (ELISA) method for quantitation using a standard curve (Eaton Laboratories).

**Morphine Assay**

Serum samples were frozen for analysis of morphine concentration. The sample preparation and liquid chromatography analysis were performed using a Waters model 510 pump and model 480 variable wavelength detector. The mobile phase consisted of methanol in 50% methanol in 0.1% phosphoric acid, and flow rate was 0.7 ml/min. High-performance liquid chromatography was used to determine the concentration of morphine in milligrams per milliliter of serum.

**Statistical Methods**

We computed mean relative changes from baseline and standard error of the mean for each of the four periods (3). These calculations were all performed using an EXCEL 5.0 spreadsheet. For the ADCC and NKCC assays, we compared the relative difference in the absolute difference of the mean values as a percentage. This difference was considered to be proportional to the amount of cell-mediated immune function.
MORPHINE AND IMMUNE FUNCTION

but with exogenous interleukin-2 at a concentration of 1,000 U/ml for 1 week. Cells were fed midway through the second culture period (day 4) with fresh medium and interleukin-2. Viral production in each culture was assayed on day 7 by measuring p24 antigen concentration by enzyme-linked immunosorbent assay (HIVag assay, Abbott Laboratories, North Chicago, IL) and quantified using a standard quantitation panel (Abbott Laboratories).

Morphine Assay

Serum samples were frozen at −70 °C and batched for analysis of morphine concentration in peripheral blood. The sample preparation method used a mixed-bed solid-phase extraction column. The eluate was dried in a Speed-Vac vacuum centrifuge (Savant, Farmingdale, NY) with heat. Chromatographic separations were performed using a cyano column maintained at 35 °C in a water bath. A guard column packed with a cyano-bonded stationary phase placed before the analytical column and renewed frequently was used to maintain column efficiency. The high-performance liquid chromatography buffer was 50 mm sodium phosphate in 50% methanol, brought to pH 7.0 with phosphoric acid, and filtered before use. The flow rate was 0.7 ml/min. High-performance liquid chromatography-grade water and methanol were used. The detector used two porous graphite cells set at +0.4 and +0.8V and a guard cell at +0.9 V. Hydromorphine, added before the extraction step, was used as an internal standard for morphine determinations. The assay has a sensitivity of 0.5 ng/ml for both morphine and hydromorphone.

Statistical Methods

We computed mean relative differences (as percentages) from baseline and standard errors for the NKCC high-dose- and low-dose–treated assays separately at each of the four periods (2 h, 24 h, 48 h, and 8 day). These calculations were also done for percent specific cytotoxicity at specific E:T ratios. Repeated-measures analysis[11–13] was used to test whether the relative cytotoxicity at each time period was different from that at baseline. For the ADCC, Fc receptor, HIV infectivity, IFN-g-stimulated NKCC, and NKCC serum assays, we computed the relative differences from baseline defined as the absolute difference divided by the baseline value reported as a percentage. We computed the relative difference because the absolute differences appeared to be proportional to the baseline cytotoxicity. Mean relative differences and standard errors were calculated for ADCC, Fc receptors, and HIV assays, and for IFN-g-stimulated NKCC and the NKCC autologous serum assays. We used a paired t test to evaluate differences in these measures from baseline for each group separately.

Results

Participants

Twenty-three participants were entered into the study protocol (13 men and 10 women). Five (4 men and 1 woman) were withdrawn before completion of the morphine infusion because of morphine-related side effects, including anorexia, nausea, vomiting, and pruritus. Two participants were given a saline infusion in a blinded manner to evaluate the effect of hospitalization on NKCC. Sixteen participants completed the study protocol with morphine; 7 received the low dose and 9 received the high dose of morphine. Five participants required a decrease in the morphine infusion rate for treatment of nausea and vomiting. 2 in the low-dose study phase and 3 in the high-dose phase. Participants in the low-dose group received an average total of 0.35 mg/kg intravenous morphine (range 0.28 mg/kg–0.40 mg/kg). Participants in the high-dose group received an average total of 0.59 mg/kg intravenous morphine (range 0.44 mg/kg–0.77 mg/kg) resulting in a mean serum morphine concentration of 18.5 ng/ml (±4.3 SE) at the end of the high-dose infusion. Except as noted above, there were no complications from the morphine infusion.

Effect of Morphine on Natural Killer Cell Cytotoxicity

Morphine resulted in significant depression of PBMNC NKCC in both the low-dose and high-dose groups (table 1). Depression of NKCC was observed by 2 h and was maximal at 24 h. Recovery of NKCC was apparent by the 48-h measurement period in the low-dose study group but remained significantly depressed in the high-dose study group. Depression of NKCC was significant at 24 h regardless of whether cytotoxicity was calculated as lytic units or expressed as percent specific lysis (table 1 and fig. 1). Suppression of unstimulated NKCC was observed both when effector cells were incubated in medium free of autologous serum (table 1) and when effector cells were incubated in autologous, morphine-exposed serum separated at 24 h (fig. 2). NK cell
suppression did not appear to be any greater in the presence of autologous serum than in serum-free medium. Suppression of NK activity in the presence of medium with serum was significant in both the low-dose and the high-dose study phases at the 24-h measurement period compared with baseline values ($P < 0.05$ for both doses). Effector cells incubated overnight with the stimulatory cytokine, IFN-g, demonstrated significantly increased cytotoxicity compared with unstimulated baseline NKCC ($P < 0.001$). However, morphine significantly decreased IFN-g-induced enhancement of NKCC in both the low-dose study phase and the high-dose study phase (table 2). Finally, an infusion of saline given in a blinded manner had no effect on NKCC in the two subjects in which it was tested. In these two participants, baseline lytic units were 177 and 132, and 24-h lytic units were 189 and 191, respectively.

**Effect of Morphine on Antibody-dependent Cell Cytotoxicity, Fc Receptor Expression, and Lymphocyte Human Immunodeficiency Virus Infectivity**

Morphine exposure in the low-dose phase of the study resulted in significant depression of ADCC similar to that previously reported. Suppression of ADCC was significant at an intermediate antibody concentration of 0.1 μg/ml (table 2) and was not observed at very low antibody concentrations, at which very little cytotoxicity was measured, or at very high antibody concentrations, at which high levels of cytotoxicity were always observed. γ-Interferon–induced enhancement of ADCC was also slightly, but significantly, decreased (table 2). There was no significant effect of morphine on Fc receptor expression on monocytes, lymphocytes, or polymorphonuclear cells (table 3). The effect of morphine exposure on HIV infectivity was measured

Anesthesiology, V 83, No 5, Sep 1995
in lymphocytes drawn from six participants in the high-dose phase of the study (table 4). The difference between the mean value of 42.8 ng/ml p24 measured with baseline cells versus 100.4 ng/ml p24 measured using cells obtained at 24 h was not statistically significant (P = 0.17).

**Discussion**

Opioid-immune interactions are potentially important, given the widespread use of opioids, the central role of the immune system in a variety of diseases, and the introduction of new immunologic treatments for diseases that range from infection to cancer.\(^5\)\(^6\)\(^7\) Results reported from this study document depression of peripheral blood spontaneous NKCC after *in vitro* morphine administration. This phenomenon may be dose-dependent because an earlier study reported no depression of NKCC after morphine doses that resulted in lower serum morphine concentrations.\(^8\) In addition, although the current study did not attempt intragroup comparisons, NKCC remained significantly depressed for 48 h after high-dose morphine but had returned to normal by 48 h after low-dose morphine.

Depressed NK activity was partially restored by IFN-γ treatment. Aside from anti-viral effects,\(^9\) IFN-γ has can activate monocyte and macrophages against a variety of pathogens\(^10\) and also activates NK cells against tumor targets.\(^11\) The latter effects have formed the basis of clinical trials of IFN-γ as a treatment for infection\(^12\) and advanced cancer.\(^13\)\(^14\) Although our results suggest that *in vitro* morphine exposure interferes with activation of NK cells by IFN-γ, the IFN-γ exposure (and testing of NK function) was performed *ex vivo* and may not reflect *in vivo* effects of IFN-γ. Resistance of splenic NK cells to IFN-γ stimulation was recently reported in mice exposed to inhalational anesthetics before IFN-γ stimulation of splenic NK cells.\(^15\)

Morphine effects on NK activity were observed in the absence of autologous serum and after incubation of effector cells for as long as 18 h. This observation, and the observation that morphine also decreased ADCC-mediated lysis after low-dose exposure of participants, suggests a durable effect of morphine on peripheral blood effector cells.

Most of the information available on opioid-immune interactions comes from animal studies or from *in vitro* testing. This study was conducted in healthy volunteers for two reasons. First, diseases commonly associated with opioid use can alter immune studies. Immune studies performed in patients who require analgesia are difficult to interpret because of the coexisting condition that requires pain therapy. Major surgery, for example, is associated with immune suppression\(^16\)\(^17\)\(^18\) as are many types of chronic cancer\(^19\)\(^20\) and substance abuse.\(^21\)\(^22\) Second, *in vitro* morphine exposure more closely approximates the physiologic conditions under which opioids may affect human immunity. Results from *in vitro* investigations fail to approach the clinical situation in which effector cells are exposed to opioids *in vivo*. In addition, morphine has active metabolites\(^23\) that may alter immune function *in vitro* but escape detection with *in vitro* testing of the parent drug.

There are several potential mechanisms by which opioids may alter human immunity. Opioids may have an indirect effect on immune function through alterations in effector cell populations. A decrease in effector cell density in any immune compartment (thymus, spleen, peripheral blood, lymph node) will alter func-

Table 3. Effect of Morphine Exposure on Leukocyte Fc Receptor Expression

<table>
<thead>
<tr>
<th>Monocyte</th>
<th>Lymphocyte</th>
<th>PMN</th>
</tr>
</thead>
<tbody>
<tr>
<td>FcR I</td>
<td>Baseline</td>
<td>17,152 (1,728)</td>
</tr>
<tr>
<td>24 h</td>
<td>16,920 (2,253)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>FcR II</td>
<td>Baseline</td>
<td>40,877 (2,792)</td>
</tr>
<tr>
<td>24 h</td>
<td>40,100 (2,585)</td>
<td>3,712 (693)</td>
</tr>
<tr>
<td>FcR III</td>
<td>Baseline</td>
<td>54,568 (6,737)</td>
</tr>
<tr>
<td>24 h</td>
<td>40,810 (7,196)</td>
<td>41,717 (13,835)</td>
</tr>
</tbody>
</table>

Monoclonal antibodies were used to detect numbers of Fc receptors per cell. Data are sites per cell (±SE); n = 6 for all determinations.

PMN = polymorphonuclear leukocyte

* Values are for the subset of positive cells, representing 5–20% of the total population. All other values are for the total population.
Table 4. Effect of Morphine on p24 Antigen Production in HIV-infected Lymphocytes from Six Study Participants in the High-dose Study Phase

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
<th>Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>3.2</td>
<td>62.3</td>
<td>16.3</td>
<td>15.1</td>
<td>76.4</td>
<td>83.2</td>
<td>42.8 ± 14.4</td>
</tr>
<tr>
<td>24 h</td>
<td>80.3</td>
<td>109.1</td>
<td>29.3</td>
<td>217.5</td>
<td>91.1</td>
<td>75.4</td>
<td>100.4 ± 25.4</td>
</tr>
</tbody>
</table>

Values are concentration of p24 (ng/ml).

release of transforming growth factor β, an immune suppressive mediator. Finally, opioids may affect immune function by suppression of endogenous, tonic enhancement of effector cell activity. For example, endogenous opioids such as β-endorphin circulate in blood at measurable concentrations that have been shown to stimulate immune effector cells in vitro. However, coinubation of PBMCs with pharmacologic concentrations of morphine or the synthetic opioid, fentanyl, inhibits β-endorphin–induced increases in NKCC in vitro. In vitro observations correlate with these findings.

Peterson et al. reported that PBMCs taken from normal humans and cocultured with morphine in the presence of HIV-infected lymphocytes showed an increase in HIV infectivity. This effect was observed with morphine concentrations at or near the pharmacologic concentration required for clinical analgesia. Enhanced HIV infectivity was reversed by opioid receptor antagonists and was of approximately the same magnitude as that observed after exposure of PBMCs to interleukin-2, which is also known to increase HIV proliferation. Enhanced HIV expression in an infected monocyctic cell line has also been observed after coculture of infected cells with morphine-exposed fetal brain cells. These studies raise the question of whether in vivo morphine exposure could alter HIV infectivity of target cells and thereby either alter susceptibility to HIV infection or alter the course of the disease. Based on these reports, we analyzed lymphocyte HIV infectivity in six morphine-exposed participants. Overall, we were not able to confirm a significant change in lymphocyte HIV infectivity after administration of morphine to study participants.

In summary, healthy volunteers who received intravenous morphine had measurable depression of peripheral blood spontaneous and IFN-γ-stimulated NKCC. These effects were observed after effector cell incubations in the absence of autologous serum separated at the time of the assay, which suggests a durable effect on effector cell number. Implications of this and other observations are unknown. No serious adverse events were observed in this study. Further studies of nonopioid-induced immune effects in patients with spiritual beliefs are warranted.

Acknowledgments

The assistance of Duane Nash, RN, and Jennifer Fulmer is gratefully acknowledged.

References

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MORPHINE AND IMMUNE FUNCTION

effect on effector cell numbers or function. The clinical implications of this and other opioid-immune interactions are unknown. No adverse immunologic consequences were observed in any of the subjects who participated in this study. The question of whether or not opioid-induced immune alterations have clinical effects in patients with specific diseases will require further study.

The assistance of Duane Nash, Esther Colby, Kim Coleman, and Jennifer Fullerom is gratefully acknowledged.

References

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Clinical Trial

Background: Transillumination using a trachlight (lightwand) technique. A newly developed trachlight incorporates modifications to the light source as well as flexibility to determine the effectiveness of the trachlight. Healthy surgical (paired) animals with known or potential problems were used. During general anesthesia using either the Trachlight system, the failure rate was defined as the time from insertion of the laryngoscope to the time of its removal (TTR), an overall measure of the success rate based on the duration of attempts. Complications, such as, injury, dental injury, and scoring complications. Nine hundred fifty groups were successfully scored and 471 in the laryngoscope. A failure rate of 36% failure rate and an 89% successful rate with the lightlens system followed by successful intubation.

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