Original Article

The Effect of Low-Dose of Ketamine Infusion on Stress Responses in Coronary Artery Bypass Graft Surgery

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Background: Open heart surgery is associated with acute perioperative changes in plasma levels of neurohormonal stress factors,cortisol,interleukin-6 and C-reactive protein. Human studies involving cardiopulmonary bypass have shown that very low doses of ketamine can attenuate the markers of inflammation without adverse effects. The aim of this study was to investigate whether, low dose infusion of ketamine when administered during 48 hours after induction , have anti-inflammatory effect and attenuate stress factors, in on-pump coronary artery bypass graft surgery.

Methods: In this prospective randomized-controlled trial, 50 patients undergoing on-pump coronary artery bypass graft were randomly assigned to receive either 1.25mcg/kg/min of ketamine (Ketamine group, n=25) or normal saline (Control group, n=25) infusion during and for 48 hours after surgery. Inflammatory and stress response markers including C-reactive protein, cortisol, White blood cell count and differential , glucose and lactate level were measured ,before induction (T1), 4 hours after surgery (T2), and on the first and the second days after surgery (T3 and T4).

Results: The level of lactate were higher in ketamine compared with control group four hours after operation ($P< 0.05$) without any significant differences detected in other measurements.

Conclusion: Low dose ketamine did not cause any change in C-reactive protein, cortisol, White blood cell count and glucose level, however lactate level was higher compared to control group.

Keywords: Low dose, Ketamine, Stress response, Coronary artery, Bypass

Introduction

In cardiac surgery, the degree of systemic inflammatory response is closely associated with patient's outcome. A systemic inflammatory response syndrome (SIRS) may develop after operations using cardiopulmonary bypass (CPB). This pathophysiologic entity reflects a hyperdynamic circulatory state including an increased cardiac output in the presence of reduced systemic vascular resistance (SVR), requiring treatment by vasoconstrictive agents and fluid replacement. In historic patients suffering from SIRS, subsequent lactic acidosis occurred in the majority of them with increasing risk for multiorgan failure and postoperative infectious complications. Deleterious effects of CPB have been reported repeatedly.[1]

Open heart surgery is associated with acute perioperative changes in plasma levels of neurohormonal stress factors. A significant rise in cortisol levels in the early postoperative phase has been shown in patients, with a partial recovery toward baseline values observed 24 hours postoperatively.[2] The secretion of pro and anti-inflammatory cytokines mediate the inflammatory cascade. Interleukin-6 (IL-6) and C-reactive protein (CRP) are markers of systemic inflammation.[3] In addition, the immune system and the nervous system communicate bidirectionally and it has been suggested that nociception and proinflammatory cytokines play a mutual up-regulatory role. Thus, increased production of proinflammatory cytokines may exacerbate pain, and vice versa. Therefore, it is conceivable that effective pain management may affect the immune responses during the postoperative period.[4]

Low dose ketamine demonstrated anti-inflammatory effect in some studies, but could not re-

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duce inflammatory mediators according to other reports.[4,5] It has been shown that small doses of ketamine exert analgesic action in the early stages of formation of pain stimuli.[4] Therefore, it may be useful in inducing pre-emptive anaesthesia and reduction of narcotic consumption.[6] The question of whether ketamine, in addition to its beneficial effect as a pain reliever, may attenuate the immunosuppressive effect of opioids in patients exposed to surgery is of interest to the clinician. Roytblat and colleagues have reported a decrease in serum IL-6, an activator of the inflammatory cytokine cascade, in patients undergoing coronary artery bypass surgery.[7, 8] Elevated blood lactate levels associated with metabolic acidosis are common among critically ill patients with systemic hypoperfusion and tissue hypoxia. Therefore, blood lactate level in type A lactic acidosis is related to the total oxygen deficiency and the magnitude of tissue hypoperfusion.[9]

So we evaluated the effect of low dose of ketamine on stress markers and tissue perfusion in patients undergoing on-pump coronary artery bypass surgery (CABG) in a prospective, randomized and controlled trial

Patients and Methods

This study was approved by the anesthesia investigation center of Shiraz University of Medical sciences. All the patients were informed and had given written consent. Fifty patients scheduled for elective CABG surgery with cardiopulmonary bypass and younger than 75 years of age were considered eligible for the study. Exclusion criteria were those with renal or hepatic insufficiency (Serum Creatinin >1.3mg/dl ,AST/ALT >2.5 × normal) , psychological problem, diabetes ,opioid addiction, acute infections, low ejection fraction (EF<40%) and reoperations. Patients who could not be weaned from mechanical ventilation within 14 hours after surgery and those who underwent a combined cardiac operation including valvular surgery were also excluded from the study.

Using a computer-generated randomization method, patients were randomly assigned to receive either continuous infusion of ketamine 1.25mcg/kg/min (ketamine group,n=25) or equivalent volume of normal saline(control group,n=25).The infusion started just before induction of anesthesia and continued for 48 hours. The infusions were administered with a syringe with an equal appearance and infusion rate (KETAMINE Hydrochloride, ROTEXMEDICA®, Germany). The code remained blinded until the end of the study. The dose estimation of S (+)-ketamine was based on the previous studies.[6, 10]

Patients were pretreated with intra muscular morphine 0.05-0.1 mg/kg 1h before anesthesia. Upon arrival in the operating room five leads ECG were attached, and leads II and V5 were continuously monitored. A 20 G radial artery catheter was inserted for continuous monitoring of arterial pressure. Central venous pressure (ARROW® catheter, Germany) was inserted into the right internal jugular vein before induction of anesthesia. Nasopharyngeal temperature probe was inserted (mode of monitor: DATEX, OHMEDA® S/5-Finland). A standardized anesthesia protocol was used for all patients. The anesthetic drug doses were calculated according to body weight, as described in the previous studies.[6]

Anesthesia was induced with midazolam 0.03-0.05 mg/kg , sufentanil 1.5-2.0 mcg/kg , sodium thiopental 1-2mg/kg . Pancruniom bromide 0.15 mg/kg was administered to facilitate tracheal intubation . Anesthesia was maintained by continuous infusion of propofol 50-150 mcg/kg/min and remifentanil 0.1-1.0 mcg/kg/min.

Nasopharyngeal temperature was maintained at 32º -34ºC throughout cardiopulmonary bypass. Intravascular volume replacement was managed with equivalent amount of crystalloid and colloid solutions to maintain a central venous pressure of 8-16 mmHg according to baseline values.

Neither corticosteroid nor anti-inflammatory drugs were used in any patients.

All surgical procedures were performed through a standard midline sternotomy ,with harvesting the saphenous vein and the use of left internal mammary artery . Inflammatory and stress markers including CRP, cortisol,WBC count (including total, monocyte, neutrophil) , glucose and lactate levels were determined before induction of anesthesia(T1), 4 h(T2) ,24 h(T3) and 48 h(T4) after completion of the anastomoses (CRP and Cortisol by ELISA microwells HUMAN® Germany and Glucose,Lactate by biosensor assay GEM Premier-3000-5700-US).

All samples were obtained through the arterial line and prepared immediately for biochemistry assays.

Statistical analysis

The data were statistically analyzed using student's t- test and chi- square or fisher exact test, whenever applicable (with a preset probability of $P< 0.05$) and considering of variance equality with Leven test. Experimental results are presented as arithmetic mean ± SD for continuous variables, female to male ratio and the ratio of yes to no for Inotrop using and bleeding state for operation time. Normality of parameters distribution was evaluated with kolmogrov-smirnov test.

The tests of within-subject contrasts were done for break down the main effect and interaction. Contrasts were compared at each level of post operation time (4, 24 and 48 hours) and so compared to before operation between ketamine and placebo patients.

Table 1. Characteristics of patients in ketamine and placebo group

variables	Ketamine group (N=25)	Placebo group (N= 25)	P value
Number of graft(median)	3	3	0.861
Age (Mean ± SD)	59.74 ± 7.96	63.7 ± 8.07	0.063
BMI (Mean ± SD)	25.98 ± 3.45	24.15 ± 2.39	0.033
Inotrop using (yes/no)	11/14	13/12	0.571
Bleeding (yes/no)	19/6	14/11	0.136
Intubation time (Mean ± SD)	8.5 ± 2.51	9.44 ± 3.05	0.24^{0}
Duration of surgery (Mean ± SD)	185±21.01	186.12±**16.66**	$o.87^{0}$
Pump time(mean ± SD)	67.96 ± 14.29	67±11.83	0.795
Gender(female/male)	11/4	12/93	0.678

Assumption of sphericity was violated in muchly test ($p< 0.05$) for glucose, CRP, WBC (including total, monocyte, neutrophil) and Cortisol and therefore average p-value of these assumptions was reported after adjustment of degree of freedom by correlation coefficient of Greenhouse – Gisser and Huynh- Feldt. Statistical analyses were performed using SPSS version 16 soft ware.

Result

Fifty- five patients were recruited and randomized, but five of these were excluded. In three patients intubation time was more than 14 hours and two patients had repeat operation

Characteristic data including sex, age, weight, height, BMI, inotrop need, number of grafts, duration of surgery, duration of CPB, amount of bleeding after surgery and intubation duration are shown in Table 1. Only the difference in BMI, between two groups were statistically significant ($P<0.05$).

Difference in trend of lactate level change was statistically significant between placebo and ketamine group ($P=0.035$). Also Four hours after operation, the patients in the ketamine group showed a statistically significant increase in the lactate level as compared with before operation ($P=0.024$), but

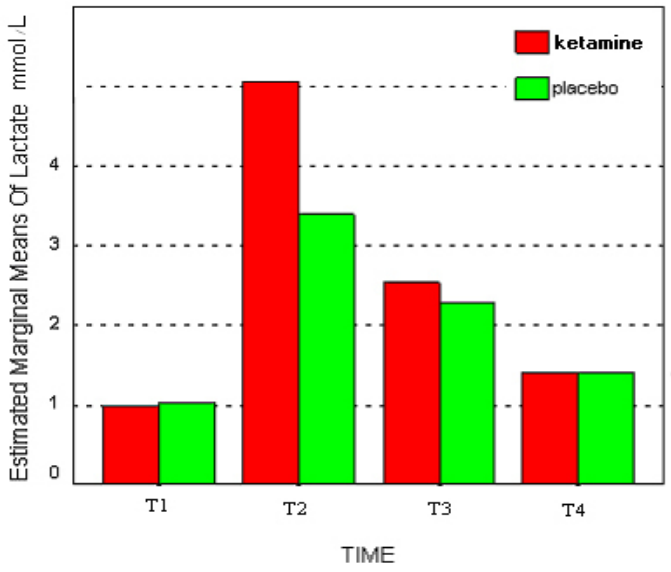

Figure 1. lactate level in ketamine and placebo group, before, 4hr, 24hr and 48hr after surgery

Table 2. level of inflammatory markers in ketamine and placebo group(4 periods)

Parameter	Effect	T1	T2	T3	T4	Pvalue
Lactate (mmol/l)	ketamine	0.87±25	5.2±3.05	2.48±1.04	1.39±0.36	0.035
	placebo	1.15±0.68	3.24±1.45	2.36±0.24	1.43±0.48	
Glucose (mg/dl)	ketamine	108.52±9.2	240.24±78.51	151.48±49.97	119.76±11.21	0.566
	placebo	113.44±53.44	222.92±32.24	162.28±30.72	120.68±13.06	
CRP (mg/dl)	ketamine	9.66±16.25	13.08±15.48	59.37±14.35	22.76±10.22	0.311
	placebo	9.88±16.02	12.68±15.68	55.1±20.33	29.75±13.51	
WBC (/µ l)	ketamine	6256±1224.09	14296±3080	12896±4259.74	9096±2836.29	0.187
	placebo	5128±1395.68	14568±4095.5	10968±3171.32	7516±1556.35	
Cortisol (ng/ml)	ketamine	176.86±163.14	437.24±160.1	518.54±243.13	107.92±126.33	0.437
	placebo	102.6±63.08	372.59±180.64	198.56±98.15	108.92±56.98	

CRP=C reactive protein WBC=White blood cell T1=Before Operation T2= 4 hour after operation
T3= 24 hour after operation T4=48 hour after operation

there was no significant difference in regard to 24 hr post-operation (P=0.356) and 48 hr after surgery between placebo and ketamine group (P=0.768). (Fig 1)(Table2)

There were not significant interaction effects between the time and the groups of patients in trend of stress markers consist of CRP (P=0.311), Cortisol (P= 0.437), Glucose (P= 0.566), WBC (P= 0.187), Monocyte (P=0.427), and Neutrophils count (P=0.483). (Table 2) Differences between levels of stress markers in before with 4 hr, 24 hr, and 48 hr after surgery were similar in ketamine and placebo groups. (P> 0.05)

Discussion

The postoperative period is associated with neuroendocrine, metabolic, and immune alterations, which are the combined result of tissue damage, anesthesia, postoperative pain, and psychological stress.[11] Suppression of immune defense mechanisms has been demonstrated in the postoperative period. Cardiopulmonary bypass has been recognized as the main cause of inflammatory activation .[12]

Cardiopulmonary bypass is accompanied by acute perioperative changes in plasma levels of leptin and cortisol. A significant rise in cortisol levels has been shown in the early postoperative phase.[2]

Anti-inflammatory effects of ketamine are thought to be mediated through inhibition of nuclear factor (NF)-KB, which regulates the transcription of genes that encode the production of pro-inflammatory cytokines.[13] Indeed, anti-inflammatory effects of ketamine has been well demonstrated mainly in terms of reducing the activity of proinflammatory mediators, such as CRP and IL-6.[14, 8] Even a small dose of ketamine administered during induction of anesthesia significantly decreased IL-6 and CRP in cardiac surgical patients undergoing CPB.[14]

The present study tested the hypothesis that intraoperative infusion of low dose of NMDA receptor antagonist ketamine would attenuate the development of CPB- induced inflammation and improve tissue perfusion.

Findings of the present study indicated no significant effect of ketamine infusion on serum concentration of inflammatory markers` including cortisol, glucose, CRP, and WBC count in patients undergoing CABG. However, a significant undesirable effect on the lactate level as a marker of tissue hypoperfusion was detected especially in the early hours after operation.

Some studies have shown that ketamine is able to modulate the immune responses and attenuate inflammation [4]or reduce postoperative pain [10]and hence suppression of lymphocyte proliferation and proinflammatory factors.[7]

Also in one study low dose of ketamine (0.5mg/kg) administered during general anesthesia decreased the inflammatory responses to CPB in high risk cardiac surgery patient[3], However, in another study in off-pump CABG, low dose of ketamine (0.5 mg/kg) could not reduce the inflammatory responses.[5]

Even though in the present study the method of ketamine administration differed from the two previous studies, its results indicated that low dose of ketamine infusion did not suppress stress markers nor provided hemodynamic stability in patient undergoing elective on-pump CABG surgery;but it could even impair tissue perfusion , on the basis of increasing lactate level.

The ketamine dose administered in this study was based on a previous research which approved ketamine as an analgesic adjunct.[6]

The most important limitation in the use of ketamine for compromised cardiac patients is determination of the dose of ketamine that provided

anti-inflammatory effects without derangement in the hemodynamic status. It has been proven that higher doses of ketamine cause increased myocardial oxygen demand and results in hemodynamic disturbances.[15]

Also, anti--inflammatory effects of ketamine is dose-dependant.[16] The effective anti-inflammatory dose of ketamine has untoward hemodynamic abnormality. Further studies on optimizing ketamine dose, are warranted to establish its anti- inflammatory and hemodynamic stabilizing effect in patients undergoing cardiac surgery.

On the basis of inflammatory and stress response markers measurement, low-dose infusion of ketamine, administered for 48 hours after induction of anesthesia, did not exert any apparent anti-inflammatory effect in patients undergoing on-pump coronary bypass graft surgery. On the other hand, we can claim that, low dose Ketamine infusion , did not play a positive role on tissue perfusion on the basis of lactate level increment.

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