REVIEW

# Continuous intravenous infusion of ketamine for maintenance sedation

A. C. MILLER [1, 2], C. T. JAMIN [3], E. M. ELAMIN [4]

[1]Department of Critical Care Medicine, National Institutes of Health, Bethesda, MD, USA; [2]Division of Pulmonary, Allergy, and Critical Care Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [3]Department of Critical Care Medicine, Stanford University Medical Center, Palo Alto, CA, USA; [4]Division of Pulmonary, Critical Care, and Sleep Medicine, The James A. Haley Veterans Hospital and the University of South Florida, Tampa, FL, USA

## ABSTRACT

Ketamine HCl is a rapidly acting general anesthetic with sedative and analgesic properties that has been reported to have favorable effects on the cardiovascular and pulmonary systems. The goal of this review is to determine the hemodynamic and pulmonary effects of continuous intravenous (IV) ketamine infusion in mechanically ventilated patients, and to determine whether sufficient evidence exists to support its use as an agent for maintenance anesthesia. PubMed/Medline, EMBASE, and Index Medicus databases as well as relevant bibliographies were searched. Studies were independently evaluated for inclusion and exclusion criteria, as well as study parameters, by two evaluators. Any discrepancy was resolved by a third evaluator. Twenty studies (281 patients) met the inclusion criteria for this review including 11 prospective studies (250 patients). Data suggests that ketamine decreases airway resistance, improves dynamic compliance, and preserves functional residual capacity, minute ventilation and tidal volume, while retaining protective pharyngeal and laryngeal reflexes. In patients with refractory bronchospasm, continuous infusion of intravenous ketamine decreases audible wheeze, bronchodilator requirements, and hypercarbia. It also improves respiratory rate and oxygenation, and does not promote respiratory depression. Additionally, ketamine does not result in significant perturbations in blood pressure, heart rate, or vascular resistance. Ketamine may be a safe and effective tool for maintenance sedation of mechanically ventilated patients, however a large prospective clinical trial is warranted. *(Minerva Anestesiol 2011;77:812-20)*

**Key words:** Infusions, intravenous - Ketamine - Deep sedation.

Ketamine HCl is a rapidly acting general anesthetic with sedative and analgesic properties. The dissociative anesthetic action of ketamine provides excellent analgesia and anesthesia, with retention of protective pharyngeal and laryngeal reflexes and without depressing respiration.[1, 2] Numerous small series have documented its favorable effects on cardiovascular and pulmonary parameters.[3, 4] Its tendency to preserve cardiac output and relax bronchiole smooth muscles have made it an attractive anesthetic option for induction and maintenance of general anesthesia, particularly in those patients with reactive airway disease. The goal of this review is to critically examine and characterize the published data regarding the hemodynamic and pulmonary effects of continuous intravenous ketamine infusion as an agent for maintenance sedation in mechanically ventilated patients. Additionally, we aim to elucidate whether sufficient evidence of improved hemodynamic or pulmonary status exists to support the further investigation and use of ketamine as an agent for maintenance anesthesia.

Table I.—*Criteria for scoring included manuscripts as published by Jadad et al.*[6]

| No. | Items* | Points |
|---|---|---|
| 1 | Study described as randomized | 1 |
| 2 | Study described as double-blind | 1 |
| 3 | Description of withdrawals and drop-outs | 1 |
| 4 | For question 1, method to generate randomization sequence described and appropriate (table of random numbers, computer generated, etc.) | 1 |
| 5 | For question 2, method of double-blinding described and appropriate (identical placebo, active placebo, dummy, etc.) | 1 |
| 6 | For question 1, method to generate randomization sequence described and inappropriate (patients allocated alternately, according to date of birth, hospital number, etc.) | -1 |
| 7 | For question 2, method of double-blinding described and inappropriate (comparison of tablet *vs.* injection with no double dummy, etc.) | -1 |
| 8 | Maximum Total | 5 |

* Score based on initial 3 item tool (1-3) with addendum criteria (4-7). "Yes" (1 or -1 points) and "No" (0 points) answers are totaled for a potential maximum score of 5 points.

A comprehensive search of PubMed/Medline, EMBASE, and Index Medicus was performed using the MESH and general search terms of ketamine, pulmonary, respiratory, blood pressure, cardiovascular, and hemodynamics. As ketamine is known to have species-specific effects,[5] the search was limited to human studies published in English, French, Spanish, or German. Relevant bibliographies were also scanned for additional studies. Inclusion criteria included 1) patients treated with intravenous (IV) ketamine; 2) maintenance IV ketamine infusion for >2 hours; 3) patient receiving mechanical ventilation via invasive positive pressure ventilation (*e.g.* endotracheal intubation, tracheostomy, etc). Exclusion criteria included 1) intermittent ketamine bolus therapy; 2) continuous ketamine infusion for <2 hours; 3) patient not on mechanical ventilation. All studies were independently evaluated and scored according to a scale adapted from that published by Jadad *et al.* (Table I).[6] Evidence was rated according to the Oxford Scheme.[7]

Inclusion and exclusion criteria, study parameters, Jadad score, and evidence level were assessed by two evaluators (AM and CJ). Any discrepancy was resolved independently by a third (EE).

## Results

Twenty studies (281 patients) met the inclusion criteria for this review including 11 prospective studies (250 patients). Additionally, 1 retrospective observational study (17 patients) and 8 case series / reports (14 patients) were included. A description of the included studies is listed in Table II.[4-46]

### *Respiratory parameters*

Overall, 9 studies and 8 case reports/series (223 patients) assessed the effects of continuous IV ketamine infusion on respiratory variables in mechanically ventilated patients. Two studies and 4 case reports (73 patients) assessed change in respiratory rate. In the 4 case reports (6 patients) with refractory bronchospasm, there was a decrease in the respiratory rates, but no reports of respiratory depression. Of the 2 studies assessing respiratory rate (67 patients) in non-asthmatics, neither reported a decrease in respiratory rate. Three studies and 2 case reports (41 patients) assessed the effects on chest wall dynamic compliance. Most of these patients had refractory bronchospasm (status asthmaticus), and each patient series showed an increase in chest wall dynamic compliance. Six case reports (7 patients) reported a decrease in wheeze following ketamine administration, 1 study (5 patients) reported a decrease in bronchodilator use, and 1 study (53 patients) reported a decrease in clinical dyspnea. One patient series (5 patients) showed a decrease in measured airway resistance, and an additional 2 studies and 3 case reports (32 patients) found a decrease in the peak inspiratory pressure. One study (14 patients) found no change in tidal volume, 2 studies (23 patients) found no change in functional residual capacity, and 2 studies (22 patients) found no change in minute ventilation. Three studies and 7 case series (64 patients) all found an increased $PaO_2$ with continuous ketamine infusion, 1 case series (2 patients) reported an increase in $SaO_2$, and 3 studies and 5 case reports (46 patients) all found a decrease in the $PaCO_2$.

TABLE II.—*Review of studies assessing the physiologic effects and clinical utility of Ketamine maintenance sedation in ventilated patients.*

| Study 1st Author (Year) | N | Age Years | Protocol | Dose | Study group | Results | Jadad Score† | Evidence Level ‡ |
|---|---|---|---|---|---|---|---|---|
| Indvall J (1979) [46] | 31 | 24-90 (67±15) | Prospective case series | 2 mg/kg IV bolus then 40 ug/kg/min titrated to sedation | Patients undergoing major abdominal surgery | Transient ↑SBP, DBP, HR, & CO resolved to baseline levels w/in minutes. No change SI. ↑ $PaO_2$ | | 4 |
| Shulman D (1985) [42] | 9 | 0.8-8.3 | Prospective case series | 1.3-1.9 mg/kg IV or 2.0-3.7 mg/kg IM bolus then 45-200 ug/kg/min | ASA-I pediatric patients for minor surgery. | No change in FRC | | 4 |
| Mankikian B (1986) [41] | 14 | Mean 28 | Prospective case series | 3 mg/kg IV bolus then 20 ug/kg/min | Patients for minor surgery. | No changes in FRC, $V_m$ or TV | | 4 |
| Rock MJ (1986) [35] | 2 | 4, 10 | Retrospective case series | 0.5-1.0 mg/kg IV bolus then 1-2.5 mg/kg/hr x24 -36 hr | Refractory status asthmaticus. | ↓ PIP, ↑$C_{dyn,}$ ↑$PaO_{2,}$ ↑$PaCO_{2,}$ | | 4 |
| Strube PJ (1986) [27] | 1 | 13 | Case report | 50 mh bolus then 90 mg/hr x 8 hrs | Refractory status asthmaticus. | ↓Wheezing , ↓RR ↑$PaO_2$, ↓$PaCO_{2,}$ no change HR or BP | | 4 |
| Tokics L (1987) [36] | 8 | 33-55 | Prospective case series | 2.4-5 mg/kg IV bolus then 0.1 mg/kg/min | Patients for minor surgery. | No change SBP, $MAP_{pa,}$ CO, ↑HR, ↑$PaO_{2,}$ ↓$PaCO_2$, | | 4 |
| Park GR (1987) [30] | 1 | 24 | Case report | 20 mg IV bolus then 20-100 mg/h (he was pre-sedated with midazolam) | Patient with ALL and bilateral pseudomonas pneumonia | Better sedation, ↓ bronchospasm, ↓PIP, ↓HR, ↑ SBP | | 4 |
| Tobias J (1990) [37] | 5 | 0.59-14 | Retrospective case series | 0.5-1 mg/kg bolus then 10-15 ug/kg/min | Pediatric ICU patients of mixed diagnoses | ↑$PaO_2$, ↓$PaCO_2$, no change MAP, no change vasopressor requirement | | 4 |
| Sarma VJ (1992) [31] | 2 | 40, 43 | Retrospective case series | Bolus 0.75mg/kg then 0.15 mg/kg/hr | Refractory status asthmaticus | ↓Wheezing, ↓RR, ↑$SaO_2$ | | 4 |
| Achar MN (1993) [32] | 1 | 53 | Case report | 2 mg IV bolus then 20-30 mg/hr then tapered to 10 then discontinued after 18 hours | Refractory status asthmaticus | ↓Wheezing ↑$PaO_2$, ↓$PaCO_2$ | | 4 |
| Hemming A (1994) [34] | 1 | 28 | Case report | 2.5 mg/kg/hr | Refractory status asthmaticus | ↓Wheezing ↑$PaO_2$, ↓$PaCO_{2,}$ ↑$C_{dyn}$ | | 4 |
| Nehama J (1996) [33] | 1 | 0.8 | Case report | Bolus 1.4 mg/kg x2 then 0.2 mg/kg/hr x 4 hours then tapered (total 40 hours) | Refractory status asthmaticus | ↓Wheezing ↑$PaO_2$, ↓$PaCO_2$ ↓PIP | | 4 |
| Kolenda H (1996) [1] | 24 | 16-70 | Prospective randomized control study | 104-180mg/kg/day | Prospective study of ketamine + midazolam vs fentanyl + midazolam in moderate-severe head trauma | ↑MAP, ↑HR, ↓ vasopressor need, | 1 | 2b |

*Table II continued*

TABLE II.—*Review of studies assessing the physiologic effects and clinical utility of Ketamine maintenance sedation in ventilated patients. (Continued)*

| Study 1st Author (Year) | N | Age Years | Protocol | Dose | Study group | Results | Jadad Score† | Evidence Level ‡ |
|---|---|---|---|---|---|---|---|---|
| Howton JC (1996) [43]* | 53 | 18-65 | Prospective randomized double-blind placebo controlled trial | 0.2mg/kg bolus then 0.5 mg/kg/hr x 3 hrs | Refractory status asthmaticus | No difference in FEV1, PEFR, RR | 4 | 2b |
| Youseff-Ahmed MZ (1996) [38] | 17 | 0.5-17 | Retrospective case series | 2 mg/kg IV bolus then 20-60 ug/kg/min x 40 ± 31 hours | Ventilated patients with refractory bronchospasm | ↑ $PaO_2/Fio_2$, ↑ $C_{dyn}$, ↓ $PCO_2$, ↓ PIP | | 4 |
| Heshmati F (2003) [39] | 11 | 15-40 | Prospective case series | Bolus 1mg/kg then 1mg/kg/hr x 2 hrs | Refractory status asthmaticus | ↑ $PaO_2$, ↓ $PaCO_2$ ↓ PIP, ↑ $C_{dyn}$ | | 4 |
| Hijazi Y (2003) [47] | 12 | 21-64 | Prospective case series | 2 mg/kg IV bolus then 2 mg/kg/hr x 2 hours | ICU patients with traumatic brain or spinal cord injury. | No change SBP, DBP, HR | | 4 |
| Allen JY (2005) [44] * | 68 | 2-18 | Prospective randomized double-blind placebo controlled trial | 0.2mg/kg IV bolus then 0.5 mg/kg/hr x 2 hours | ED patients with acute asthma exacerbation | No change in pulmonary index score | 5 | 2b |
| Williams GD (2007) [40] | 15 | 0.3-18 | Prospective case series | 2 mg/kg IV bolus then 10 ug/kg/min | Pediatric pulmonary HTN patients for cardiac catheterization | No change in PVR, ↑ $PaO_2$, no change $PCO_2$, ↑ HR, no change MAP, no change $MAP_{pa}$, no change pH, $HCO_3$, or BE | | 4 |
| Elamin EM (2007 & 2009) [4]** | 5 | 19-55 | Prospective randomized double-blind controlled study | 1 mg/kg IV bolus then 1.0 mg/kg/hr continuous infusion titrated by 0.5 mg/kg/h every 5-20 minutes to reach a Ramsay Sedation Scale of 4 or to a max dose of 4.5 mg/kg/h | Prospective study of ketamine vs fentanyl in adult med-surgical ICU | ↑ MAP, ↓ incidence of shock, ↓ Raw, ↑ $C_{dyn}$, ↓ bronchodilator use | 5 | 2b |

SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; CO: cardiac output; FRC: functional residual capacity; Vm: minute ventilation; TV: tidal volume; PIP: peak inspiratory pressure; Cdyn: dynamic compliance; PaO2: partial pressure of oxygen arterial; PaCO2: partial pressure of carbon dioxide; RR: respiratory rate; MAPpa: pulmonary artery mean arterial pressure; SaO2: oxygen saturation; FEV1: forced expiratory volume in 1 second; PEFR: peak expiratory flow rate; BE: base excess; Raw: airway resistance. †The scoring system reported by Jadad et al. was designed to assess clinical trials, therefore results were not calculated or reported for case reports, case series, or observational studies.6 ‡According to the Oxford Scheme. *These studies used a sub-anesthetic dose of ketamine. **The results of hemodynamic and respiratory parameters were published independently. For this table they have been consolidated into 1 entry.3-4

*Hemodynamic parameters*

A total of 6 studies and 3 case reports/series (102 patients) assessed the effect of continuous IV ketamine infusion on hemodynamic and cardiovascular variables. The results of these studies were less unanimous than with the respiratory parameters. Two studies (20 patients) found no change in systolic blood pressure (BP), whereas 1 case report (1 patient) found a decreased systolic BP. One study (12 patients) found no change in diastolic BP. Two studies and 1 case report (21 patients) found no change in mean arterial pressure (MAP) during continuous ketamine infusion, whereas 2 studies (29 patients) found an increased MAP. Two studies (29 patients) reported no change in the pulmonary artery pressure ($MAP_{pa}$). With regard to vasopressor usage, 1 study (5 patients) found no change in vasopres-

sor use whereas another study (24 patients) reported decreased vasopressor use in the ketamine group. An additional study (5 patients) reported a decreased incidence of shock amongst patients treated with continuous ketamine infusion. No studies reported an increase in vasopressor use amongst patients treated with ketamine.

### *Grading the evidence*

Overall, no studies containing level 1 evidence were identified (Table II). Four of 21 included studies/reports were level 2b evidence. The remaining 17 studies were all comprised of level 4 evidence. As such, the current level of evidence only supports a Grade C recommendation.

## Discussion

Ketamine HCl is a rapidly acting general anesthetic with sedative and analgesic properties. It is rapidly-acting with a short half-life, and the dissociative effects allows for excellent analgesia and anesthesia, with retention of protective pharyngeal and laryngeal reflexes and preserved respiratory effort.[1, 2] Its versatility, efficacy, safety profile, and low cost have promoted its widespread use and inclusion in the World Health Organization's list of "Essential Medicines" for a basic health care system.[8] As a phencyclidine derivative, ketamine is in a unique class that induces a functional disorganization between the thalamoneocortical and limbic systems, producing a "dissociative state". The effects of Ketamine are the product of a number of different mechanisms of action. The primary anesthetic properties of ketamine are due to its antagonism of Central Nervous System (CNS) N-methyl-D-aspartate (NMDA) receptors.[9-11] Ketamine is also a potent analgesic and has been used effectively for post-surgical analgesia, spinal analgesia, and in chronic pain management settings. Its analgesic mechanism is multifactorial and is in part due to its effects on mu and kappa opioid receptors.[9] Additionally, ketamine inhibits the 'Wind-up" phenomenon of pain. This action is mediated through its inhibition of long-term potentiation in dorsal horn neurons in the spinal cord via NMDA receptor antagonism.[9, 11] Ketamine also promotes central sympathetic stimulation and inhibition of neuronal catecholamine uptake.[9, 10, 12] Moreover, it has also been reported to have immune modulating effects including the inhibition of TNF-$\alpha$, IL-1, and IL-6 effects to endotoxemia.[13]

Ketamine's popularity as an agent for maintenance sedation has been related in part to its favorable effects on the pulmonary and cardiovascular systems. Historically, its tendency to relax the bronchiole smooth muscle and preserve cardiac output have led to ketamine's use as an agent for induction and maintenance of general anesthesia, particularly in patients with pulmonary disease (*e.g.* asthma) or cardiovascular instability.[14-16] Ketamine is frequently used in situations requiring a short, rapidly-acting general anesthetic, post-operative short term analgesia, and procedural sedation, particularly in pediatrics and emergency medicine.[17] Additionally, it is used as a co-analgesic in both general and spinal anesthesia.[18-20]

Ketamine has been successfully used to treat patients with severe bronchospasm, refractory to conventional bronchodilators.[21-24] Because of its beneficial effect on airway resistance, some have advocated for its use as a preferred agent for rapid induction and continuous anesthesia in patients with reactive airways disease.[25-27] Huber *et al.* reported a two-thirds reduction in airways resistance compared to pretreatment values, 90 seconds following injection of ketamine in patients with moderate to severe bronchospasm.[26] Prior studies have reported that the respiratory response to $CO_2$ is maintained during ketamine anaesthesia,[28] and significant respiratory depression is uncommon. The ability of ketamine to antagonize antigen-induced bronchospasm may be related to its vagolytic and direct smooth muscle relaxant effects.[27] However, the major effect in vivo appears to be secondary to its sympathomimetic properties. Whether or not the beta-adrenergic receptor stimulation is required to achieve ketamine-induced bronchodilation is still a subject of debate.[5, 29] Such bronchodilator effects can be prevented by beta-adrenoceptor blockade. Reappearance of asthma each time the depth of ketamine anesthesia is lightened and clearing of the wheezing with the deepen-

ing of the dissociative state, has been previously observed.[22]

In addition to its efficacy in relieving bronchospasm via bolus administration, continuous infusion of ketamine has also been shown to safely improve pulmonary function. Ketamine improves air entry and decreases wheezing in patients with refractory bronchospasm, as well as improving other objective measurements of respiratory dynamics.[3, 27, 30-34] Numerous studies have demonstrated that ketamine infusion increases $PaO_2$ and decreases $PaCO_2$.[27, 31-40] These effects can be seen even after ketamine is added to conventional treatment for patients with refractory bronchospasm.[27, 31-35, 38-40] Tachypneic patients in status asthmaticus who are placed on ketamine infusion show an improved respiratory rate, increased oxygenation, and decreased hypercapnia.[27, 31, 32, 35] This is a reflection of the improvement in their respiratory mechanics. In fact, unlike with many other anesthetics, patients receiving ketamine infusion for maintenance sedation maintain their respiratory tone. Despite general anesthesia, patients treated with ketamine exhibit preservation of functional residual capacity, minute ventilation and tidal volume.[36, 41, 42] In addition to preserving respiratory tone, ketamine also augments thoracic compliance.[27, 34-36, 38-39] Dynamic compliance ($C_{dyn}$) is an important factor in the successful management of status asthmaticus, especially in asthmatics on mechanical ventilation. Dynamic compliance represents airway resistance and can be considered a surrogate marker for degree of bronchospasm.[38] Likewise, increased peak inspiratory pressure (PIP) also reflects airway resistance. In a retrospective review of 17 pediatric patients with refractory bronchospasm on mechanical ventilation, Youssef-Ahmed *et al.*, found a significant decrease in PIP and increase in $C_{dyn}$ in patients who received continuous ketamine infusion.[38] Other studies have shown a similar increase in dynamic compliance and/or a decrease in peak inspiratory pressure (PIP) in patients with bronchospasm who are placed on continuous ketamine infusions.[30, 33-35, 39] Of note, one study failed to show similar improvement in FEV1, peak expiratory flow rate, and respiratory rate with continuous ketamine infusion in patients with status asthmaticus. However, in this emergency department-based study, patients were administered sub-anesthetic, and potentially subtherapeutic, doses of ketamine.[43] In the Howton et al. study, patients were administered ketamine bolus of 0.2 mg/kg followed by continuous infusion of 0.5 mg/kg/h × 3 hrs instead of the typical 2 mg/kg bolus followed by 1-2 mg/kg/h typically administered in other studies.[43] Similarly, one other emergency department based study failed to find significant improvement in the Pulmonary Index Score amongst asthmatics treated with maintenance ketamine infusions; however, this study suffered from a similar design flaw in that patients were administered a sub-anesthetic ketamine dose of 0.2 mg/kg IV bolus followed by 0.5 mg/kg/h for 2 hours. [44]

In addition to its favorable respiratory dynamics profile, the hemodynamic effects of ketamine for maintenance sedation are also promising.[45] In normotensive patients, ketamine has not been shown to significantly alter systolic, diastolic, mean arterial or pulmonary artery pressures.[27, 40, 46, 47] Similarly, it has not been shown to change peripheral vascular resistance.[40] In tachycardic and hypotensive patients, the heart rate and systolic blood pressure have been reported to improve following ketamine infusion.[30, 40] Additionally, vasopressor requirements during ketamine maintenance infusion have variably been reported to be decreased or unchanged.[1, 37] This was supported by a recent pilot study in which the hemodynamic and bronchodilator effects of continuous sedation with ketamine compared to fentanyl in ICU patients.[3] Although the study included a small number of patients, the investigators reported that as compared to sedation with fentanyl, the ketamine group demonstrated a higher MAP, fewer vasopressor requirements, and were less likely to be diagnosed with a shock state.[3] Moreover, the phenomenon of decreased vasopressor requirements in patients sedated with ketamine as compared to fentayl has also been observed in neurosurgical patients.[48] This trend was likewise observed in patients who sustained head trauma; Bourgoin *et al.*, demonstrated significantly lower fluid requirements and a trend toward lesser use of vasopressors in patients with severe head injury who were rand-

omized to ketamine plus midazolam vs sudfentanil plus midazolem.[49] To date, there have been no published reports of increased vasopressor requirements during ketamine maintenance infusions.

## Cautions

Despite ketamine's safety and efficacy, clinicians should remain mindful of cautions and potential adverse events. Ketamine may cause hypersalivation which is easily treated with atropine or glycopyrrolate.[9, 10] Emergence reactions may be successfully prevented or treated with benzodiazapines, promethazine, thiopental or propofol,[9, 50] If available, the clockwise isomer S(+)-Ketamine may improve recovery from anesthesia and decrease incidence of emergence phenomena.[48]

Ketamine should be avoided in decompensated heart failure or cardiogenic shock. Whereas ketamine has a favorable cardiovascular profile related to central sympathetic stimulation and inhibition of neuronal catecholamine uptake which counteracts its direct negative inotropic effects, this favorable profile may not be seen in patients with decompensated heart failure. In such patients, ketamine's negative inotropic effects may be unmasked, resulting in deterioration in cardiac performance and cardiovascular instability.[12, 51] Also, ketamine may raise pulmonary artery pressures, thus it should be used with caution in patients with pulmonary hypertension.[45] Furthermore, since ketamine has been reported to cause hypertension and supraventricular tachycardia in patients on thyroxine replacement; clinicians should employ additional caution with such patients.[9]

Ketamine should be avoided in patients with seizure disorder as it has variably been reported to have both pro- and anti-convulsant properties.[10] In the meantime, a recent literature review of ketamine's effect on the brain in patients with, or at risk for, neurological injury reported that it does not increase intracranial pressure when used under conditions of controlled ventilation, co-administration of a γ-aminobutyric acid (GABA) receptor agonist, and without nitrous oxide (level II evidence).[52] Moreover, the same authors suggest that ketamine may be a preferred agent in sedative regimens for patients with brain injury due to the hemodynamic stimulation that it induces and the resultant improvement cerebral perfusion pressures that have been observed (level II and III evidence).[52] Such findings were supported by recent evidences that suggested the safety of ketamine for maintenance of anesthesia and analgesia in the neurosurgical patients.[48]

Ketamine should be avoided in patients with glaucoma as it may further increase intraocular pressure [10] or in those with a history of psychosis as it may induce a "dissociative state".[9]

Finally, although ketamine infusion related laryngospasm has been reported to occur in 0.4% of patients, such cases are generally easily managed with non-invasive ventilation techniques and rarely requires intubation (0.02%).[2]

### *Limitations of the study*

Strengths of this review include our systematic approach in the searching the literature, selecting the relevant studies, and the independent duplicate assessment of trial validity. However, the heterogeneity of patients, medications, and dosing regimens precluded a systematic meta-analysis of results. As with all systematic reviews, readers are advised to review the original publications for any further details.

The review outcome of primary interest was the quality of ketamine induced sedation. While most trials assessed this end point using the Ramsay scale,[53, 54] this and other commonly used sedation scales have not been rigorously and formally validated.[55] Furthermore, reported sedation scales were numerical, and most assess only a single item. Accordingly, such scoring systems limit the reproducibility and ability to interpret results across studies. Moreover, difficulty arises when different definitions of ideal level of sedation were used. For example, studies reported ideal sedation levels ranging from Ramsay level 2 to 5. Hence, this review highlights the need for a reliable and valid sedation and analgesia scoring system to improve the interpretability of future studies.

Blinding both patients and evaluators to treatment is of utmost importance when evaluating

subjective outcomes. Among the studies reviewed, blinding was neither routinely employed nor reported. Accordingly, interpretation of variables such as degree of sedation, audible wheeze, duration of mechanical ventilation and length of ICU stay may be biased.

Finally, all co-interventions, including general anesthesia, use of analgesics (other than those being directly studied), use of neuromuscular blocking agents, and approach to weaning from mechanical ventilation were neither standardized nor consistently reported. Monitoring and reporting such measures will help reduce bias in end-point interpretation, for example, quality of sedation and length of ventilation and ICU stay.

## Conclusions

Ketamine has been shown to have beneficial pulmonary and hemodynamic effects when administered as maintenance sedation via continuous infusion. It has been reported to decrease airway resistance, improve dynamic compliance, and preserve functional residual capacity, minute ventilation and tidal volume while retaining protective pharyngeal and laryngeal reflexes. In patients with refractory bronchospasm, ketamine has been reported to decrease audible wheeze, decrease bronchodilator requirements, and improve respiratory rate and oxygenation, and decrease hypercarbia when administered via continuous IV infusion. Also, ketamine does not promote respiratory depression. Additionally, it offers a favorable hemodynamic profile compared to fentanyl, midazolam, or propofol in that it does not result in significant blood pressure, heart rate, or vascular resistance perturbations. The available evidence suggests that ketamine may be a safe and effective tool for maintenance sedation; however a large prospective clinical trial is necessary to further clarify the utility of ketamine as an agent for continuous IV maintenance sedation of patients on mechanical ventilation.

## References

1. Kolenda H, Gremmelt A, Rading S, Braun U, Markakis E. Ketamine for analgosedative therapy in intensive care treatment of head-injured patients. Acta Neurochir (Wien) 1996;138:1193-9.
2. Green SM, Krauss B. The semantics of ketamine. Ann Emerg Med 2000;36:480-2.
3. Demirer E, Miller AC, Elamin EM. Impact of ketamine on dynamic compliance (DC) & airway resistance (AR) of sedated & mechanically ventilated ICU Patients. Eur Respir J 2009;34:P3521.
4. Elamin EM, Drew D. Is ketamine the right agent for mechanically ventilated patients? Chest 2007;132:574S.
5. Hill GE, Anderson JL, Whitten CW. Ketamine inhibits agonist-induced cAMP accumulation increase in human airway smooth muscle cells. Can J Anaesth 1999;45:1172-7.
6. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1-12.
7. Oxford Center for Evidence Based Medicine (CBEM). Levels of evidence [Internet]. Available from. Accessed on line at: http://www.cebm.net/index.aspx?o=1025 [cited 2009, Mar 31].
8. World Health Organization (WHO). Essential Medicines. 14th edition. March 2005.
9. Craven R. Ketamine. Anaesthesia 2007;62(Suppl 1):48-53.
10. Bergman SA. Ketamine: review of its pharmacology and its use in pediatric anesthesia. Anesth Prog 1999;46:10-20.
11. Kohrs R, Durieux ME. Ketamine: teaching an old drug new tricks. Anesth Analg 1998;87:1186-93.
12. Bovill JG. Intravenous anesthesia for the patient with left ventricular dysfunction. Semin Cardiothorac Vasc Anesth 2006;10:43-8.
13. Taniguchi T, Yamamoto K. Anti-inflammatory effects of intravenous anesthetics on endotoxemia. Mini Rev Med Chem 2005;5:241-5.
14. Corssen G, Gutierrez J, Reves JG, Huber FC Jr. Ketamine in the anesthetic management of asthmatic patients. Anesth Analg 1972;51:588-96.
15. Nettles DC, Herrin TJ, Mullen JG: Ketamine induction in poor-risk patients. Anesth Analg 1973;52:59-64.
16. Rees DI, Howell ML. Ketamine-atracurium by continuous infusion as the sole anesthetic for pulmonary surgery. Anesth Analg 1986;65:860-4.
17. Mistry RB, Nahata MC. Ketamine for conscious sedation in pediatric emergency care. Pharmacotherapy 2005;25:1104-11.
18. Goel S, Bhardwaj N, Jain K. Efficacy of ketamine and midazolam as co-induction agents with propofol for laryngeal mask insertion in children. Pediatr Anaesth 2008;18:628-34.
19. Frizelle HP, Duranteau J, Samii K. A comparison of propofol with a propofol-ketamine combination for sedation during spinal anesthesia. Anesth Analg 1997;84:1318-22.
20. Nayar R, Sahajanand H. Does anesthetic induction for Cesarean section with a combination of ketamine and thiopentone confer any benefits over thiopentone or ketamine alone? A prospective randomized study. Minerva Anestesiol 2009;75:185-90.
21. Petrillo TM, Fortenberry JD, Linzer JF, Simon HK. Emergency department use of ketamine in pediatric status asthmaticus. J Asthma 2001;38:657-64.
22. Lau TT, Zed PJ. Does ketamine have a role in managing severe exacerbation of asthma in adults? Pharmacotherapy 2001;21:1100-6.
23. Fischer MM. Ketamine hydrochloride in severe bronchospasm. Anaesthesia 1977;32:771-2.
24. Sheref SE. Ketamine and bronchospasm. Anaesthesia 1985;40:701-2.
25. Corssen G, Gutierrez J, Reves JG, Huber FC Jr. Ketamine in the anesthetic management of asthmatic patients. Anesth Analg 1972;51:588-96.
26. Huber FC Jr, Gutierrez J, Corssen G. Ketamine: its effect on airway resistance in man. South Med J 1972;65:1176-80.

27. Strube PJ, Hallam PL. Ketamine by continuous infusion in status asthmaticus. Anaesthesia 1986;41:1017-9.
28. Soliman MG, Brindle GF, Kuster G. Response to hypercapnia under ketamine anaesthesia. Can Anaesth Soc J 1975;22:486-94.
29. Bevan RK, Rose MA, Duggan KA. Evidence for direct interaction of ketamine with α- and $\beta_2$-adrenoceptors. Clin Exp Pharm Phys 1997;24:923-6.
30. Park GR, Manara AR, Mendel L, Bateman PE. Ketamine infusion. Its use as a sedative, inotrope and bronchodilator in a critically ill patient. Anaesthesia 1987;42:980-3.
31. Sarma VJ. Use of ketamine in acute severe asthma. Acta Anaesthesiol Scand. 1992;36:106-7.
32. Achar MN, Achar KN. Efficacy of ketamine infusion in refractory asthma complicated by acute myocardial infarction. Anaesth Intensive Care 1993;21:115-7.
33. Nehama J, Pass R, Bechtler-Karsch A, Steinberg C, Notterman DA. Continuous ketamine infusion for the treatment of refractory asthma in a mechanically ventilated infant: case report and review of the pediatric literature. Pediatr Emerg Care 1996;12:294-7.
34. Hemming A, MacKenzie I, Finfer S. Response to ketamine in status asthmaticus resistant to maximal medical treatment. Thorax 1994;49:90-1.
35. Rock MJ, Reyes de la Rocha S, L'Hommedieu CS, Truemper E. Use of ketamine in asthmatic children to treat respiratory failure refractory to conventional therapy. Crit Care Med 1986;14:514-6.
36. Tokics L, Strandberg A, Brismar B, Lundquist H, Hedenstierna G. Computerized tomography of the chest and gas exchange measurements during ketamine anaesthesia. Acta Anaesthesiol Scand 1987;31:684-92.
37. Tobias JD, Martin LD, Wetzel RC. Ketamine by continuous infusion for sedation in the pediatric intensive care unit. Crit Care Med 1990;18:819-21.
38. Youssef-Ahmed MZ, Silver P, Nimkoff L, Sagy M. Continuous infusion of ketamine in mechanically ventilated children with refractory bronchospasm. Intensive Care Med 1996;22:972-6.
39. Heshmati F, Zeinali MB, Noroozinia H, Abbacivash R, Mahoori A. Use of ketamine in severe status asthmaticus in intensive care unit. Iran J Allergy Asthma Immunol 2003;2:175-80.
40. Williams GD, Philip BM, Chu LF, Boltz MG, Kamra K, Terwey H *et al.* Ketamine does not increase pulmonary vascular resistance in children with pulmonary hypertension undergoing sevoflurane anesthesia and spontaneous ventilation. Anesth Analg 2007;105:1578-84.
41. Mankikian B, Cantineau JP, Sartene R, Clergue F, Viars P. Ventilatory pattern and chest wall mechanics during ketamine anesthesia in humans. Anesthesiology 1986;65:492-9.
42. Shulman D, Beardsmore CS, Aronson HB, Godfrey S. The effect of ketamine on the functional residual capacity in young children. Anesthesiology 1985;62:551-6.
43. Howton JC, Rose J, Duffy S, Zoltanski T, Levitt MA. Randomized, double-blind, placebo-controlled trial of intravenous ketamine in acute asthma. Ann Emerg Med 1996;27:170-5.
44. Allen JY, Macias CG. The efficacy of ketamine in pediatric emergency department patients who present with acute severe asthma. Ann Emerg Med 2005;46:43-50.
45. Hedenstierna G. Pulmonary perfusion during anesthesia and mechanical ventilation. Minerva Anestesiol 2005;71:319-24.
46. Indvall J, Ahlgren I, Aronsen KF, Stenberg P. Ketamine Infusions: Pharmacokinetics and clinical effects. Br J Anesth 1979;51:1167-72.
47. Hijazi Y, Bodonian C, Bolon M, Salord F, Boulieu R. Pharmacokinetics and haemodynamics of ketamine in intensive care patients with brain or spinal cord injury. Br J Anaesth 2003;90:155-60.
48. Schmittner MD, Vajkoczy SL, Horn P, Bertsch T, Quintel M, Vajkoczy P *et al.* Effects of fentanyl and S(+)-ketamine on cerebral hemodynamics, gastrointestinal motility, and need of vasopressors in patients with intracranial pathologies: a pilot study. J Neurosurg Anesthesiol 2007;19:257-62.
49. Bourgoin A, Albanèse J, Wereszczynski N, Charbit M, Vialet R, Martin C. Safety of sedation with ketamine in severe head injury patients: comparison with sufentanil. Crit Care Med 2003;31:711-7.
50. Erden IA, Pamuk AG, Akinci SB, Koseoglu A, Aypar U. Comparison of two ketamine-propofol dosing regimens for sedation during interventional radiology procedures. Minerva Anestesiol 2010;76:260-5.
51. Christ G, Mundigler G, Merhaut C, Zehetgruber M, Kratochwill C, Heinz G *et al.* Adverse cardiovascular effects of ketamine infusion in patients with catecholamine-dependent heart failure. Anaesth Intensive Care 1997;25:255-9.
52. Himmelseher S, Durieux ME. Revising a dogma: ketamine for patients with neurological injury? Anesth Analg 2005;101:524-34.
53. Ricker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F *et al.* SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group. JAMA 2009;301:489-9.
54. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. BMJ. 1974;2:656-9.
55. De Jonghe B, Cook D, Appere-De-Vecchi C, Guyatt G, Meade M, Outin H. Using and understanding sedation scoring systems: a systematic review. Intens Care Med 2000;26:275-85.


*Funding.*—This project was funded in part by a grant from the American Lung Association. The opinions expressed in this manuscript represent those of the authors, and do not represent official policy of the National Institutes of Health.

Received on May 25, 2010 - Accepted for publication on October 25, 2010.

Corresponding author: A. C. Miller MD, Division of Pulmonary, Allergy, and Critical Care Medicine, University of Pittsburgh Medical Center, NW 628 MUH, 3459 Fifth Avenue, Pittsburgh PA 15213, USA. E-mail: taqwa1@gmail.com