

## **Ketamine-Fentanyl Combination Improves Outcomes in the Intensive Care Settings**

**Duraiyah Thangathurai\* and Maggy Riad**

*Department of Anesthesiology, University of Southern California, USA*

**\*Corresponding Author:** Duraiyah Thangathurai, Department of Anesthesiology, University of Southern California, USA.

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### **Abstract**

Pharmacological interventions using analgesics and sedatives has its advantages and disadvantages. The ideal combination of pharmaceutical agents would aim at improving symptoms while causing the least side effects. The aim is to improve patients' experience, decrease organ damage, increase quality of care and thereby decrease ICU length of stay. For the last 30 years, our institution has adopted a multimodal approach for our ICU patients in order to facilitate pain relief and sedation. The purpose of the multi-modal approach is to reduce the number days on ventilators, optimize pain relief, provide sedation while decreasing undesirable side effects, and improving the overall outcome. We found that out of all possible pharmacological agents available to us, the combination of low dose ketamine with low dose fentanyl produces the desired analgesic and sedative effects with minimal side effects.

**Keywords:** *Ketamine; Fentanyl; Psychological Disturbance; ICU; Patient Outcomes*

Pain, anxiety and sleep deprivation are commonly experienced by the of majority of ICU patients. These can often result in various psychological disturbances, such as depression, delusions, delirium, and psychosis, which in turn may have negative effects on vital organ functions. The post intensive care syndrome or PICS is a well-known illness that manifests after the patients' discharge from intensive care units and may persist for months following discharge from the hospital. This syndrome is comprised of physical symptoms as well as disturbances related to the patient's feelings, thoughts, and mind. Such disturbances can cause patients to experience an overwhelming sense of demoralization, and dehumanization [1]. Severe hopelessness and helplessness can be associated with post-traumatic stress disorders or PTSD or can lead to suicidal ideations in patients who have experienced critical illnesses. In addition, learned helplessness may cloud sound decision making to the extent that patients may decide to make changes to their advance directives or living wills based on their past experiences. Consequently, some patients opt for premature termination of care or discontinuation of life supporting measures if they experience any type of disability, even if only reversible or temporary. Family members and caregivers are equally affected and it can lead to confusion, fatigue and worry about their loved ones. Pain, anxiety, stress and psychological disturbances often result in adverse hemodynamic changes, both during a critical illness as after discharge from an ICU setting. In addition, they result in neuro-endocrine abnormalities, suppression of the immune system, release of pro-inflammatory mediators, poor nutritional function, and can result in a catabolic, or chronic deconditioned state.

Prevention or timely intervention and treatment of early symptoms can minimize the need for escalation of therapy or the administration of large doses of sedatives for symptom control. Patients who receive large doses of opioid sedatives may require longer periods of mechanical ventilation. Indwelling endotracheal tubes can cause patients to experience extreme irritation, pain, agitation, intense coughing, or bronchospasm. Prolonged mechanical ventilation may provoke vagal reflexes, asynchrony between spontaneous breaths and machine-delivered breaths (often described as "fighting the ventilator"), breath-stacking, and diaphragmatic weakness, which can all

interfere with both oxygenation and ventilation, and may result in pulmonary barotrauma and hemodynamic disturbances. Often high doses of intravenous sedatives and opiates are required in intubated patients to prevent self-extubation, which may interfere with or prolong the weaning process and prolong the ICU stay. For this reason, ideal sedation practice is mandated. In the past, muscle relaxants were often used in the ICU for mechanically ventilated patients to provide paralysis and prevent dyssynchrony with ventilators. This had to be accompanied with adequate levels of sedation to avoid awareness in awake paralytic states. Prolonged use of muscle-relaxants may cause permanent myopathic states. PTSD is commonly seen in ICU patients who have received neuromuscular blocking agents while mechanically ventilated. These patients may appear sedated, maybe because of the muscle weakness, but could in fact be in the paralyzed state while still awake [2]. Intensivists currently refrain from using neuromuscular blockers and synchronize ventilator settings to patients' breathing efforts, and thereby minimize the use of large doses of sedatives.

The choice of sedatives in the ICU has long been based on the administration of intermediate or long acting opioid such as morphine sulfate, meperidine, or methadone. The use of opioids medications can be associated with development of undesirable gastrointestinal complications, like paralytic ileus, nausea, vomiting, and may increase the incidence of aspiration pneumonia and prolonged ventilator dependence. Meperidine and morphine derivatives may cause histamine release and bronchospasm. The highly addictive nature of opioid medications, and the potential for development of withdrawal states makes opiates undesirable as the sole sedative in the ICU.

Barbiturates, such as phenobarbital and pentobarbital, are used in some non-surgical ICU patients for sedation and symptom control. In the 1970s, when benzodiazepines were introduced, diazepam was widely used as a sedative in ICU patients. Diazepam has a long half-life and produces active metabolites. Other benzodiazepines commonly used in the past include lorazepam, which has an intermediate half-life with prolonged effects, and midazolam which has a shortest half-life. All benzodiazepines have strong addiction potential and their withdrawal is associated with severe symptoms including anxiety, psychotic states, and seizures. Withdrawal symptoms can last for many months and up to one year. Dexmedetomidine is another commonly used agent that can facilitate amnesia and sedation in selected patients, especially while weaning ICU patient from mechanical ventilation. The unwanted side effects are hypotension and bradycardia.

Other sedatives like propofol are widely used nowadays in most of the ICUs. However, the dosages commonly used in ICU patients is often subtherapeutic. The administration of large sedating doses of propofol in ICU patients is often not possible because of its effect on the hemodynamic parameters. Prolonged use of propofol in the ICU is undesirable and can be associated with increased lipid intake. Propofol infusion may interfere with mitochondrial fatty acid chain metabolism or may directly inhibit the mitochondrial respiratory chain resulting in a state of metabolic acidosis known as propofol infusion syndrome (PRIS).

During the past five decades, ketamine was not commonly used in ICU settings. And even though it was introduced in the 1960s, the mechanism of action and its beneficial effects in humans were not fully understood then [3,4]. The knowledge relating to pathophysiology, neurobiology, pharmacokinetics, pharmacodynamics, receptor mechanisms, and anti-inflammatory properties were limited and not fully understood. Ketamine use was initially limited to human anesthesia practices in field trauma triage situations (e.g. Moorgate underground train accident, 1975 in London), and for veterinary practices (otherwise known as "horse tranquillizer"). During that time, an earlier drug phencyclidine (PCP) became a street drug with high abuse potential, which clouded the usefulness and therapeutic potentials of ketamine, and consequently, the use of ketamine became restricted. Even when it was reintroduced as an anesthetic agent for humans, larger doses were used for induction of anesthesia than those used in our current practice. It was not uncommon to use doses as large as 3 mg - 5 mg/kg intravenously or 10 mg/kg intramuscularly. Improper use with higher doses resulted in restlessness, tachycardia, hypertension, hypotension, excitations, increased salivation and hallucinations. Researchers and pharmaceutical companies were motivated to look for other induction agents that did not have such an undesirable drug profile. It was at that time that benzodiazepines, etomidate, methohexital emerged as possible agents to be used for the induction of anesthesia.

Pharmacological interventions using analgesics and sedatives has its advantages and disadvantages. The ideal combination of pharmaceutical agents would aim at improving symptoms while causing the least side effects. The aim is to improve patients' experience,

decrease organ damage, increase quality of care and thereby decrease ICU length of stay. For the last 30 years, our institution has adopted a multimodal approach for our ICU patients in order to facilitate pain relief and sedation. The majority of our ICU patients are post-surgical patients who have undergone major oncologic surgeries at the Norris Cancer Institute/USC and at Keck Medical Center of USC. The purpose of the multi-modal approach is to reduce the number days on ventilators, optimize pain relief, provide sedation while decreasing undesirable side effects, and improving the overall outcome. We found that out of all possible pharmacological agents available to us, the combination of low dose ketamine with low dose fentanyl produces the desired analgesic and sedative effects with minimal side effects [5].

We conducted a pilot study of different combinations of ketamine-fentanyl, and ketamine-fentanyl-midazolam to find the appropriate doses to render the maximum therapeutic effects with the minimal side effects. We found two of these pharmacological combinations to be highly effective:

1. A mixture of ketamine 2 mg/ml and fentanyl 5 mcg/ml administered at an infusion rate of 3 - 15 ml/hour.
2. A mixture of ketamine 2 mg/ml and fentanyl 5 mcg/ml and midazolam 0.1 mg/ml administered at an infusion rate of 3 - 15 ml/hour.

We observed that increasing the ketamine doses above these levels did not result in improved analgesic levels, but was accompanied by development of psychotomimetic effects, anxiety, or restlessness. We also observed that increasing infusion rates above 15 ml/hour was associated with more pronounced agitation or psychotic side effects. We used the combination of ketamine-fentanyl-midazolam only for our patients who were either intubated and mechanically ventilated on ventilators, or for those who had a history of dependence on moderate doses of benzodiazepines and narcotic medications [6,7].

Based on our observation and experience over the last 30 years with various pharmacological agents and dosage combinations of agents, we found this pharmacological multimodal approach in these doses to be superior to other methods with minimal side effects. We also observed that the dosing requirements in post-surgical patients becomes less over the course of the post-operative period. The analgesic effects that this pharmacological mixture provides is probably the result of the blockade of long-term potentiation (LTP) of pain mediated by N-methyl-d-aspartate (NMDA) receptors. Low dose ketamine helps to provide analgesia while causing minimal changes on hemodynamic stability or respiratory functions. In low doses, ketamine does not result in depression of the respiratory reflexes, and does not decrease the respiratory rate or the tidal volume. It has bronchial-dilatory effects and maintains the integrity of bronchial mucosal membranes without causing dryness [8,9]. The latter is a great advantage in patients that require prolonged periods of mechanical ventilation.

The analgesic effect of ketamine is mediated through several mechanisms: as it acts to block the excitatory pathways mediated mainly by NMDA receptors (glutamate receptors). It also has an effect on serotonin pathways, opioid mu and kappa receptors, and can block the hyperalgesia associated with the use of narcotics. Hyperalgesia is commonly seen with the use of morphine, and many of the fentanyl group of drugs and is mediated via the NMDA presynaptic receptors. Ketamine prevents the winding up phenomenon in the spinal cord and minimizes the intensity of pain. Preemptive analgesic properties of ketamine enhance the analgesic effects of fentanyl, while decreasing the total dose required to achieve symptom relief.

Ketamine is used as a therapeutic agent for symptom relief in patients showing psychiatric disorders. Many acute psychiatric disorders and abnormal psychological conditions manifest themselves for the first time in ICU. It is not uncommon for prolonged ICU stay to be associated with acute depression (over 50%), panic attacks, phobias, fear of dying, hopelessness, helplessness, anxiety states (50 - 70%), and PTSD (30%) [10]. The syndrome of learned helplessness and lack of motivation may cause a psychological dependence on ventilators, which contributes to worsening of clinical outcomes. Ketamine not only prevents anxiety, PTSD, depression, suicidal ideations, but also

provides rapid relief of symptoms. Psychiatrists are now using ketamine as a first line pharmacological treatment in patients with depressive symptoms [11]. Ketamine acts on the hippocampus and increases the production of the brain derived neurotrophic factor (BDNF), in the central nervous system, and promotes neuronal growth and synaptic-plasticity [12]. This effect is observed in the prefrontal cortex, hippocampus, and in other areas resulting in rapid relief of depression and anxiety. Its effect in the amygdala includes NMDA receptor blockade, which is beneficial in the prevention and treatment of PTSD. Ketamine prevents microglial activation, which is implicated in the development of chronic neuropathic states. It also prevents neuro-inflammation, which causes cognitive dysfunction.

Gastrointestinal function is commonly affected in ICU patients, manifesting as paralytic ileus, bloating and abdominal distension. In severe cases, the increased intra-abdominal pressure causes basal lung atelectasis, shallow breathing, and increases the risk of aspiration pneumonia. Pharmacological therapy with opioid medications, anticholinergic and sympathomimetic agents is well known to cause diminished bowel activity. We observed that the patients who receive ketamine combination for postoperative analgesia to have an early return of gastrointestinal functions, even when they undergo intra-abdominal operations.

Postoperative cognitive dysfunction (POCD) is a neuroinflammatory process that is commonly seen in the aging and the susceptible patient populations. It can be the result of perioperative events associated with hypotension, hypoxemia, acute blood loss, prolonged stay on mechanical ventilation, or it can be secondary to pre-existing cerebrovascular, neurodegenerative, cardiovascular disorders, or diabetes.

Low perfusion states are common in the ICU and can be seen in patients with sepsis, hypovolemia due to bleeding, vasoplegia, adrenal failure, or increased intra-thoracic pressure with mechanical ventilation. Low cardiac output state may be caused by myocardial depression or cardiac dysrhythmias such as atrial fibrillation, or it can be a side effect from medications.

Inflammatory states, systemic inflammatory response syndrome (SIRS), are common in surgical and ICU patients, and are characterized by the liberation of multiple pro-inflammatory mediators. Cytokines such as tumor necrosis factor (TNF) alpha, , interleukin (IL) -6, IL-8 are elevated during surgical procedures and in other clinical conditions, such as sepsis and shock states [13,14]. Surgical procedures commonly associated with SIRS include open cardiac procedures requiring a prolonged cardiopulmonary bypass run, major oncological operations, massive blood transfusion, critical trauma, and major burns. The use of stored blood is also associated with the high levels of circulating cytokines. The use of ketamine for patients experiencing SIRS may be beneficial as it possesses anti-inflammatory properties and is was shown to inhibit the activity of inflammatory cytokines and nuclear factor (NF)-kappa B expression in sepsis [15-17].

Based on our ICU experience for the last 3 decades, we have observed that the administration of low dose infusions of ketamine-fentanyl combination has helped us with early liberation of post-surgical and oncological patients from mechanical ventilation and led to improved patient outcomes [18]. Consequently, patients can experience early ambulation, early enteral feeding, return of bowel function and overall decreased ICU length of stay. Patient satisfaction surveys that we have conducted over the years indicate patients experiencing adequate levels of pain relief, symptom relief, no recall for events associated with mechanical ventilation or extubation and minimal nausea.

The use of ketamine as a sole agent for sedation in ICU is not desirable, as the dose requirement for symptom control is high and may be associated with undesirable side effects, like restlessness, agitation, tachycardia with involuntary movements. Higher doses of ketamine alone can precipitate psychotic states in patients with schizophrenia or similar psychiatric disorders. We found that using sub-anesthetic doses of ketamine in combination with either low-dose fentanyl or midazolam, minimizes the incidence of psychotic symptoms in ICU patients. Occasionally, we supplement ketamine with low-dose dexmedetomidine infusion or quetiapine (Seroquel) in those who develop persistent psychotic symptoms [19]. We acknowledge that even low-dose ketamine and supplementary analgesic/sedative agents can precipitate unwanted medication-induced psychotic symptoms and other side effects, thus, continued close monitoring of postoperative ICU patients under this multimodal regimen is advised.

### Conclusion

We found this dose of ketamine and fentanyl combination with or without midazolam to be very effective in symptom control and pain relief in postoperative patients in the ICU. Compared to other pharmacological sedatives and pain management options, we found ketamine-fentanyl combination to provide superior pain relief, with minimal side effects in adult and geriatric patients.

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