Ketamine in adult cardiac surgery and the cardiac surgery Intensive Care Unit: An evidence-based clinical review

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ABSTRACT

Ketamine is a unique anesthetic drug that provides analgesia, hypnosis, and amnesia with minimal respiratory and cardiovascular depression. Because of its sympathomimetic properties it would seem to be an excellent choice for patients with depressed ventricular function in cardiac surgery. However, its use has not gained widespread acceptance in adult cardiac surgery patients, perhaps due to its perceived negative psychotropic effects. Despite this limitation, it is receiving renewed interest in the United States as a sedative and analgesic drug for critically ill-patients. In this manuscript, the authors provide an evidence-based clinical review of ketamine use in cardiac surgery patients for intensive care physicians, cardio-thoracic anesthesiologists, and cardio-thoracic surgeons. All MEDLINE indexed clinical trials performed during the last 20 years in adult cardiac surgery patients were included in the review.

Key words: Cardiac surgery; dissociative anesthesia; intensive care; ketamine

INTRODUCTION

Ketamine is a unique anesthetic drug that provides profound analgesia, hypnosis, and amnesia. It also causes less respiratory depression than other intravenous anesthetics at clinically relevant doses and has sympathomimetic properties that make it a useful drug for patients with impaired cardiac function (e.g.,: Cardiac tamponade or systolic heart failure). Ketamine also has anti-inflammatory properties that are potentially useful in attenuating the inflammatory response to cardiopulmonary bypass (CPB).[1,2] To date, there has been no concise review of ketamine use in adult cardiac surgery and the cardiac surgery Intensive Care Unit (ICU). For this reason, we provide an evidence-based clinical review of the current literature for cardiac surgeons, cardio-thoracic anesthesiologists, and intensive care providers.

LITERATURE REVIEW

To identify relevant articles for the review we conducted a systematic review of MEDLINE with the following phrases: "Ketamine and cardiac surgery," "ketamine and coronary artery bypass," "ketamine and valve surgery," "ketamine and aortic surgery," "ketamine and heart transplant," "ketamine and cardiac ICU," and "ketamine and ICU." The authors also identified studies of interest from the reference lists in articles that were reviewed. All authors agreed upon which studies to include in the review. Only studies that were performed during the last 20 years were included in the list of clinical studies.

BRIEF HISTORY

In 1962 Calvin Stevens Ph.D., an organic chemistry professor at Wayne State University (Detroit, Michigan, USA), synthesized a

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number of phencyclidine derivates for Parke Davis Pharmaceuticals.[3] Parke Davis had been investigating phencyclidine as a human anesthetic agent but found that it lead to the unpleasant side effect of prolonged emergence delirium. For this reason, they hoped to identify a short-acting chemical derivative that would limit these adverse effects. The derivative compounds were tested in nonhuman primates and one compound, CI-581, appeared to be short-acting and provide excellent anesthesia. This compound was selected for human trials and later became known as "ketamine."

Ketamine was first tested in humans at the Parke Davis Research Unit of Jackson Prison in Michigan. The first human received the drug on August 3, 1964 and in 1965 Domino *et al.* published their initial data from human subjects coining the term "dissociative anesthesia."[4] Further studies of the drug in human subjects continued throughout the 1960s. By 1970, it was approved as an anesthetic agent by the United States Food and Drug Administration.

Pharmacology
Ketamine's basic chemical structure is a chlorophenyl group attached to a modified cyclohexanone ring. The cyclohexanone ring contains a chiral carbon at the C-2 position and thus there are two enantiomers (S^+ or R^-). Most commercial preparations contain a racemic mixture. The S^+ and R^- enantiomers have similar pharmacodynamic properties, but the S^+ enantiomer is more potent.

Ketamine is readily soluble in water and has a pKa of 7.5. Parenteral preparations are commercially available, and oral preparations can be compounded; however, only a small amount of an oral dose is absorbed due to extensive first pass metabolism.[5] When injected intravenously its effects are rapid, occurring in approximately 30 s. Once in the bloodstream it has minimal protein binding and its pharmacokinetics can be described by a two-compartment model with an α $T^{1/2}$ (redistribution) of approximately 7 min and β $T^{1/2}$ (elimination) of approximately 2–4 h.[6] Blood levels of approximately 2,000–3,000 ng/ml are required to produce and maintain surgical anesthesia and levels as low as 50–100 ng/ml can produce a dissociative state.[3] Blood concentrations in the range of 370 ng/ml have been shown to decrease pain perception by 50%.[7]

Metabolism takes place in the liver via hepatic microsomal enzymes (CYP3A4, CY2B6, and CYP2C9).[8] First ketamine is N-demethylated to norketamine, which is then hydroxylated and conjugated to form more water-soluble metabolites. There is also a small amount of drug excreted unchanged in the urine.

Mechanism of anesthesia
Ketamine's principal anesthetic action is believed to take place via noncompetitive antagonism of the N-methyl-D-aspartate (NMDA) receptor, which plays a critical role in excitatory neurosynaptic transmission as well as neuronal plasticity. Lodge *et al.* first elucidated this mechanism in 1983.[9] It is now known that the NMDA receptor is a transmembrane protein complex composed of four subunits.[10] There is a large N-terminal extracellular portion and a shorter intracellular C terminal portion. The 4 subunits are derived from one of the 3 families NR1, NR2, or NR3. The NR1 subunit contains a binding site for glycine, and the NR2 subunit contains a binding site for glutamate. Functionally, the NMDA receptor is an ion channel that permits passage of multiple cations into cells (including sodium and calcium). The channel is particularly permeable to calcium. A number of molecules are able to noncompetitively inhibit the NMDA receptor by plugging the channel pore when it is in an open conformation. These include phencyclidine, thienylcyclohexylpiperidine, and ketamine.

In addition to blocking the NMDA receptor, ketamine has a number of additional pharmacodynamic actions. For example, it binds to opioid receptors including mu (μ), delta (∂), and kappa (κ). In a knockout mouse model, Sarton *et al.* demonstrated that it produces analgesic effects via supraspinal opioid receptors.[11] Gupta *et al.* further elucidated this mechanism, demonstrating that ketamine induces phosphorylation of mitogen-activated protein kinases by 2–3 times that of traditional opioid drugs.[12]

There is also evidence that ketamine produces its analgesic effects via central nervous system muscarinic receptors. Morita *et al.* showed that repeated doses lead to upregulation of muscarinic acetylcholine receptors in the central nervous system of mice.[13] Ketamine also effects other ion channels including sodium channels and voltage sensitive calcium channels leading to local anesthetic and gabapentin like effects.[14,15]

Cardio-vascular effects
Ketamine is a potentially useful anesthetic drug in patients with impaired ventricular function because it has sympathomimetic properties that may augment cardiac output. Johnstone published one of the largest

early reports of ketamine's cardiovascular effects in humans. In a study of 45 "relatively fit" patients ranging from 19 to 36 years of age who had the noncardiovascular surgery, he concluded that ketamine was a direct myocardial stimulant whose effects could be blocked using verapamil.[16]

In a more contemporary evaluation of ketamine's cardiovascular effects, Sigtermans *et al.* found that ketamine increases cardiac output in healthy volunteers by 40–50% at blood concentrations of 40–320 ng/ml.[7] The sentence that begins "Ketamine's mechanism for increasing" should read as follows: "Ketamine's mechanism for increasing cardiac output remains controversial though some studies have suggested that it is a direct myocardial depressant which augments cardiac output through indirect mechanisms such as potentiation of catecholamines. Ketamine's mechanism for increasing cardiac output remains somewhat controversial though as some studies have suggested that ketamine is a direct myocardial depressant that augments cardiac output through indirect mechanisms such as potentiation of catecholamines.[17,18] Other studies; however, have demonstrated direct positive ionotropic effects of ketamine on human myocytes.[19]

The important question is whether ketamine's cardiovascular effects are different in healthy volunteers and the critically ill. Our literature review supports the idea that its effects are dependent upon the degree of illness. Waxman *et al.* studied ketamine as an induction drug in a cohort of critically ill surgical patients (doses ranged from 25 mg to 140 mg) and found that ketamine increased heart rate and decreased total body oxygen consumption (VO_2).[20] However, its effects on mean arterial pressure (MAP), ventricular performance, and systemic vascular resistance (SVR) were less consistent with approximately half of patients experiencing decreases in MAP, SVR, and ventricular performance after induction. Similarly, Marlow *et al.* found that in coronary artery bypass patients, ketamine (2 mg/kg) caused significant decreases in stroke volume when used as an induction agent.[21] The magnitude of the decrease appears to have been insignificant though as no patient in the cohort required intervention.

Adverse effects

Despite ketamine's previously mentioned advantages as an anesthetic drug in patients with impaired ventricular function, it has a number of important side effects that have limited its wide spread use. First, it predictably leads to tachycardia, which can be harmful in patients with stenotic heart lesions or coronary artery disease. In an animal model, ketamine increased myocardial oxygen consumption by up to 50%.[22] It may also increase the arrhythmogenic potential of epinephrine, a drug that is commonly used for hemodynamic support during cardiac surgery.[23]

Perhaps the most significant concern that has prevented wider adoption of ketamine as an anesthetic and sedative agent is emergence delirium and the drug's potentially unpleasant psychotropic effects. In his original description of ketamine use in humans, Domino described a side effect rate of 1 in 3 subjects with many patients experiencing strange feelings of floating in space or not being able to feel their bodies.[3] In a recent systematic review of 30 ketamine trials, the rate of hallucinations was 7.4% in patients who received the drug compared to 3.7% in controls.[24] Benzodiazepine premedication appeared to have no protective effect. This same review found that in 13 trials, the rate of nightmares was 2.4% in those who received ketamine compared to 0.8% in controls. Interestingly, 8 trials also demonstrated that 18.2% of patients who received ketamine had pleasant dreams compared to 9.7% of controls.

Intraoperative ketamine use in cardiac surgery

The current body of literature regarding ketamine use in cardiac surgery is not robust; however, there have been a number of important trials. Table 1 summarizes the clinical studies published since 1990. These trials can be categorized by the outcomes that they investigated, which are the following: (1) Effects on levels of inflammatory biomarkers (2) effects on postoperative pain and patient satisfaction (3) effects on hemodynamic variables and myocardial injury (4) effects on pulmonary function (5) miscellaneous outcome measures.

Our literature review identified seven trials that examined ketamine's effects on inflammatory biomarkers including C-reactive protein (CRP), interleukins (IL) 6, 8, and 10, and tumor necrosis factor alpha.[25-31] Six trials showed significantly lower inflammatory biomarkers in CPB patients who received ketamine. One of the trials correlated lower CRP levels with a decreased risk of delirium and another correlated lower CRP with improved cognitive outcomes.

Only one trial examined ketamine's effect on poststernotomy pain and overall patient satisfaction.[32] This trial showed no improvement in overall pain scores compared to placebo; however patient satisfaction

Table 1: Studies using ketamine in cardiac surgery patients

Intraoperative studies since 1995					
Author/Year	Total *N*	Patient population	Study Design	Control Group	Outcome measures	Findings
Roytblat 1998[25]	31	CABG	RCT	Y, placebo	Postoperative IL-6 levels	Significantly lower IL-6 levels in patients receiving 0.25 mg/kg ketamine at induction
Cao 2001[26]	24	Valve replacement surgery	RCT	Y, placebo	IL-6 and IL-8 levels at various points	1mg/kg ketamine given at induction and prior to CPB decreased IL-6 and IL-8 levels
Bartoc 2006[27]	50	Mixed cardiac surgery	RCT	Y, placebo	Post operative CRP, IL-6, IL-8, and IL-10 Mean arterial pressure and systemic vascular resistance	Lower postoperative IL-6, IL-10, and CRP in group receiving 0.25-0.5 mg/kg ketamine at induction Increased post-CPB SVR and MAP in ketamine group
Cho 2009[28]	50	CABG (off pump)	RCT	Y, placebo	Post op CRP, IL-6, TNF-alpha, and troponin	0.5 mg/kg ketamine at induction did not decrease inflammatory markers compared to placebo
Hudetz 2009[29]	54	Mixed cardiac surgery	RCT	Y, placebo and, non-surgical group	Cognitive battery before surgery and 1 week after, CRP levels before surgery and on POD 1	Ketamine treated group had lower post operative CRP level and improved cognition compared to control group
Hudetz 2009[30]	58	Mixed cardiac surgery	RCT	Y, placebo	Delirium using ICU delirium checklist, CRP level on POD 1	0.5mg/kg bolus of ketamine at induction reduced POD 1 CRP and reduced delirium incidence
Welters 2011[31]	128	CABG (on pump)	RCT	Y, sufentanil	IL-6, IL-8, IL-10, TNF alpha	Lower cytokine levels in ketamine group after reperfusion
Lahtinen 2004[32]	90	CABG	RCT	Y, placebo	Pain scores, patient satisfaction, oxycodone use for breakthrough pain	No difference in pain scores Increased patient satisfaction in ketamine group and less oxycodone use
Botero 2000[33]	78	CABG	RCT	Y, fentanyl	Hemodynamics, postoperative myocardial infarctions, extubation time	Ketamine group had less requirement for ionotropes, earlier extubation, and reduced incidence of myocardial infarction
2009 Neuhauser[34]	209	CABG	RCT	Y, sufentanil	Post-operative troponin levels and major postoperative cardiac events	No difference in postoperative troponin levels or major cardiac events
Riha 2012[35]	38	CABG	Retrospective, observational	Y, sevoflurane, sufentanil	POD 1 troponin level	Decreased troponin release in ketamine, dexmedetomidine group compared to sevoflurane, sufentanil group
Basagan-Mogol 2010[36]	30	CABG	RCT	Y, propofol	Hemodynamic indices after induction	2mg/kg ketamine provided more stable hemodynamics during induction compared to 0.5 mg/kg propofol. Midazolam, fentanyl, and rocuronium doses were standardized
Parthasarathi 2011[37]	80	CABG (on pump)	RCT	Y, placebo	P/F ratios and number of ventilator days	1mg/kg bolus of ketamine at induction did not improve oxygenation after CPB or reduce ventilator days
Smith 2006[38]	42	Mixed cardiac surgery	RCT	Y, sufentanil	Quantitative EEG	No difference in postoperative quantitative EEG
Hess 2001[39]	31	CABG	RCT	Y, fentanyl	Postoperative holter monitoring for arrhythmia	Fewer ventricular arrhythmias in ketamine group during ICU stay
Ziberstein 2002[40]	35	CABG	RCT	Y, placebo	Postoperative neutrophil superoxide generation	0.25 mg/kg ketamine bolus at induction attenuates superoxide generation by neutrophils
Intensive care unit studies					
Piper 2009[44]	48	CABG	RCT	Y, placebo	Pain satisfaction, Recovery	Ketamine improved patient satisfaction and recovery
Piper 2008[45]	54	CABG	RCT	Y, placebo	Postoperative shivering and nausea and vomiting	Ketamine administration in the intensive care unit decreased the incidence of shivering and PONV after cardiac surgery

*CABG=coronary artery bypass graft, CPB=cardiopulmonary bypass, CRP=c reactive protein, ICU=intensive care unit, IL=interleukin, POD=postoperative day, PONV=postoperative nausea and vomiting, P/F ratio is P02 to Fi02 ratio, RCT=randomized controlled trial, TNF=tumor necrosis factor

was improved, and there was significant postoperative opioid sparing with ketamine use. Four trials evaluated ketamine's effects on postoperative myocardial injury through either troponin levels or electrocardiogram criteria.[28,33-35] Two of these trials suggested that ketamine decreases myocardial injury after surgery.

One study examined hemodynamic response to ketamine in cardiac surgery patients.[36] This study found that ketamine provided satisfactory hemodynamics during induction, but commonly led to tachycardia. The one study that examined ketamine's effect on postoperative pulmonary complications found no benefit (extubation time or oxygenation indices).[37] Finally, one study examined postoperative quantitative electroencephalogram (EEG) (as a surrogate for brain dysfunction), one study examined postoperative ventricular arrhythmias, and one study examined neutrophil activation after surgery.[38-40] In these studies ketamine had no effect on postoperative EEG, it decreased the incidence of ventricular arrhythmias, and it decreased neutrophil activation.

Ketamine in the cardiac surgery Intensive Care Unit

Ketamine would seem to be an excellent choice for ICU sedation and pain management in postcardiac surgery patients given its stable hemodynamic profile, minimal respiratory depression, and potent analgesic properties. However, it has not gained widespread acceptance in this setting, possibly because of concerns about its psychogenic profile. In the most recent pain, agitation, delirium guidelines from the Society for Critical Care Medicine it was only recommend as a second line analgesic agent and was not even listed as a "sedative" agent.[41] The guideline goes on to state that there are "two low-quality studies comparing clinical outcomes in those receiving dexmedetomidine and propofol for sedation and that there are no studies comparing clinical outcomes in those receiving ketamine or other sedative agents." The guidelines recommend propofol and dexmedetomidine as first line agents, but this is based primarily upon trials that compare these drugs against benzodiazepines, which showed longer length of ICU stay and mechanical ventilation in those who receive benzodiazepines.

In the adult burn ICU and general surgical ICU, ketamine has been studied sparingly but has been found to be an acceptable sedative and analgesic agent with minimal impact on hemodynamics and respiratory effort.[42,43] Surprisingly, our literature review identified only two studies of ketamine use in the adult cardiac surgery ICU [Table 1]. These studies, both by Piper *et al.*, showed

that ketamine improved postoperative patient satisfaction, postoperative recovery and decreased the incidence of shivering, nausea, and vomiting after CABG surgery.[44,45]

The paucity of studies examining ketamine as a sedative and analgesic agent in the cardiac surgery unit is surprising given the drug's excellent hemodynamic profile. We believe that ketamine has the potential to be an excellent drug for patients with ventricular assist devices, patients requiring veno-arterial extracorporeal membrane oxygenation for cardiogenic shock, and for other postcardiac surgery patients with poor ventricular function. Ketamine could also be an excellent sedative and analgesic agent for patients with an open chest and refractory right ventricular failure or in patients with high opioid requirements who are being weaned from opioids.[46,47]

Potential opportunities for ketamine in cardiac surgery and the cardiac surgery Intensive Care Unit

A number of opportunities remain for ketamine to be studied in cardiac surgery patients. The current literature supports the idea that ketamine attenuates the inflammatory response to cardiac surgery with CPB. Whether this consistently leads to improved clinical outcomes remains unclear. Furthermore, not all patients who undergo CPB develop the systemic inflammatory response syndrome, but perhaps ketamine could be useful as an anti-inflammatory drug in high-risk patients who have prolonged exposure to CPB. As previously mentioned ketamine also has the potential to be an excellent sedative and analgesic for patients with postcardiotomy shock; however, the risk of a negative psychotropic experience must always be considered and the risk must be weighed against the risks of using other agents, which may cause systemic hypotension (e.g.,: Propofol and dexmedetomidine).

Other areas where ketamine could potentially prove beneficial include neuroprotection during deep hypothermic circulatory arrest and spinal cord protection during descending thoracic aortic surgery. The role of ketamine as a neuroprotective agent remains particularly complex and uncertain at the present time and requires further clarification in clinical trials. On the one hand, it has been shown that excessive NMDA receptor agonism is harmful in the setting of neurologic injury.[48] This would seem to make ketamine an ideal neuroprotective agent during planned ischemic insults. On the other hand, there are concerns that ketamine increases cerebral blood flow and intracranial pressure (ICP). In a recent review of randomized controlled trials, Himmelseher and

Durieux concluded that under conditions of controlled mechanical ventilation ketamine does not increase ICP.[49] In the same review, he concluded that "although a wealth of animal and cellular studies demonstrate neuroprotective effects, virtually no clinical trial data are available" to validate ketamine as a neuroprotective agent. There is also the potential problem that ketamine's psychotropic effects could make an early evaluation of neurologic status challenging after surgery.

Finally, ketamine could prove to be a beneficial adjunct in preventing chronic poststernotomy pain and depression, which occur at relatively high rates after cardiac surgery.[50,51] Early trials have not shown that ketamine can reliably prevent postthoracotomy pain; however, to our knowledge no trial has examined its effects on poststernotomy pain or chronic pain due to internal mammary artery harvest.[52,53] Recently ketamine has been shown to be highly effective in treating refractory depression.[54] Future studies may help to determine whether it can also help to decrease the incidence of postcardiac surgery depression.

SUMMARY

Ketamine remains a useful and unique drug in cardiac anesthesia that can provide excellent hemodynamic stability during induction of general anesthesia in patients with poor ventricular function. However, it commonly causes tachycardia that can be detrimental in patients with coronary artery disease or stenotic heart lesions. It has been shown to attenuate the inflammatory response to CPB, but the correlation with clinical benefits remains uncertain. It also has potential use in the postcardiac surgery ICU because of its excellent hemodynamic profile, minimal respiratory depression, and potent analgesic properties. However, at this time there is a paucity of studies to support its use in this setting. Future studies comparing ketamine to other commonly accepted sedative regiments, such as propofol and dexmedetomidine are critically needed in cardiac surgery patients.

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