Effect of Ketamine on Inflammatory and Immune Responses After Short-Duration Surgery in Obese Patients

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Abstract: In non-obese patients ketamine decreases inflammatory responses and prevents overexpression of immune responses. Its effect in obese patients is unknown. This prospective, blinded, randomized controlled trial was designed to determine the effect of ketamine on cytokines and immune cell responses after short-duration surgery in obese patients. Thirty-six patients received either ketamine 0.15 mg/kg IV prior to induction of general anesthesia, or an equal volume of normal saline. Cytokine concentrations and immune cell responses were determined pre-operatively and at 4, 24, and 48 h after operation. Interleukin (IL)-6 production was significantly greater in the control group (126.0 ± 18.8 ng/ml, mean ± SEM, n = 19) than in the ketamine group (57.9 ± 8.4 ng/ml) at 4 h. At other time periods IL-6 and tumor necrosis factor α increased and IL-2, lymphocyte proliferation, and natural killer cell cytotoxity decreased compared to pre-operative values in the control group but not in the ketamine group. We conclude that effects of ketamine on inflammatory and immune responses after short-duration surgery in obese patients are similar to those previously reported in non-obese patients.

Keywords: Ketamine, cytokines, interleukins, inflammation, immune response.

INTRODUCTION

The human immune system is complex, consisting of both inflammatory and immune cell responses. Major surgery causes release of pro-inflammatory cytokines which, in excessive amounts, may cause undesirable consequences such as postoperative complications, immune cell suppression, and end-organ injury, resulting in multiple organ failure and death [1-3]. In contrast, release of anti-inflammatory cytokines together with immune cell proliferation and natural killer (NK) cell activity attenuate and regulate pro-inflammatory mediators [1-3].

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, may favourably affect the balance between inflammatory and immune cell responses in humans. There are over 30 published studies in humans and the majority report that ketamine decreases inflammatory responses and prevents overexpression of immune responses [4-35] (Table **1**). However, none of these reports studied the effect of ketamine in obese patients.

Obesity is becoming increasingly prevalent and is associated with metabolic, hormonal, and physiologic changes, the pathophysiologic consequence of which affect every major organ system [36]. There is an extensive literature examining the relationship between obesity and inflammation. Chronic inflammation is an integral component of obesity, and obesity is the strongest independent predictor of inflammation [37-39]. It is not certain whether the metabolic, hormonal, and physiologic changes occurring with obesity affect the inflammatory and/or immune responses to ketamine previously reported in non-obese patients. The present study was designed to determine, in obese patients, the effect of ketamine on cytokines [interleukin (IL)-1β, IL-2, IL-6, and tumor necrosis factor (TNF)-α], a specific immunity cell response (lymphocyte proliferation), and a nonspecific immunity cell response (NK cell activity).

MATERIALS AND METHODS

The study was approved by the institution's Human Subjects Helsinki committee of the Rabin Medical Center. Informed, written consent was obtained from all the patients. Thirty-six obese (as defined by Roizen and Fleisher, body mass index greater than 28 kg/m^2), non-smoking, male and female patients between the ages of 23-67, with an ASA status of 1-II undergoing elective gastric or uterine surgery participated in the study [36]. Exclusion criteria for patient selection were endocrine disorders, immune system disorders, patients on immunosuppressive treatment, chronic inflammatory disease, patients with any sign of infection after surgery, malignant disease, allergy to ketamine, kidney or liver disorders, and blood transfusion perioperatively. The decision to enroll 36 patients was based on two-sided sample size determination (power analysis) assuming σ (standard deviation) of 0.4 for our primary measures (i.e., cytokine

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Table 1. Previously Reported Effects of Ketamine in Humans or Human Cells

Reference	Finding	Source
Decreased Pro-Inflammatory Factors or Exerted Anti-Inflammatory Effect		
Roytblat *et al*. [13]	IL-6	adult surgical patients (hysterectomy)
Larsen *et al*. [17]	IL1β and TNF	cultured whole blood
Roytblat *et al*. [18]	IL-6	adult surgical patients (cardiac)
Zahler *et al*. [20]	reactivity	leukocytes
Kawasaki *et al*. [22]	IL-6 and 8, TNF alpha	whole blood
Weigand *et al*. [23]	IL-6, CD 18, CD 62	neutrophils
Cao *et al*. [25]	IL-6 and 8	adult surgical patients (cardiac)
Hoff *et al*. [26]	TNF alpha	cultured whole blood
Kawasaki *et al*. [27]	IL-6 and 8, TNF	whole blood
Xia *et al*. [35]	IL-1 and 6, TNF alpha	burn patients
No Change in Inflammatory Factors		
Marone *et al*. [7]	Histamine	basophils, mast cells (skin, lung, heart)
Larsen *et al*. [17]	IL-10	cultured whole blood
Zahler *et al*. [20]	IL-6 and 8, adhesion molecules	leukocytes, cultured endothelial cells
Takano *et al*. [30]	IL-6 and 10	mononuclear cells
Zeyneloglu *et al*. [32]	IL-6	infant surgical patients (cardiac)
Increased Pro-Inflammatory Factors		
Stellato *et al*. [4]	Histamine	basophils, mast cells (skin, lung, heart)
Rossano *et al*. [6]	IL-4 and 6, TNF	monocytes, lymphocytes
No Change in Immune Responses		
Hashimoto *et al*. [5]	natural killer cell activity	adult surgical patients
Davidson *et al*. [9]	phagocytosis, respiratory burst activity	polymorphonuclear leukocytes
Krumholz *et al*. [10]	bactericidal activity	polymorphonuclear leukocytes
Toyota *et al*. [11]	phagocytosis	polymorphonuclear leukocytes
Nishina *et al*. [14]	chemotaxis, reactive oxygen species	neutrophils
Hellar *et al*. [15]	phagocytosis, burst activity	neutrophils, monocytes
Larsen *et al*. [17]	CD 14, HLA-DR	cultured whole blood
Krumholz *et al*. [21]	chemotaxis	polymorphonuclear eosinophilic leukocytes
Loop *et al*. [31]	NFkB	T lymphocytes
Bentley *et al*. [33]	natural killer cell activity	adult surgical patients (oral maxillofacial surgery)
Buyukkocak *et al*. [34]	acute phase proteins	pediatric surgical patients (circumcision)
Decrease Immune Responses		
Weiss *et al*. [8]	oxygen radical production	polymorphonuclear leukocytes
Krumholz *et al*. [12]	phagocytosis, bactericidal activity	polymorphonuclear cells
Nishina *et al*. [14]	phagocytosis	neutrophils
Heller *et al*. [15]	phagocytosis, bacterial elimination	monocytes
Hofbauer *et al*. [16]	migration	leukocytes
Krumholz *et al*. [19]	chemotaxis	monocytes
Weigand *et al*. [23]	oxygen radical production	neutrophils
Sakai *et al*. [24]	NFkB	cultured glioma cells
Lewis *et al*. [28]	proliferation	mononuclear cells
Increased Immune Responses		
Krumholz *et al*. [29]	non-oxidative bactericidal activity	polymorphonuclear leukocytes

IL = interleukin; NFkB = nuclear transcription factor kappa B; CD18 = β-integrin; CD 62 = L-selectin; CD14 = lipopolysaccharide recognition; HLA-DR = major histocompatability complex class II, human leukocyte locus A; TNF = tumor necrosis factor.

concentrations, lymphocyte proliferation, and NK cell activity; based on preliminary data), a 30% difference between μ_0 and μ_1 (difference between means), power of 0.85, significance of 0.05, an unbalanced randomization design, and a minimum number of patients failing to complete the study after ascertaining that no exclusion criteria applied.

Ninety minutes before surgery, all patients were premedicated with diazepam, 5-10 mg orally, and upon arrival in the operating room received midazolam, 2-3 mg IV. The patients were then randomly divided in two groups: the treatment group (17 patients) received ketamine, 0.15mg kg $^{-1}$IV, five minutes before induction of general anaesthesia and the control group (19 patients) received a similar volume of normal saline 5 minutes before induction of anaesthesia. Selection of the dose of ketamine was based on a previous report that this dose suppressed IL-6 productions in non-obese patients having abdominal hysterectomy [13]. Anaesthesia was induced with fentanyl 2-3mcg kg $^{-1}$ and thiopental 4-6 mg kg $^{-1}$IV. Vecuronium, 0.1mg kg $^{-1}$IV was given for muscle relaxation. Anaesthesia was maintained with nitrous oxide 60-70% and isoflurane 1.0-1.5% (inspired concentrations) in oxygen. Additional fentanyl (1-2 mcg kg $^{-1}$) was given as needed to maintain a mean arterial blood pressure within 20% of baseline values. The patients received upper body forced-air warming, and intravenous fluids were warmed to 37°.

Venous blood samples (15 ml) were collected just before administration of ketamine or normal saline and at 4, 24, 48, and 72 h after operation for determination of cytokines and immune cell responses. The persons performing sample analysis were blinded as to whether the sample originated from treatment or control patients. Peripheral blood mononuclear (PBMN) cells were isolated from heparinized venous blood using a histopaque (Sigma) gradient centrifugation, washed twice in RPMI-1640 medium containing 1% penicillin, streptomycin and nystatin and supplemented with 10th fetal calf serum (FCS), designated as complete medium (CM), and then suspended in FCS containing 10% dimethyl sulphoxide (DMSO, Sigma) and frozen at -70°C until used. On the day of assay, the cells were thawed quickly, washed three times in CM and their viability tested by trypan blue dye exclusion. The viability was over 95%.

For IL-1β, IL-6 and TNF-α assay, PBMN cells (xx10^6) suspended in 1 ml of RPMI-1640 supplemented with 5% FCS were incubated for 24 h in the presence of 10 ng ml $^{-1}$ lipopolysaccharide (E. coli, Sigma). For IL-2 production, 2x10^6 PBMN cells were suspended in 1 ml of CM and incubated for 48 h with 1% phytohemagglutinin (PHA-M, Difco). These concentrations of lipopolysaccharide and PHA previously were reported to induce maximal release of the respective cytokines [40, 41]. Following incubation, the culture media were collected, the cells were removed by centrifugation, and the supernatants were kept at -70°C until assayed for cytokine content. Cytokine concentration in the supernatants was tested using ELISA kits specific for human IL-1β (Biosource International, Camarillo, CA), IL-6 and TNF-α, (Pharmingen, San Diego, CA), and IL-2 (R&D Systems, Minneapolis, MN, USA). The detection level of these cytokines in the assays was 30 pg ml $^{-1}$ for IL-1β, IL-2 and TNF-α and 15 pg ml $^{-1}$ for IL-6.

0.1 ml of PBMN cell suspension (2x10^6 cells ml $^{-1}$) was aliquoted into each well of 96-well plates (flat bottom, Nunc) containing 0.1 ml of CM or PHA, concanavalin A (Con A, 10 μg ml $^{-1}$), or pokeweed mitogen (PWM, Sigma, 20 μg ml $^{-1}$). Cultures were set up in triplicate, with each culture in a single well, and were incubated for 3 days. 0.5 μCI/well of ^{3}H-TdR (methyl-^{3}H-thymidine, 5 μCI mmol^{-1}, Amersham, England) was added 18 h before harvesting. Radioactivity was measured using a liquid scintillation counter (LKB model 3380).

Cytotoxicity was assessed using a standard chromium specific release assay with a ^{51}Cr labeled K562 cell line used as target cells and PBMN cells serving as effector cells. Final effector to target (E:T) ratio was 100:1. Following 4 hrs of incubation at 37^{O}C, the supernatants were collected, and the radioactivity was measured using a gamma counter (LKB). All reactions were carried out in triplicate and the specific ^{51}Cr release was calculated as described previously [42].

Statistics

Categorical data were described with frequency counts and were compared between groups using Fischer's exact test. Parametric data were normally distributed, were expressed as mean ± SEM, and were compared within and between groups using repeated measures analysis of variance (ANOVA) followed by post hoc testing with Student-Newman-Keuls multiple comparison test. P values <0.05 were considered significant.

RESULTS

The treatment and control groups were similar with respect to age, gender, body weight, ASA status, and type and duration of surgery (Table **2**). None of the patients required a blood transfusion and none dropped out of the study. The fentanyl dose for induction of anaesthesia, 245 ± 48 mcg and 236 ± 45 mcg, and the fentanyl dose for maintenance of anaesthesia, 142 ± 28 mcg and 140 ± 27 mcg, did not differ significantly between the control and ketamine groups. The effect of pre-induction ketamine, compared with saline, on the production of cytokines and immune cell responses is summarized in Table **3**.

Table 2. Patient Demographics

	Control Group	Ketamine Group
Number of Patients	19	17
Sex (M/F)	5/14	4/13
Age (years)	43.5±10.3	39.0±10.7
Body Mass Index (kg/m^2)	34.7±7.4	34.3±8.3
Body Weight (kg)	97.5±26.3	95.4±29.9
ASA Physical Status	I = 8, II = 11	I = 7, II = 10
Type of Surgery (gastric/uterine)	9/10	9/8
Duration of Surgery (min)	69±25	75±22

ASA = American Society of Anesthesiologists.
Values expressed as means +/- SEM.

Table 3. Cytokine and Immune Responses

Response	Group	Preop	4 hrs	24 hrs	48 hrs	72 hrs
IL-1β	Control	6.5±0.3	8.2±0.9	8.8±0.7	8.4±0.9	8.4±0.9
(ng ml $^{-1}$)	Ketamine	6.4±0.5	8.1±0.8	8.9±0.7	9.2±0.8*	8.8±0.9
IL-6	Control	57.4±5.0	126.0±18.8	136.4±14.1*	141.2±17.1*	140.6±31.6*
(ng ml $^{-1}$)	Ketamine	52.7±7.5	57.9±8.4#	110.4±20.0	105.5±9.5	102.7±14.3
TNF-α	Control	12.5±0.8	15.4±1.3	15.0±1.7	16.0±1.7	16.6±1.2*
(ng ml $^{-1}$)	Ketamine	11.4±1.1	11.8±1.1	14.9±1.2	16.5±1.6	15.9±2.2
IL-2	Control	5.0±0.5	3.6±0.6	3.2±0.5†	3.2±0.5†	4.0±0.5
(ng ml $^{-1}$)	Ketamine	5.5±0.5	4.6±0.6	4.5±0.5	4.3±0.5	4.8±0.4
Lymphocyte	Control	19.2±1.7	16.4±2.1	14.3±1.7†	18.3±2.1	17.3±1.7
proliferation (Cpm x $10^{3)}$	Ketamine	19.9±1.6	17.4±1.6	17.3±1.5	18.1±2.1	18.2±1.7
NK Cell	Control	35.4±2.7	40.8±3.1	22.4±2.4†	25.6±2.5*	30.5±2.6
Cytotoxicity (%)	Ketamine	33.5±3.4	34.0±3.5	24.9±3.4	23.5±1.9*	26.2±2.3

IL-1β = Interleukin-1β, IL-2 = Interleukin-2, IL-6 = Interleukin-6, TNF-α = Tumor necrosis factor-α, Lymphocyte proliferation = Phytohemagglutinin-induced response (concanavalin A- and pokeweed mitogen-induced responses not shown), NK = Natural killer.
* $p<0.05$ *vs* preoperative value.
† $p<0.01$ *vs* preoperative value.
# $p<0.05$ between groups.
N=19 in the Control group and N=17 in the Ketamine group.
Values expressed as mean ± SEM.

Before operation, concentrations of cytokines and immune responses did not differ between groups. Postoperatively, IL-6 production was significantly greater in the control group (126.0±18.8 ng ml $^{-1}$, mean ± SEM) than in the ketamine group (57.9 ± 8.4 ng ml $^{-1}$) at 4 h. At 24, 48, and 72 h, IL-6 production increased compared to preoperative values in the control group but not in the ketamine group. At 48 h, IL-1β increased in the ketamine group but not in controls. At 72 h TNF-α increased in controls but not in the ketamine group.

Production of IL-2, PHA-stimulated lymphocyte proliferation, and NK cell cytotoxicity all decreased at 24 h compared to preoperative values in the control group but not in the ketamine group. Con A- and PWM-induced proliferation did not change significantly during the 72 h after operation in either group (data not shown).

DISCUSSION

Cytokine and Immune Cell Responses

IL-6 is an integral pro-inflammatory cytokine involved in the acute phase response to injury and infection [43]. It is inducible in nearly every human tissue and cell type and production can be stimulated by numerous factors, including TNF-α and IL-1. It is the inflammatory mediator most consistently identified systemically after elective surgery, increasing within 1 –3 h after laparotomy, peaking at 4-24 h and remaining elevated for 48 –72 h [44]. The greater the surgical trauma, the greater the serum IL-6 response. For example, abdominal surgery produces a bigger response than hip replacement [2]. It follows that most randomized studies show laparotomy triggering a larger inflammatory response than laparoscopy [13, 44-46]. Laparoscopic surgery appears to induce a smaller injury, resulting in proportionally decreased immunological changes, although the exact mechanism is unclear [47]. Comparatively, IL-1β and TNF-α are detectable in much lower serum concentrations than IL-6 after elective surgery. However, hemorrhagic and septic shock both result in significantly elevated levels of IL-1β, TNF-α and IL-6, which are associated with an increased risk of acute respiratory distress syndrome, multiple organ failure, and death [48-50]. In trauma patients, increased IL-6 levels are associated with the development of infection [48-50]. The enhanced local release of inflammatory cytokines associated with abdominal surgery is thought to be related to postoperative ileus secondary to inhibition of muscularis function [44, 51].

Serum concentrations of IL-2, a promoter of T lymphocyte proliferation, and host defense against infection, are reduced as early as 2 h after surgical trauma and may remain depressed for up to five days after trauma-hemorrhage [52]. T lymphocytes are one component of specific immunity in humans providing antimicrobial and antitumor defense. Hallmarks of T lymphocytes are specificity and memory. CD4 T lymphocytes promote cell mediated immunity or humoral immunity and allergy, while CD8 T lymphocytes destroy major histocompatibility complex-bearing cells. NK cells are one component of nonspecific immunity in humans. NK cells possess large granules containing enzymes that induce apoptosis in target cells and can mediate death of Fas-bearing targets through the action of Fas ligand. NK cells lack the specificity of T lymphocytes, instead relying on the ability to detect abnormally low expression of class 1 major histocompatibility complex molecules, as occurs in viral-infected cells. Proliferation of PHA-stimulated lymphocytes and NK cell cytotoxicity have been found to be suppressed postoperatively [44, 52].

Results of the Present Study

Our results demonstrate that the effect of ketamine on inflammatory and immune responses in obese patients is

similar to that previously reported in non-obese patients [4-35]. In previous studies in humans ketamine decreased pro-inflammatory factors or exerted an anti-inflammatory effect in 10 studies, caused no change in 5 studies, and increased pro-inflammatory factors in 2 studies. As regards immune responses, ketamine caused no change in 11 studies, suppressed immune responses in 9 studies, and augmented in immune responses in one study [4-35]. Alterations in inflammatory and immune responses may affect clinical outcomes such as postoperative pneumonia, membrane permeability, acute lung injury, ARDS, wound infections, and sepsis. In general, attenuation of cytokine responses is beneficial. However, in certain clinical situations such as in the immunocompromised patient, blunting the release of inflammatory mediators and failure of neutrophil migration into an inflamed lung, may predispose to a greater risk of pulmonary infections. In addition, cytokine responses are sensitive and are affected by many factors. Altering ventilation strategy alone may modify lung cytokine responses to lipopolysaccharide. Positive pressure ventilation in the absence of anesthesia may also exacerbate inflammatory responses.

Ketamine may have direct effects on pro-inflammatory, anti-inflammatory and immune responses, or may influence those responses indirectly by reducing postoperative pain. Pain itself is a promoter of pro-inflammatory cytokine production and suppression of IL-2, and therefore ketamine may have additional benefits in the postoperative patient secondary to its preemptive analgesic effects and opioid sparing properties. Several studies have shown that adding subanaesthetic doses of ketamine to general anaesthesia reduces postoperative pain and opioid requirements in a variety of surgeries, including major abdominal, arthroscopic knee, laparoscopic gynecologic, and adenocarcinoma surgery [53-56]. Ketamine acts as a noncompetitive antagonist at NMDA receptors, which play an important role in the concept of the "wind-up" phenomenon and pain sensitization. It is also thought to mediate pain by interaction with spinal μ receptors and *via* activation of the descending pain inhibitory monoaminergic pathways [53]. It is possible that the same results seen here with ketamine may have been found with any analgesic agent.

Volitile anesthetics and thiopental may have affected the inflammatory and immune responses we examined. Under controlled conditions, volatile anesthetics tend to increase cytokine formation and appear to enhance inflammatory responses. In contrast, using models of acute lung injury by stimulation with lipopolysaccaride, E Coli endotoxin, or interleukin 1, volatile anesthetics appear to exert anti-inflammatory effects including, inhibition of cytokine formation; reduction of neutrophil migration into the lung interstitium and alveolar space; and attenuation of protein leakage and publmonary edema [57-60].

In summary, ketamine given at the time of induction of anaesthesia attenuated production of IL-6, did not significantly change concentrations of other cytokines in comparison to concentrations in controls, and tended to preserve immune responses after short-duration surgery in obese patients. These effects are similar to those generally reported in previous studies of non-obese patients.

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