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ORIGINAL ARTICLE

# Ketamine does not inhibit interleukin-6 synthesis in hepatic resections requiring a temporary porto-arterial occlusion (Pringle manoeuvre): a controlled, prospective, randomized, double-blinded study

Francisco Carlos Bonofiglio[1], Ernesto P. Molmenti[3] & Eduardo de Santibañes[2]

[1]Department of Anaesthesiology, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [2]Department of Surgery, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, and [3]Department of Surgery, North Shore – LIJ Health System, Long Island, NY, USA

## Abstract

**Introduction:** Previous studies have shown that interleukin-6 (IL-6) levels correlated with mortality in critically ill patients.

**Goal:** To determine the effect of ketamine on IL-6 levels in liver resections patients with a temporary porto-arterial occlusion (Pringle manoeuvre).

**Materials and methods:** Controlled, prospective, randomized, double-blinded study. One group ($n = 21$) received ketamine whereas the other group ($n = 17$) received placebo. IL-6 levels were obtained at baseline, 4, 12, 24 h, 3 and 5 days.

**Results:** There were no significant differences in IL-6 levels between the groups (basal $P = 089$, 4 h $P = 0.83$, 12 h $P = 0.39$, 24 h, $P = 0.55$, 3 days $P = 0.80$ and 5 days $P = 0.45$). Both groups had elevated IL-6 levels that became almost undetectable by day 5. There was no major morbidity and no mortality in either group.

**Conclusions:** Ketamine does not seem to have an effect on plasma levels of IL-6. This could be interpreted as a potential finding associated with outcome as we did not encounter any deaths or major complications. Further studies will likely be needed to determine the range of IL-6 levels associated with survival and mortality, and whether it could be a predictor of survival.

## Keywords

resection < liver, post-operative dysfunction and ischaemia re-perfusion < liver, basic science < liver, basic science < biliary, functional disorders < biliary

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## Correspondence

Eduardo de Santibañes, Hospital Italiano de Buenos Aires, Gascon 450 (C1181ACH), Buenos Aires, Argentina. Tel: +54 11 4981 4501. Fax: +54 11 4981 4041. E-mail: eduardo.desantibanes@hospitalitaliano.org.ar

Correction added after online publication 1 September 2011: Figure 1 legend updated: 'memales' was changed to 'females'.

## Introduction

The modern surgical era of liver surgery began in 1952 when Lortat-Jacob reported the first surgical resection of a liver tumour.[1] More than two decades later, in 1977, the first multicentre study with 621 hepatectomies established guidelines[2] but the overall intra-operative mortality rate was 13%, with a rate exceeding 20% for major resections. Most deaths and complications were attributable to surgical haemorrhage. By the 1990s, mortality rates had decreased to 5% or less,[3,4] and over half of all resections involved colorectal liver metastases.[5] Surgery was found to provide a better survival than chemotherapy alone for both primary and metastatic lesions, and provided the only potentially for a cure.[5,6]

Although improvements in surgical and anaesthetic techniques have improved outcomes,[7] an intra-operative haemorrhage and post-operative liver failure remain the two most feared

complications.[8] Hepatic insufficiency can result either from a remnant liver volume unable to satisfy the physiological demands of the body, or from a surgical trauma-induced inflammatory process that leads to progressive cellular demise.

Two intra-operative manoeuvres that can potentially reduce blood loss during liver resections are total hepatic vascular occlusion and porto-arterial inflow occlusion (the Pringle manoeuvre).[9] The latter, in the setting of low central venous pressure (CVP), has provided superior outcomes to the point of even completely avoiding blood transfusions.[10] These manoeuvres, however, may lead to ischaemia/reperfusion (I/R) and activation of leukocytes and Kupffer cells.

Activated leukocytes within the hepatic vasculature generate cytokines that amplify the inflammatory mechanisms, weaken the immune response and lead to unpredictable outcomes.[11] In severe cases, cell death can cause post-operative multi-organ failure as a result of the local and systemic effect of cytokines.[12–14]

Hepatic trauma, as well as liver resection and transplantation are characterized by an initial period of I/R followed by an inflammatory response that can be associated with significant tissue injury. Interleukin-6 (IL-6), one of the major cytokines encountered in inflammation and cancer, has been implicated in post-surgical cellular damage when present in high concentrations.[15] It has also been found to be involved with hepatic tissue repair.[15–18] Over the past decade, researchers working mostly in vitro and with animal models, have attempted to further evaluate the effect of IL-6 on hepatic regeneration and growth after tissue loss.[19]

Previous studies attempted to minimize the production of free radicals and IL-6 in an effort to minimize cell death. In cardiac interventions with cardiopulmonary bypass, administration of low doses of ketamine was found to be associated with decreased IL-6 levels over the ensuing days. It remained unclear, however, whether this finding was associated with a decrease in morbidity and mortality.[20]

Ketamine, a widely used anaesthetic agent, has been postulated as an inhibitor of IL-6 synthesis in procedures with a significant pro-inflammatory response, such as in cardiac surgery with cardiopulmonary bypass.[20–26]

The purpose of the present study was to evaluate the effect of ketamine on IL-6 synthesis in hepatic resections requiring temporary porto-arterial occlusion (the Pringle manoeuvre).

## Materials and methods

This prospective, controlled, randomized, double-blinded study was approved by the Research Ethics Committee of the Hospital Italiano of Buenos Aires (CEPI) and carried out according to the Declaration of Helsinki. All patients voluntarily consented to the study and signed the appropriate informed consent approved by the CEPI.

Inclusion criteria were age of 21 years or older and planned liver resection with the Pringle manoeuver lasting 30–60 min. Those with chronic illnesses requiring corticosteroids, cirrhosis, haemodynamic instability before the surgery, diabetes, sepsis, surgical interventions or chemotherapy treatment within the past 30 days, pregnancy, illness that could potentially affect the hepatic circulation, arterial or ocular hypertension (contraindications for the use of ketamine), a ketamine allergy, pre-operative portal embolization/radiofrequency ablation or requiring emergency surgeries were not included in the present study. From March 2002 to June 2008, 44 consecutive patients agreed to participate and were enrolled in the study. Those who did not require the Pringle manoeuver during the resection, as well as those who did not undergo the planned procedure or whose haematocrit was less than 20% for over 30 min, were excluded from the present study.

Patients were assigned to one of two groups according to computer-generated randomization. The study group received ketamine 0.25 mg/kg, whereas the control group was administered an identical volume of saline. Syringes containing 10 ml of either ketamine or saline were delivered by hospital pharmacy personnel to the anaesthesiologist, who was blinded to their contents. To calculate the correct dose that was administered immediately after induction of anaesthesia, the ketamine (placebo) concentration was established at 10 mg/ml. All cases involved the same anaesthesia and surgical teams. Members of both teams as well as all personnel involved with blood collection remained blinded at all times.

All patients were transported to the operating room with an intravenous (i.v.) line in place and premedicated with midazolan 0.04 mg/kg. Once in the operating room, they received i.v. antibiotics, invasive cardiac monitoring, blood pressure monitoring and pulse oxymetry. Remifentanil 0.25 mg/kg/min was administered before induction with sodium thiopental 2–2.5 mg/kg. Vecuronium 0.1 mg/kg was used for muscle relaxation. After waiting approximately 3 min, patients were endotracheal intubated and a nasogastric tube was placed. Remifentanil 0.5 mg/kg/min, ibuprofen 10 mg/kg and morphine 0.15 mg/kg were administered. Anaesthesia was maintained with sevorane in the setting of an $FiO_2$ of 0.70. Mechanical ventilation was adjusted to allow an $EtCO_2$ of 25–30 mmHg and a plateau pressure < 30 cm $H_2O$. An arterial line was placed after induction of anaesthesia for invasive monitoring as well as for blood sampling. A central line was placed in the right internal jugular vein to monitor intra-operative central venous pressure (CVP). All patients received body warmers and warmed fluids. A target CVP of <5 cm $H_2O$ was sought at the time of resection to diminish bleeding. Intravenous 10- to 20-mg doses of furosemide as well as fluid restriction were utilized when necessary to reach the desired parameters. Potassium levels were kept at or above 3.5 mEq/l. Phenylephrine was used when necessary to maintain a median arterial pressure of at least 70 mmHg.

Patients who underwent extensive resections were admitted to the intensive care unit (ICU) and maintained on mechanical ventilation for 6–8 h before extubation. All other patients were extubated at the end of the procedure, observed in the post-anaesthesia care unit (PACU) for at least 8 h and subsequently transferred to the ward area if haemodynamically stable.

Pain management in patients extubated intra-operatively was with synthetic opioids (dextropopoxifen 1 mg/kg and dipyrone 2.5 mg). In cases of persistent pain (4 or more in a visual scale of 10), analgesia was supplemented with 2 mg of morphine every 20 min until relief of symptoms, somnolence or a respiratory rate ≤8 per min was observed.

Blood samples for IL-6 levels were obtained before surgery, upon placement of the first intravenous line, at 4 and 12 h after the Pringle manoeuver, on the 3rd and on the 5th postoperative days. In all cases peripheral venous blood was sampled at a site where no contamination with any of the infused fluids could occur. Immediately after obtaining the sample, the blood was centrifuged, the serum isolated and frozen to −70°C. In all cases, two plasma tubes of each sample were individually labelled and stored.

IL-6 was quantified by means of the IL-6 ELISA (Biosource, Europe Belgium) based on oligoclonal antibodies coupled with monoclonal antibodies to various IL-6 epitopes. This method showed both low and standard IL-6 range sensitivity. The results expressed represent the mean of both samples obtained at each time point.

### Statistical analysis

Based on previous studies that reported >100 pg/ml difference among both groups with a standard deviation (SD) < 50 pg/ml, we based our calculations on a predicted difference among both groups of 50 pg/ml with a SD of 50 pg/ml.[17] A total of 36 patients were randomized based on the observation that 16 patients in each group would allow rejection of the null hypothesis with an 80% confidence in the setting of a difference >50 pg/ml. $P < 0.05$ was considered significant.

## Results

Forty-two patients enrolled in the study. Of these, 4 (3 in the placebo and 1 in the ketamine group) were excluded because no Pringle manoeuver was undertaken during the hepatic resection. Thus, 38 patients, 21 (55.3%) in the ketamine group and 17 (44.7%) in the placebo arm, were considered in our analysis.

Demographic and clinical characteristics of all patients are described in the CONSORT diagram (Fig. 1) as well as in Table 1. All patients underwent surgery without major complications, and were discharged in a stable condition.

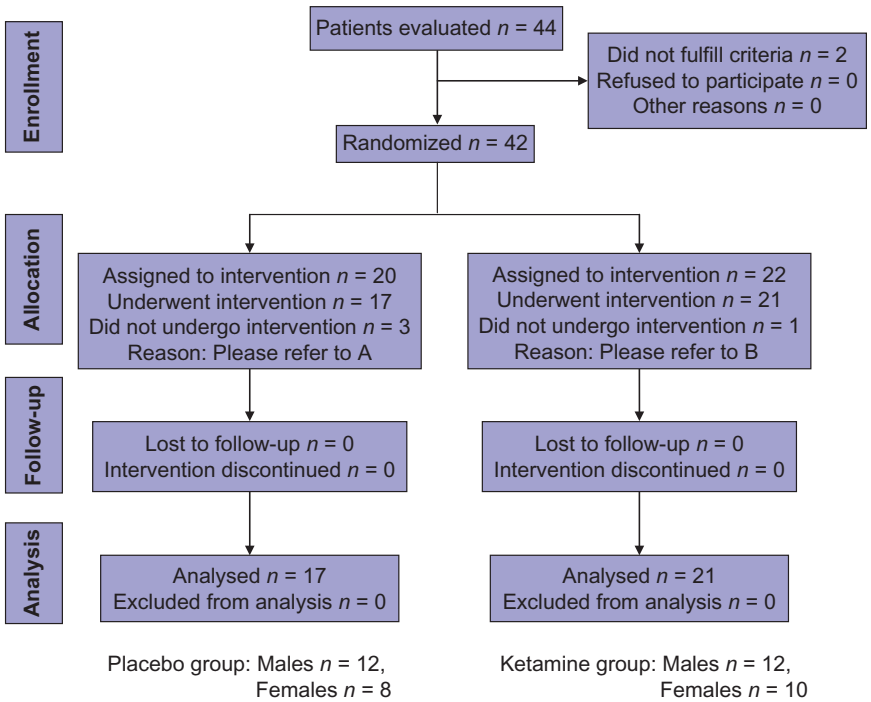


**Figure 1** CONSORT diagram detailing the study. Placebo group: males $n = 12$, memales $n = 8$. Ketamine group: males $n = 12$, females $n = 10$. (a) one patient with a haematocrit <20% for >30 min during surgery. Two patients did not require the Pringle manoeuver. (b) One patient did not undergo the planned surgical procedure

**Table 1** Demographic characteristics of both groups comparing surgical procedures, frequency of transfusions, intra-operative vascular occlusion times and post-operative intensive care unit admissions

| | Ketamine ($n = 21$) | Placebo ($n = 17$) |
|---|---|---|
| Age (year) | 62 ± 13.4 | 54.5 ± 13.8 ($P = 0.09$) |
| Weight (kg) | 73.5 ± 9.1 | 73.3 ± 12 ($P = 0.95$) |
| Gender | M/F 13/8 | M/F 11/6 |
| Major resections *n* (%) | 12 (60%) | 11 (66%) |
| Duration of surgery (min) | 254 (185–286) | 234 (190–275) |
| Transfusions (*n*) | 2/21 | 3/17 |
| Duration of Pringle manoeuver w/o unclamping (min) | 31 (24–37) | 33 (26–36) |
| Total duration of Pringle manoeuver including unclamping (min) | 41 (34–48) | 46 (36–53) |
| Patients admitted to ICU (*n*) | 12 | 11 |

w/o, without.

**Table 2** Interleukin-6 (IL-6) levels (mean ± SD) according to time periods for both groups

| Time period | Placebo ($n = 17$) | Ketamine ($n = 21$) | *P*-value |
|---|---|---|---|
| Basal | 7.71 ± 13.21 | 6.86 ± 7.08 | 0.89 |
| 4 h | 186.71 ± 175.87 | 162.98 ± 142.7 | 0.83 |
| 12 h | 216.43 ± 219.75 | 139.39 ± 130.66 | 0.39 |
| 24 h | 151.29 ± 135.38 | 116.14 ± 81.65 | 0.55 |
| 3 days | 110.17 ± 99.12 | 88.24 ± 61.5 | 0.80 |
| 5 days | 58.23 ± 74.41 | 53.92 ± 45.4 | 0.46 |

IL-6 levels are expressed in pg/ml. Statistical analysis based on Mann–Whitney Rank Sum Test.

Evaluation showed the data distribution to be non-parametric. A Mann–Whitney Rank Sum Test was used to compare the groups. Table 2 shows mean ± SD as well as *P*-values for both groups. There were no significant differences in IL-6 levels between both groups at any of the time periods considered. The study was based on an intention-to-treat analysis.

Figure 2 depicts IL-6 levels for both groups at the various time intervals of the study. Although IL-6 levels in the ketamine group showed a decline after only 4 h, the 32.4 pg/ml (95% CI 90.5–25.6) difference among both groups was smaller than the 100 pg/ml considered as clinically relevant in our statistical analysis.[20]

## Discussion

Most of the very few previous reports that have addressed the effect of ketamine on the post-operative inflammatory response involve *in vitro* or laboratory animal trials. Royblat *et al.* who were the first to address this topic, observed that subanaesthetic doses of ketamine administered at induction decreased IL-6 levels in women undergoing hysterectomies.[23] In a follow-up study, the same authors evaluated IL-6 levels in patients undergoing coronary revascularization with cardiopulmonary bypass.[20] Complex surgical interventions such as surgical trauma, I/R injury and cardiopulmonary bypass became the preferred models to evaluate the systemic inflammatory response.

The purpose of the present study was to evaluate whether ketamine could lower IL-6 levels, decreasing the inflammation and potentially lowering morbidity and mortality rates. Ketamine was administered i.v. in doses smaller than those required to achieve hypnosis or analgesia (0.25 mg/kg).

Almost a decade after the initial publications by Royblat *et al.* similar results were observed with sub-anaesthetic doses of ketamine, when IL-6 and tumour necrosis factor (TNF) production decreased with no effect on IL-2 levels. The authors concluded that this was the result of a direct effect on IL-6 and TNF synthesis[27].

In ophthalmic surgery, ketamine was not associated with decreased cytokine concentrations even at therapeutic doses equivalent to four times those used by Royblat *et al.*[28] Except for a trend in decreased leukocyte chemotaxis, ketamine had no major effect on inflammatory changes in cultured human endothelial cells.[29] In a recent study evaluating low-risk cardiac surgery with no cardiopulmonary bypass, low doses of ketamine had no inhibitory effect on the synthesis of IL-6, TNF or C-reactive protein. These findings, inconsistent with those of Royblat *et al.*, could be potentially attributed to a diminished inflammatory response associated with the absence of a cardiopulmonary bypass, to different anaesthetic agents, or to the use of statins in patients with coronary artery disease.[30]

The present results showed that patients who received ketamine had slightly lower plasma IL-6 levels than the control group at 4 and 12 h, as well as on the 2nd and 3rd days. Our groups also showed different IL-6 kinetics after performance of the Pringle manoeuver. IL-6 levels peaked at 12 h in the control group and at 4 h in the ketamine group. Concentrations were similar in both groups by day 5. Eight patients in the control group vs. only 2 in the ketamine group reached IL-6 levels >300 pg/ml. All eight reached their peak 4 to 24 h post-Pringle manoeuver. One of them was as high as 900 pg/ml. IL-6 levels remained elevated 4 to 12 h post Pringle manoeuver in only one patient in the ketamine group, and had normalized by 24 h. All patients had very low IL-6 levels after the 3rd day. In the ketamine group, levels started to decrease by 24 h.

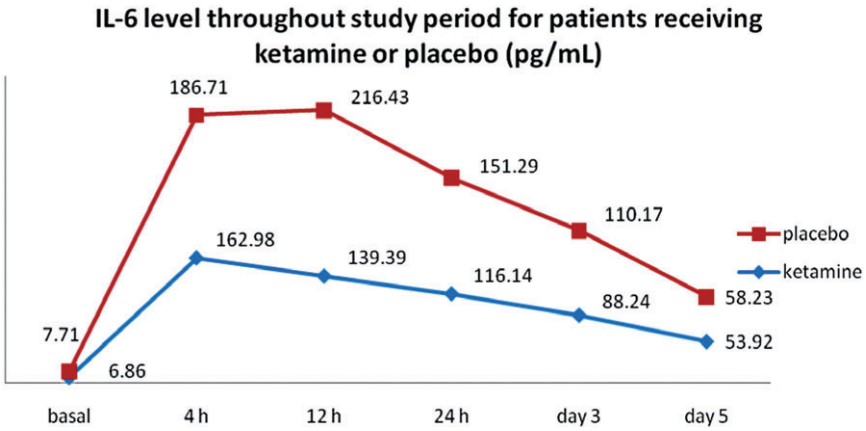


**Figure 2** Line graph comparing plasma levels of interleukin-6 (IL 6) (in pg/ml) for both groups of the study

None of the IL-6 values achieved in this series resembled those in patients with serious pathologies. Critically ill patients in septic shock had plasma levels persistently as high as 3000 pg/ml. In these instances, levels correlated directly with mortality. Polytrauma patients exhibited IL-6 levels in the 600 pg/ml range, but showed no association with clinical evolution. Levels were only higher in the setting of superimposed infections. These differences among septic and polytrauma patients could be attributable to the massive inflammatory response associated with sepsis.[31] When IL-6 levels were compared among various types of surgical interventions, they were found to be lower in orthopaedic cases and higher in colonic surgeries where the immune challenge was greater.[32] In critically ill patients, IL-6 levels remained elevated for a prolonged period of time and correlated not only with mortality but also with the severity of illness as determined by predictive scores such as sepsis-related Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) II.[33,34]

It would probably be difficult to determine the reasons for the lack of the difference between both groups in the present study. The anaesthetic drugs were identical to those used in previous studies, and the anaesthetic technique was based on sevofluorane, an agent that inhibits neutrophils in a dose-dependent fashion, preventing the synthesis of cytokines.[35] Morphine, used as analgesic in our series, seems to have less of an inhibitory effect on cytokines than synthetic drugs with a similar action. Recent studies have shown that morphine can inhibit synthesis of TNF, IL-6, and IL-10 in monocytes but not in polymorphonuclear leukocytes.[36] Another possible explanation could be derived from laboratory animal studies, where ketamine in physiological concentrations inhibited NF-kB but had no effect on IL-6 or TNF. Only at supra-therapeutic doses of 50 mg/kg (approximately 10 times higher than the usual i.v. dose) did ketamine inhibit all inflammatory mediators.[37] Therapeutic doses of ketamine inhibited phagocytosis, production of oxygen radicals and synthesis of cytokines without causing cell damage in murine macrophages *in vitro*. These observations led to the proposal that ketamine could have an effect on mitochondrial membrane depolarization.[38] An alternate explanation is based on the fact that in the setting of hepatic resections, IL-6 could lead to localized injury associated with a repair mechanism rather that with a systemic threat as seen in massive sepsis. Both groups in the present study had elevated IL-6 levels that became almost undetectable by day 5. The fact that IL-6 did not show elevations similar to those in terminal patients could be interpreted as a potential finding associated with outcome as we did not encounter any deaths or major complications. Further studies will be needed to determine the IL-6 range associated with survival, and whether it could represent a predictor of outcome.

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### Conflicts of interest

None declared.

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