Introduction
Agitation means excessive irritation and akathisia resulted from internal dysfunction or irritations (1 & 2). Agitation is a prevalent dysfunction in patients admitted at ICU. It is reported in %71 patients (2).
Agitation etiology is not well understood. Yet, among its factors are underling diseases, metabolic dysfunctions, pain, anxiety, and delirium (2). In agitation, patient’s movements are continuous and aimless. Invasive agitation can be dangerous. It can lead to patient’s disharmony with ventilator, oxygen consumption increase, unwanted separation of equipments and counters connected to patient, and further consequences and mortality (1 & 2).
Cardiac surgeries can be accompanied by neurological consequences due to factors such as cardiopulmonary pump and the probability of macro and micro embolus (6 & 7). Among neurological consequences, neuro-focal deficiencies, cognitive dysfunctions such as delirium, agitation, memory loss, concentration suppression, illusions, and delusion can be implied (3, 4 & 5).

Despite considerable attention paid to delirium issue in cardiac surgeries, these patients are barely examined with specific respect to agitation. Regarding the fact that there is no reliable preventive treatment for postoperative agitation, carrying out an applied study for coping with this dysfunction seems necessary. Numerous clinical and laboratory evidences show ketamine protective effects during topical and generalized cerebral ischemia (8-10), trauma (11), chronic cerebral hypoperfusion resulted from hypocapnia (12), and cerebral vasogenic (distributive) edema (13). Ketamine is a N-Methyl-D-Aspartate (NMDA) receptor antagonist. It alleviates neurons loss in cortex via preventing from injuries resulted from brain evoked response (14) and apoptosis after cerebral ischemia (9). It also maintains brain blood circulation via increasing sympathetic nervous system activity (11). Ketamine can also protect brain by hindering systemic inflammatory reactions and central nervous system (3). It also protects brain against post cardiac surgery cognitive dysfunctions in elders (15). Ketamine can also be effective in

The effect of Intravenous Ketamine during Cardiopulmonary Bypass on Postoperative Agitation

1 Mansoor Soltanzadeh*, MD, 2 Ahmad Ebadi, MD, 3 Mehdi Dehghani Firoozabadi, MD, 4 Seyyed Kamaladdin Tabatabee, MD, 5 Anahita Babaee, MD

1 Associate Professor, Anesthesia Department, Jundishapur University of Medical Sciences, Ahvaz
2 Associate Professor, Anesthesia Department, Jundishapur University of Medical Sciences, Ahvaz
3 Assistant Professor, Anesthesia Department, Jundishapur University of Medical Sciences, Ahvaz
4 Assistant Professor, Anesthesia Department, Jundishapur University of Medical Sciences, Ahvaz
5 Assistant, Anesthesia Department, Jundishapur University of Medical Sciences, Ahvaz

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*Corresponding Author
Mansoor Soltanzadeh
Associate Professor, Anesthesia Department, Jundishapur University of Medical Sciences, Ahvaz

e-mail: sultanman84@yahoo.com

Background and objective: Postoperative cognitive dysfunctions are prevalent in cardiac surgeries. Ketamine - as a NMDA (N-Methyl-D-Aspartate) receptor antagonist - exerts neuroprotective effects. We studied the effect of intravenous Ketamine on postoperative agitation during open-heart surgery.

Material Methods: In a double blind clinical trial, 40 males (at least 55 years) undergoing open heart surgery were randomly divided into 2 groups: intervention group (received 0.5 mg/kg IV ketamine before sternotomy and the same dose before pumping) and control group (the same volume of normal saline at the same interval). After the end of surgery, agitation signs were assessed by every 2 hours until 8h and then every 8 hours until 3 days.

Results: Incidence of agitation on 2nd and 3rd days after operation was significantly lower in patients received ketamine as compared to control group. In 6, 16, and 24h after surgery, again number of agitated patients in control group was higher than ketamine group. Yet, the difference was not significant.

Conclusion: Intravenous ketamine administration during open-heart surgery can reduce post-operative agitation by its neuroprotective effect.

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alleviating pain and increasing sleep depth at the time of sternotomy as well as in warming stage (in the end of placing patient on cardiopulmonary pump). This study determines the effect of intravenous ketamine during cardiopulmonary bypass surgeries on postoperative agitation in these patients.

**Materials and Methods**

In this double blind clinical trial, 40 male candidates (at least 55 years of age) of cardiopulmonary bypass via open heart surgery were selected. Patients’ mental and physical status was examined by neurological and psychological assessment a week before surgery. Omission measure included CVA history in three past years, the existence of permanent pacemaker, hepatic dysfunctions with AST and ALT higher than twice normal level, chronic kidney disease (serum creatinine >2), delirium incidence history a week before surgery, proved cognitive dysfunctions, taking drug for treating psychosis and drug abuse.

Patients were randomly divided into 2 similar groups: intervention and control groups. Intervention group received 0.5mg/kg ketamine twice; that is, first before sternotomy and second the same dose before pumping. Control group received %0.9 saline with the same volume and at the same time. All patients underwent medication with 0.1mg/kg intramuscular morphine and 0.5mg/kg intramuscular promethazine 30min before operation. Then, anesthetic induction was carried out by 0.15mg/kg diazepam, 3-10μg/kg fentanyl, 2mg/kg thiopental sodium, and 0.5 mg/kg atracurium or 0.15mg/kg Cis atracurium were administered. Nanasthetics also included 0.3 mg/kg atracurium or Cis atracurium, 50μg/kg/min propofol and %0.4-1.6 isoflurane.

All patients underwent the standard sternotomy of cardiac surgery. Heart protection includes using 15cc/kg cold hypercalcemic cardioplegic solution in 20min intervals (by the aids of normal saline) and systemic hypothermia (temperature on pump was 32℃). Blood flow speed on pump was 2.4-2.5l/min/m² and mean arterial blood pressure 60-80mmHg.

300unit/kg heparin was prescribed for systemic anticoagulation so as to keep active coagulation time over 480s. After surgery, 1.3mg protamine sulfate was administered for each 1mg heparin to return its effect.

All patients underwent postoperative agitation signs assessment every 2h during the first 8h after surgery and then every 8h until two days after operation (totally, 3 days). Assessment was carried out separately for each patient by experienced anesthesiology resident using Riker Sedation-Agitation Scale (SAS) (Table 1). Data was analyzed by SPSS19. Demographic data was compared using chi-square and Fisher exact test. Hemodynamic data and SAS score were compared between control and test groups in hours under study using t-test. Significance level was considered 0.05.

**Results**

Mean patients age was 61.27±5.85 (55-77 years old). Mean surgery time was 206.75±42.46min. There was no significant difference between two groups regarding mean age, class, and operation time (Table 2).

Patients’ neurological and psychological assessment results a week before surgery showed that none of them suffered from any known cognitive dysfunctions and neurological diseases. Postoperative agitation was examined by SAS during 72h after surgery. Based on SAS score>4, there was significant difference between ketamine and placebo groups regarding agitation in 32, 40, 48, 56, and 64h after surgery. That is, number of agitated patients was lower in ketamine groups (versus placebo group) (Table 3) (p<0.05). In 6, 16, and 24h after surgery, again number of agitated patients in control group was higher than ketamine group. Yet, the difference was not significant (p>0.05).

There was also no significant difference between two groups regarding heart rate and mean arterial blood pressure at the time of anesthetic induction, before pumping, after pumping, and before and after sternotomy (p<0.05) (Table 4).

Table 1: The sedation agitation scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Dangerously agitated</td>
<td>Pulls at ET tube, has physical reactions</td>
</tr>
<tr>
<td>6</td>
<td>Very agitated</td>
<td>Does not obey verbal commands</td>
</tr>
<tr>
<td>5</td>
<td>Agitated</td>
<td>Calm, awakens with verbal command</td>
</tr>
<tr>
<td>4</td>
<td>Calm, cooperative</td>
<td>Difficult to arouse</td>
</tr>
<tr>
<td>3</td>
<td>Sedated</td>
<td>Unresponsive or follow commands</td>
</tr>
<tr>
<td>2</td>
<td>Very sedated</td>
<td>Minimal or no response</td>
</tr>
<tr>
<td>1</td>
<td>Unarousable</td>
<td>No response</td>
</tr>
</tbody>
</table>

Abbreviation: ETT, Endotracheal tube.

Table 2: Comparing demographic data and operation time between two groups under study

<table>
<thead>
<tr>
<th></th>
<th>Ketamine</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>60/55±5/48</td>
<td>62/00±6/27</td>
<td>0/44</td>
</tr>
<tr>
<td>Mean execution time</td>
<td>208±46/97</td>
<td>205/5 ±38/62</td>
<td>0/85</td>
</tr>
<tr>
<td>ASA Class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class 1</td>
<td>%0</td>
<td>%5</td>
<td>0/59</td>
</tr>
<tr>
<td>Class 2</td>
<td>%85</td>
<td>%80</td>
<td></td>
</tr>
<tr>
<td>Class 3</td>
<td>%15</td>
<td>%15</td>
<td></td>
</tr>
</tbody>
</table>
NMDA receptor non-competitive antagonist, ketamine can suppress brain ischemia by several mechanisms. First, it can prevent from cells necrosis by inhibiting brain evoked response injuries (14 & 19). Ischemic neurons release glutamate into extracellular space. It leads to NMDA receptor hyperactivity and cells death (20). Ketamine protects brain by temporarily inactivating these receptors. Then, receptors are barely apt to activation after ischemia and reperfusion (15). Second, ketamine changes apoptosis-regulating proteins (9). Apoptosis can alleviate cerebral ischemia intensity. Third, ketamine can disrupt cerebral and systemic inflammatory response to cardiac surgery (21). It seems that inflammatory response plays a critical role in neural damage after cardiopulmonary bypass (3). Ketamine suppresses IL6 response after cardiopulmonary bypass (22). It also hinders TNFα, IL6, and IL8 production mediated by lipopolysaccharides (23). Ketamine controls kB nucleus factor participating in copying proinflammatory cytokine codifying genes (24 & 25).

In texts review, no studies were found specifically examining the effect of ketamine on postoperative agitation. Yet, several clinical trials have been carried out on human using NMDA receptor antagonists regarding ischemic cerebral injuries and cognitive dysfunctions (15, 16, 26, and 27). Arrowsmith et al studied remacemide (a NMDA receptor antagonist) effect on neuroprotection of brain after cardiopulmonary bypass (26). In that study, despite low number of patients manifested neuro-psychological dysfunction, significant patients’ improvement was observed totally in three out of nine tests. Hudetz et al carried out two studies on the effect of ketamine on cognitive dysfunctions and delirium after cardiac surgery. They have approved the effect of intravenous ketamine on brain protection and reduction of cognitive dysfunctions (15). In our study, patients had similar hemodynamic status in both groups. It may indicate that the reduction of postoperative agitation in intervention group is not resulted from changes in cerebral blood flow. Here, we used low dose of ketamine. This is because it was shown in previous studies that ketamine anti-inflammatory response is seen in lower doses as compared to dose required for anesthesia. High doses of ketamine are not recommended due to cardiovascular and psychotropic consequences (22, 28, and 29).

**Discussions**

Based on results, intravenous ketamine during cardiac surgery significantly suppresses postoperative agitation on the 2nd and 3rd days as compared to control group. Although again agitation cases in ketamine group were less than control group during the first 24h after surgery, the difference was insignificant. Postoperative cognitive dysfunctions can be a combination of neural injuries resulted from surgery stress, inflammatory responses, coagulation increase, anesthetics, and factors related to hospital environment (16).

Ketamine is bound to phencyclidine bind locus on NMDA receptor (17). This receptor has also other loci for binding to glutamate and glycine. It allows sodium and calcium to enter into cell by the aids of ion channels (18). As a competitive antagonist, ketamine can suppress brain ischemia by several mechanisms. First, it can prevent from cells necrosis by inhibiting brain evoked response injuries (14 & 19). Ischemic neurons release glutamate into extracellular space. It leads to NMDA receptor hyperactivity and cells death (20). Ketamine protects brain by temporarily inactivating these receptors. Then, receptors are barely apt to activation after ischemia and reperfusion (15). Second, ketamine changes apoptosis-regulating proteins (9). Apoptosis can alleviate cerebral ischemia intensity. Third, ketamine can disrupt cerebral and systemic inflammatory response to cardiac surgery (21). It seems that inflammatory response plays a critical role in neural damage after cardiopulmonary bypass (3). Ketamine suppresses IL6 response after cardiopulmonary bypass (22). It also hinders TNFα, IL6, and IL8 production mediated by lipopolysaccharides (23). Ketamine controls kB nucleus factor participating in copying proinflammatory cytokine codifying genes (24 & 25).

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**Conclusion**

Prescribing intravenous ketamine during cardiopulmonary bypass can lead to protective effects on patients’ brain and cardiopulmonary pump. As a result, it reduces postoperative agitation.

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**References**

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