Original Article

Effect of ketamine on pro- and anti-inflammatory cytokine response in paediatric cardiac surgery: A prospective randomised controlled study

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ABSTRACT

Background and Aims: Paediatric cardiac surgery with cardiopulmonary bypass (CPB) is associated with a marked inflammatory response and triggers release of inflammatory cytokines. The aim of this study was to study the effect of ketamine on the inflammatory response during correction of congenital cyanotic heart diseases. **Methods:** Sixty-six patients with congenital cyanotic heart diseases scheduled for cardiac surgery were randomised into three groups. Group A patients did not receive ketamine (control group), Group B patients received 2 mg/kg ketamine intravenous (IV) and Group C patients received ketamine 2 mg/kg IV and an IV infusion of ketamine (50 μg/kg/min). Interleukin (IL) levels for IL-6, IL-8, IL-10, C-reactive protein (CRP) and tumour necrosis factor-α (TNF-α) levels were examined in the three groups at four timings: pre-operative (baseline), intraoperative (after weaning off the CPB) and post-operative (6 and 24 h after weaning off CPB). Paired sample *t*-test and ANOVA test were used for statistical analysis and $P < 0.05$ was considered statistically significant. **Results:** Within each group, the intra- and post-operative serum levels of IL-6, IL-8, IL-10 and CRP were significantly elevated from the baseline, however, TNF-α was not significantly elevated. There were no statistically significant differences in the IL, CRP or TNF-α levels between the three groups. **Conclusion:** Paediatric cardiac surgery for congenital cyanotic heart disease is a triggering factor for the inflammatory response, yet we could not detect any beneficial effect of ketamine on that response whether given either as an IV induction dose or continued as an IV infusion.

Key words: Cardiac surgical procedures, congenital heart defects, interleukins, ketamine

INTRODUCTION

Surgery for congenital heart defects requires cardiopulmonary bypass (CPB) and evokes an acute systemic inflammatory response with the activation of cellular and humoral cascades that can lead to organ failure and increased post-operative morbidity.[1] Causes and clinical appearance of the systemic inflammation after cardiac surgery are not well understood. The inflammatory response to CPB is often evaluated using inflammatory markers such as cytokines, acute phase proteins and white blood cells in the peripheral blood. The most important cytokines related to cardiac surgery are tumour necrosis factor-α (TNF-α), interleukin (IL)-6, IL-8 and IL-10, that are studied in blood samples[2] or bronchoalveolar fluid.[3]

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Cytokines are regulators of host responses to infections, inflammation and trauma. Some cytokines act to make the disease worse (pro-inflammatory) as IL-6, IL-8 and TNF α. Others serve to reduce inflammation and promote healing (anti-inflammatory). IL-10[4] is a potent anti-inflammatory cytokine produced by monocytes and macrophages and inhibits production of pro-inflammatory cytokines as IL-6 and IL-8.[5] Ketamine influences the immune response by interfering with cytokine balance.[6] It reduced TNF-α production in mice immune-stimulated with lipopolysaccharide and reduced the production of IL-6 and IL-8.[7] The ratio between IL-6 and IL-10 was used to evaluate the magnitude of the inflammatory response. Ketamine-induced a significant lowering of this ratio which means that ketamine has a dominant anti-inflammatory effect.[8]

The aim of this study was to examine if ketamine alone could modulate the pro- and anti-inflammatory cytokine response in cardiac surgical procedures for patients with congenital cyanotic heart disease. The primary outcome was the effect of ketamine on IL-6 levels in blood, and secondary outcomes included levels of IL-8, IL-10, TNF-α and C-reactive protein (CRP).

METHODS

This prospective randomised controlled study approved by the Hospital Institutional Review Board and registered with the Australian New Zealand Clinical Trial Registry on 13/05/2015 (registration number: ACTRN12615000468527). Written informed consent was obtained from patient's parents.

Patients were randomised using block randomisation technique and a research randomiser program; each patient was given a particular code number which was applied to the laboratory tubes and was different from his/her medical number. These numbers were determined by the anaesthesiologists in the research team so that the laboratory team was blinded to patient's data. Allocation concealment to groups was performed using sealed envelope technique.

Patients younger than 5 years with congenital cyanotic heart disease, baseline oxygen saturation 70%–85% and admitted for cardiac surgery with CPB were included. Patients with recent pre-operative infection, elevated baseline CRP levels, on steroid therapy or having surgery requiring total circulatory arrest were excluded from the study.

Patients were randomised into three equal groups each with 22 patients. Group A (control group) included patients who did not receive ketamine. Group B included patients who received only an induction dose of ketamine 2 mg/kg intravenous (IV), while Group C included patients who received induction doses of ketamine 2 mg/kg IV and ketamine IV infusion 50 μg/kg/min started after induction of general anaesthesia and continued till weaning off bypass. Baseline IL-6, IL-8, IL-10, TNF α and CRP were measured 1 day before surgery. Demographic data as patient's age, sex and weight were recorded.

Patients were sedated preoperatively with 0.5 mg/kg midazolam syrup orally 30 min before the operation. In the operation room, patients received additional doses of IV midazolam 0.05–0.1 mg/kg if needed, monitored by electrocardiogram, pulse oximeter and non-invasive blood pressure. Anaesthesia for patients in Group A was induced with fentanyl 1–2 μg/kg IV, etomidate 0.2 mg/kg IV and the tracheal intubation facilitated with rocuronium 0.5 mg/kg IV, while Groups B and C were given ketamine 2 mg/kg IV, in addition. Patients received cefazolin 40 mg/kg IV within 60 min before surgical incision and repeated every 4 h intraoperative. Central venous and arterial catheters were inserted, nasal and rectal temperatures were monitored. Anaesthesia was maintained with sevoflurane 1%–2% and additional doses of fentanyl IV and rocuronium IV. Group C patients were maintained on ketamine IV infusion 50 μg/kg/min started after induction of anaesthesia till weaning the patients off bypass. None of our patients received steroids intraoperatively or within the first 24 h postoperatively.

Anticoagulation was achieved by heparin 4 mg/kg IV. CPB circuit was primed with blood (200–300 mL packed red blood cells), 500–1000 mL crystalloids (lactated ringer and normal saline) and 75–150 mL human albumin 20%. Patients were cooled to an average temperature of 32°C–34°C. Milrinone infusion 0.5 μg/kg/min IV was started in all patients with the initiation of the bypass and continued all through the procedure and in the Intensive Care Unit (ICU).

After coming off bypass, anticoagulation was reversed with protamine sulphate 4 mg/kg IV. Post-bypass samples for IL-6, IL-8, IL-10, TNF-α and CRP were collected. Ketamine IV infusion was turned off in Group C patients. In the cardiac surgery ICU, the third and fourth set of inflammatory markers and cytokines were extracted 6 h and 24 h after coming off CPB, respectively.

Each blood sample was collected in a coded red-top tube (CAT-BD vacutainer, NJ, USA). Serum concentration of IL-6 was determined using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Invitrogen, CA, USA). IL-8, IL-10 and TNF-α serum levels were determined using ultrasensitive ELISA kits (Invitrogen, CA, USA). All four markers were analysed on the fully automated microtitre plate analyser (ETI-Max3000, DiaSorin, Germany). CRP level was determined using high sensitive assay kit that was performed on the Chemistry analyser (Cobas C501, Roche Diagnostic, Germany).

Sample size calculation revealed that at least 22 patients were needed in each group to detect a difference of at least 25% of mean IL-6 with a power of 0.85 and significance level of 0.05, assuming that the mean and standard deviation of IL-6 (our primary outcome) in patients with congenital cyanotic heart disease is 19 pg/ml and 4.7 pg/ml, respectively.[9-11]

Within each group, the baseline levels were compared to the levels after coming off bypass, 6 and 24 h after using the paired sample *t*-test while ANOVA test was used to compare results in between the three groups. The significance was identified by the $P < 0.05$ was considered statistically significant.

RESULTS

Between July 20, 2015, and December 10, 2015, 66 patients with congenital cyanotic heart disease were randomised and included in the study. Twenty-six patients with Tetralogy of Fallot, 23 with double outlet right ventricle, 6 with transposition of great vessels, 5 with pulmonary atresia, 3 with tricuspid atresia and 3 with truncus arteriosus were included.

Demographics are presented in Table 1. There were no significant differences between the three groups. Cytokines levels were measured in pg/mL, and data were represented as a mean and standard deviation.

IL-6 levels in the three groups were significantly elevated from the baseline levels reaching its maximum 6 h after coming off bypass, yet the differences in-between the groups were non-significant [Figure 1].

In Group (A), baseline levels were 22.018 ± 7.44 and increased after coming off bypass to 208.83 ± 47.21 ($P = 0.001$) then 226 ± 53.33 ($P < 0.001$) and 210 ± 46.05 ($P = 0.001$) at 6 and 24 h after coming off bypass, respectively. In Group (B), baseline levels were 10.71 ± 2.77 and increased to 102.00 ± 12.01 after coming off bypass ($P < 0.001$), then 310.18 ± 46.14 ($P < 0.001$) and 258.05 ± 27.9 at 6 and 24 h after bypass respectively ($P < 0.001$). In Group (C), IL-6 levels were 14.91 ± 4.94 at baseline, 115.55 ± 13.34 ($P < 0.001$) after coming off bypass then 366.14 ± 41.38 ($P < 0.001$) and 327.33 ± 36.16 ($P < 0.001$) at 6 and 24 h after coming off bypass, respectively.

IL-8 levels increased significantly reaching its peak 24 h after coming off bypass however differences in the IL-8 levels between the three groups were non-significant [Figure 2].

Table 1: Demographic data, bypass time, operation room time, Intensive Care Unit stay and types of lesions

Characteristic	Group A	Group B	Group C	*P*
Age (years)	2.89±0.85	2.67±0.61	1.91±0.42	0.542
Sex (male/female)	11/11	14/8	10/12	0.401
Weight (kg)	11.53±2.38	10.5±1.47	9.75±1.26	0.778
Bypass time (min)	98.74±47.47	69.84±28.61	73.53±29.82	0.111
OR time (h)	4.66±1.28	4.16±0.7	4.44±1.1	0.347
ICU stay (days)	2.1±0.83	1.72±0.77	3.53±1.38	0.249
Types of lesions (number of patients)				
Tetralogy of Fallot	8	8	10	0.721
Double outlet right ventricle	8	8	7	0.776
Transposition of great vessels	3	1	2	0.145
Pulmonary atresia	2	2	1	0.119
Tricuspid atresia	0	1	2	0.204
Truncus arteriosus	1	2	0	0.226

OR time – Total time in OR from patient in room to the point patient is out of the room; ICU stay – Total duration of ICU stay. ICU – Intensive Care Unit, OR – Operation room

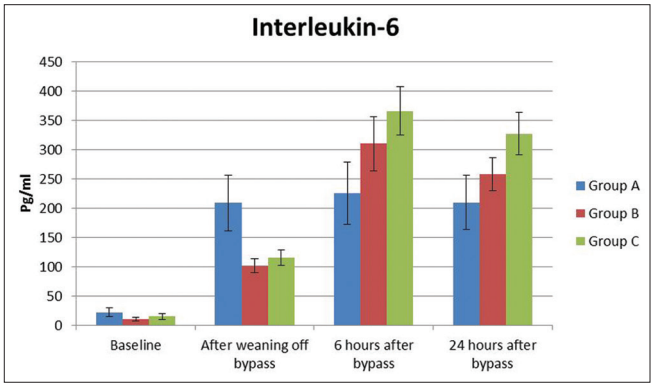

Figure 1: Interleukin 6 results: The significant increase of interleukin-6 levels within each group as compared to the baseline with the maximum increase at 6 h post-operative, however there were no statistically significant findings when the three groups were compared together at each of the four points of measurement (*P* values: baseline = 0.33, after weaning off bypass = 0.13, 6 h after bypass = 0.67 and 24 h after bypass = 0.21)

IL-10 levels became maximally and significantly elevated immediately after weaning off bypass in the three groups then started to decrease. However, the differences between the three groups were non-significant [Figure 3].

In the three groups, TNF-α did not change significantly at any time compared to the baseline levels. Furthermore, the differences between the groups were non-significant [Figure 4].

CRP response to inflammation was delayed compared to IL response as CRP levels remained nearly as the baseline levels and became maximally and significantly elevated 24 h after coming off bypass. Differences between CRP levels of the three groups were non-significant [Figure 5].

DISCUSSION

CPB promotes the secretion of pro- and anti-inflammatory cytokines which mediate an inflammatory response in cardiac surgery. Triggering factors include surgical trauma, endotoxemia and the contact of blood with non-biologic tubing surfaces releasing ILs such as IL-6, IL-8, IL-10 and TNF-α.[12]

The inflammatory response after CPB in adult cardiac surgery is well described, and the effect of ketamine on such response was examined in some studies. Although the inflammatory response is reported to be more pronounced in the paediatric cardiac surgery as a greater portion of blood is exposed to the artificial surface of the circuit and the cardiotomy suction,[13]

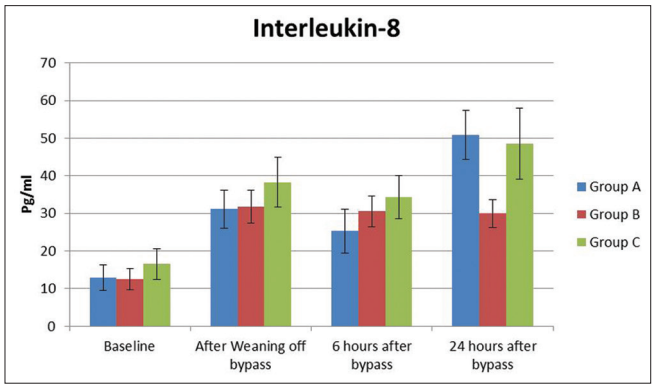

Figure 2: Interleukin-8 results: The significant increase of interleukin-8 levels within each group as compared to the baseline reaching the maximum levels 24 h post-operative, however, there were no statistically significant findings when the three groups were compared together at each of the four points of measurement (*P* values: baseline = 0.65, after removing off bypass = 0.61, 6 h after bypass = 0.85 and 24 h after bypass = 0.14)

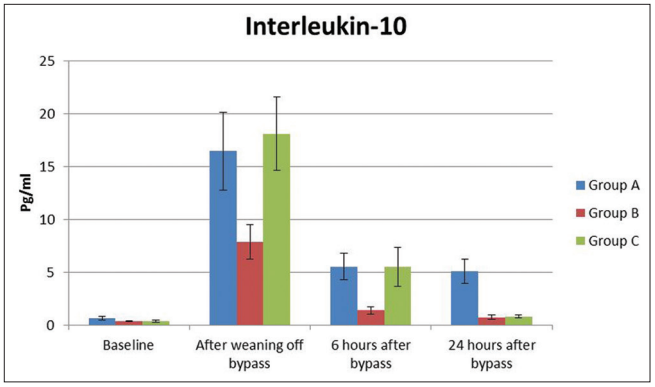

Figure 3: Interleukin-10 results: A maximum increase of interleukin-10 levels in the three groups immediately after weaning off bypass then the levels started to drop again but was still significantly higher than the baseline, however, there were no statistically significant findings when the three groups were compared together at each of the four points of measurement (*P* values: baseline = 0.18, after weaning off bypass = 0.15, 6 h after bypass = 0.17 and 24 h after bypass = 0.33)

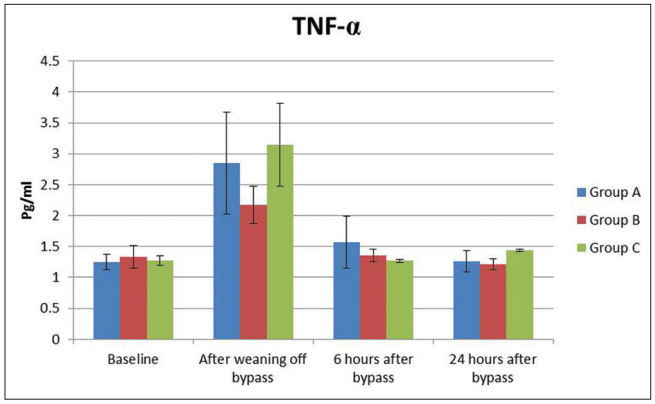

Figure 4: Tumour necrosis factor-α results: The non-significant changes of the tumour necrosis factor-α levels in the three groups when compared to the baseline levels, in addition, comparing the three groups together at the four points of measurement the results were also non-significant (*P* values: baseline = 0.92, after weaning off bypass = 0.85, 6 h after bypass = 0.77 and 24 h after bypass = 0.62)

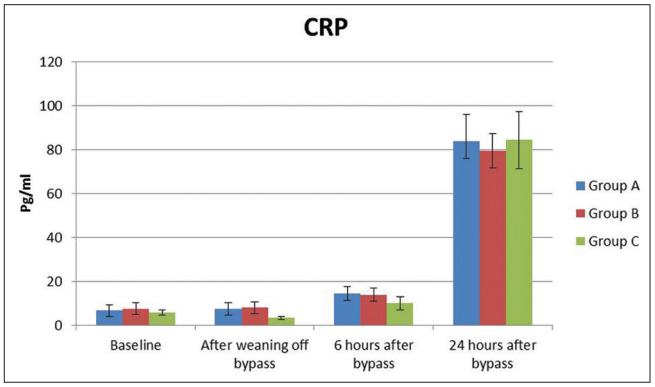

Figure 5: C-reactive protein results: A significant increase in C-reactive protein levels in the three groups 24 h after bypass reflecting a delayed response compared to the other markers, however, there was no statistically significant findings when the three groups were compared together at each of the four points of measurement (*P* values: baseline = 0.88, after weaning off bypass = 0.41, 6 h after bypass = 0.76 and 24 h after bypass = 0.95)

only a few studies examined this inflammatory response and the effect of ketamine on it in paediatric cardiac surgery.

IL-6 concentration is a good indicator of activation of the inflammatory cascade and a predictor of subsequent organ dysfunction and death.[14] It has been associated with negative inotropic effects[15] and myocardial stunning.[16] It has been suggested that the acute cardio depressant effect of cytokines is related to the enhanced production of nitric oxide (NO).[17]

We examined the inflammatory and anti-inflammatory cytokines response to paediatric cardiac surgery for cyanotic heart diseases and the effect of two different doses of ketamine on that response.

Our results demonstrate that cardiac surgery with CPB is a major initiating factor for the inflammatory response which was evident by the significant increase of IL-6, IL-8, IL-10 and CRP in the three groups.

TNF-α was the only marker non-significantly elevated in response to CPB.

However, we could not prove any beneficial effect of ketamine on the inflammatory response as the inflammatory markers in both Groups (B) and (C) follow the same trend as in Group (A). The difference between these markers in the three groups was non-significant.

In 2012, Dale *et al*. published a systematic review of 6 studies including 331 adult patients (four studies performed for patients undergoing coronary artery bypass grafting (CABG) and two studies for patients undergoing major abdominal surgery). They found that intraoperative ketamine administration significantly inhibited the early post-operative IL-6 inflammatory response.[18] Ketamine was given at a dose 0.15–0.25 mg/kg with induction in 5 studies and 1–3 mg/kg in the sixth study. IL-6 levels were assessed in 5 studies up to 5 h post-operative and in one study it was extended up to 48 h. In spite that this systematic review concentrated only on IL-6, they reported that CRP, TNF-α and IL-8 were also examined in some studies but their concentrations either did not show differences or decreased in a fashion similar to IL-6 in ketamine-treated patients while IL-10 levels increased in two studies.[18]

Welters *et al*. investigated the anti-inflammatory effects of ketamine in patients undergoing elective CABG. Patients received induction dose of ketamine 1–3 mg/kg and were kept on ketamine infusion 2–4 mg/kg/h. Blood samples for IL-6, IL-8, IL-10 and TNF-α were obtained before induction of anaesthesia, 1, 6 and 24 h after unclamping. The results were compared to a placebo group in which no ketamine was administered. Post-operative IL-6, IL-8 and IL-10 levels increased from baseline in both groups; however, they observed a significantly diminished post-operative increase in pro-inflammatory cytokines such as IL-6 and IL-8 in the ketamine group compared to the other group. Furthermore, patients of the ketamine group showed significantly higher plasma levels of the anti-inflammatory cytokine IL-10 1 h after opening the aortic cross clamp.[19] They did not observe any significant increase in TNF-α production during cardiac surgery or any significant differences between both groups regarding pro- and post-operative plasma levels of TNF-α and CRP.[19]

Our results are different from the previous two studies, especially regarding IL-6, IL-8 and IL-10. This may be due to the fact that the previous two studies were carried on adult patients undergoing CABG while our study was performed on paediatric patients in whom the inflammatory response might be more pronounced due to the large surface area of contact between the blood and the foreign surface of the bypass machine circuit.[13] In addition, the bypass machine for paediatric patients is almost always primed with blood which could be another cause for the marked inflammatory response,[20] thus ketamine alone was not sufficient to abort or antagonise this reaction. However, as in our study, ketamine did not affect the levels of CRP as in Welters study as well.

Mcbride *et al*. found a persistently low plasma levels of TNF-α (<7 pg/ml) examined up to 24 h after the end of CBP in 10 paediatric cardiac surgery cases.[21] This was similar to our TNF-α results.

Pinar *et al*. examined the effect of ketamine on serum and tracheobronchial aspirate IL-6 as compared to isoflurane in 34 patients aged 2–24 months in a prospective randomised controlled study. Patients were divided into two groups; in the ketamine group, patients received an induction dose of ketamine 1–2 mg/kg and were maintained with an infusion of ketamine 25–75 μg/kg/min, while in the other group patients did not receive ketamine and anaesthesia was maintained with isoflurane. IL-6 and white blood cells count were measured

six times starting preoperatively and up to 24 h post-operative. In both groups, the IL-6 levels in serum and tracheobronchial aspirate increased significantly after the termination of the bypass, and there were no significant differences between both groups at any stage indicating that ketamine did not help in attenuating the inflammatory response.[22]

A limitation of our study was that we only examined the ILs as the markers of inflammation, however, the anti-inflammatory effects of ketamine may not be picked up by examining only ILs and may be related to other mechanisms or involve other pathways.

Ketamine inhibits NO production. *In vivo* studies, it has been observed that ketamine administration reduces NO production in immunostimulated macrophages and that this effect is dose- and time-dependent.[23] The vagal nerve is known to have anti-inflammatory properties. Acetylcholine released by the vagal nerve interacts with the α7 subunit of the nicotinic receptors of macrophage. By antagonising the N-methyl-D-aspartate receptor, ketamine acts as an inhibitor of the vagal nerve and blunts its anti-inflammatory properties.[24]

CONCLUSION

There was a systemic inflammatory response produced and triggered by the CPB evidenced by the significant elevation of the inflammatory markers measured. However we could not detect any beneficial effect of ketamine on such response when assessed by the IL levels.

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Conflicts of interest

There are no conflicts of interest.

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