Systemic inflammation: Role of ketamine, opiates and other interventions

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INTRODUCTION

Although the mortality rate for major surgery is low (1-5%), postoperative morbidity is common (10-20%). Complications include cardiac and non-cardiac related etiologies such as infection, gastrointestinal dysfunction, acute lung injury, stroke, and renal dysfunction. Many postoperative complications appear to be caused by an exaggerated systemic pro-inflammatory response to surgical trauma. The systemic inflammatory response syndrome (SIRS) refers to an inflammatory process that can arise from or in the absence of infection. The systemic elaboration of inflammatory mediators may be beneficial by heightening the host’s general defenses. It, however, may lead to the “autodestruction” of the host through secondary damage to tissues/organs not originally affected by the primary injury or infection. The most severe form of this inflammatory response leads to multiple organ dysfunction syndrome and death. Milder forms of a pro-inflammatory response cause less severe organ dysfunction which do not lead to admission to an intensive care unit, but nevertheless cause suffering, increased hospital length of stay, and increased cost.

According to most theories, tissue injury, endotoxemia, and contact of blood with the foreign surface of the cardiopulmonary bypass (CPB) circuit are some of the major factors postulated to initiate a systemic inflammatory response. Nevertheless, there is controversy surrounding the etiology as well as pathogenesis of inflammation in the perioperative period.

POTENTIAL THERAPIES FOR THE PREVENTION OF INFLAMMATION RELATED COMPlications

Numerous strategies and pharmacological agents have been postulated to reduce the severity and incidence of systemic inflammation. Many studies have demonstrated reductions in intermediate endpoints, for example laboratory indices of complement activation and cytokinemia. Most of these studies, however, have been too small to detect improvements in clinically meaningful postoperative outcomes. Currently there are no therapies in widespread clinical use for the prevention or treatment of organ dysfunction resulting from systemic inflammation although several promising strategies are under development. Several promising and commonly reported (glucocorticoids) interventions will be discussed.

KETAMINE

Ketamine, an intravenous anesthetic agent, was approved by the United States Food and Drug Administration in 1970. It has been administered to millions of patients and has a favorable safety profile[1-7]. Initial intravenous anesthetic doses are in the range of 1-4.5 mg/kg. Ketamine’s anti-inflammatory effects were discovered over a decade ago (see below) and appear to be mediated through an antagonism of nuclear factor-kappa B (NFkB) based on several lines of evidence: 1) NF-kappa B regulates the transcription of genes that encode the production of proinflammatory cytokines[8-10], and 2) Ketamine suppresses endotoxin induced NFkB expression[11-15].

Initial observation by Roytblat et al: One of the most important initial observations was made by Roytblat et al. in 1998 in a study designed to assess the impact of low dose
ketamine on serum IL-6 levels\(^1\). In this double-blind randomized clinical trial conducted in Israel, 31 relatively low risk patients undergoing elective CABG were randomized to either placebo or standard racemic ketamine (0.25 mg/kg) administered IV in conjunction with general anesthetic agents (fentanyl and midazolam) on induction of general anesthesia prior to surgery. Groups were comparable preoperatively. Speaking to the safety of low dose ketamine co-administered with anesthetic agents, no statistically or clinically significant differences in blood pressure or heart rate were observed in ketamine treated patients. Indeed, all patients (n = 3) who exhibited hemodynamic instability or low output syndrome postoperatively had been randomized to the placebo group.

In this study, patients randomized to a single small prophylactic dose of ketamine (0.25 mg/kg) exhibited statistically significantly lower serum IL-6 levels at the end of surgery and postoperatively from 4 hours after CPB through postoperative day number 7. IL-6 levels at these and other time points are shown in the Figure.

Emergence reactions/psychotomimetic side effects were not observed in any patient, which is consistent with their being a low incidence of these reactions in patients administered low dose ketamine in conjunction with benzodiazepines and other general anesthetic agents\(^4\). With only 17 and 14 patients in each study arm, this trial was not powered to assess the impact of low dose ketamine administration on morbidity and mortality after cardiac surgery.

The study described above was published in 1998. A subsequent study published in 2002 by the same investigators randomized 35 cardiac surgical patients to placebo or low dose ketamine (0.25 mg/kg) in a double-blind manner\(^7\). No adverse hemodynamic or psychotomimetic side effects were observed in ketamine treated patients. They found that low dose ketamine attenuated neutrophil activation postoperatively, which may another mechanism by which ketamine may reduce lung injury given the putative role of neutrophil activation in lung/endothelial injury\(^16,17\).

**Confirmation of ketamine’s effects:** Bartoc et al. confirmed Royblat et al.’s findings (0.25 mg/kg of ketamine) and extended them by testing an additional regimen of low dose ketamine (0.5 mg/kg)\(^18\). Consistent with Roytbat et al.\(^1\) in this study the administration of low dose ketamine in conjunction with benzodiazepines, had minimal hemodynamic effects and did not cause an increased incidence of emergence reactions. They showed that a single dose of ketamine administered preoperatively significantly attenuated increases in serum interleukin (IL)-6 levels (pg/mL) at 24 hours postoperatively. A decrease in the systemic inflammatory response was also manifested by a significant effect of ketamine on attenuating increases in C-reactive protein levels (mg/dL) during the same period.

Despite these interesting observations it is unknown if low dose ketamine reduces complications in cardiac surgery or major non-cardiac surgery since no large randomized trials have been conducted.

**OPIATES**

There is some experimental evidence that morphine may have anti-inflammatory effects. This finding was confirmed in a 30 patient randomized double blind trial of cardiac surgical patients\(^19\). Patients were randomized to receive morphine (40 mg) or fentanyl (1,000 microg) in conjunction with isoflurane. Serum IL-6 levels were significantly lower in the morphine treated patients both at 3 and 24 hour after CPB. No patients receiving morphine (0%) had postoperative hyperthermia compared with 74% of patients in the fentanyl group. These data are very interesting and the clinical impact of this intervention should be tested in a larger randomized trial.

**STEROID ADMINISTRATION**

Several attempts have been made to prevent elevations in pro-inflammatory cytokines and complement activation during cardiac surgery with steroid administration. For example, in a randomized double blind study of 25 cardiac surgical patients, dexamethasone administration (1 mg/kg on induction of anesthesia) prevented increases in TNF as well as reduced postoperative hyperthermia and hypotension. Most of the studies referenced have been too small to detect improvements in postoperative outcome in patients.
administered steroids. They have also had insufficient power to detect differences in potential steroid related complications such as wound infections and poor wound healing. More recent investigations have continued to assess the effects of methylprednisolone on biochemical markers of SIRS as well as clinical outcomes. Recently reported randomized clinical trials by Chaney et al. evaluated the effects of methylprednisolone (30 mg/kg) or placebo in cardiac surgical patients. Patients randomized to the steroid groups exhibited statistically significantly prolonged extubation times and received more vasoconstrictors. These investigators also observed significantly more hyperglycemia in the postoperative period in the methylprednisolone treated patients.

**PENTOXIFYLLINE**

Pentoxifylline is a non-specific phosphodiesterase inhibitor similar in chemical structure to theophylline, a common antiinflammatory used to treat asthma. Pentoxifylline has multiple rheological and antiinflammatory properties, but the exact mechanism of its pharmacological effects are poorly understood. Clinically pentoxifylline is approved by the FDA to treat intermittent claudication, presumably by increasing red cell deformability, which may improve oxygen delivery to ischemic tissues. Animal studies have shown that treatment with pentoxifylline significantly attenuates endothelial damage and the formation of oxygen radicals following ischemia/reperfusion, prevents fever after the administration of LPS, and prevents leakage of bacteria from the gut during hemorrhagic shock. Clinical research studies using pentoxifylline have been performed in the setting of lung transplantation, cardiac surgery, and anemia requiring red blood cell transfusion.

In an initial study, Hoffman et al. randomized 40 patients with an Apache II score 3 19 after cardiac surgery to placebo or pentoxifylline (1.5 mg/kg/hr for 48 hours) (20). In this study, patients administered pentoxifylline had significantly fewer days on mechanical ventilation, less need for hemofiltration and a shorter ICU length of stay. In a historical control study, Thabut et al. administered pentoxifylline to 23 consecutive patients undergoing lung transplantation. Compared to historical controls, patients administered pentoxifylline experienced less allograft dysfunction and a significant reduction in 60-day mortality was noted. These findings need to be confirmed in a prospective randomized clinical trial.

Boldt and colleagues randomized 30 elderly (≥ 80 years) patients undergoing cardiac surgery to placebo or pentoxifylline (300 mg bolus administered immediately after induction of general anesthesia followed by a continuous infusion of 1.5 mg/kg/hr for 48 hours) (21,22). In this study, pentoxifylline administration minimized intraoperative and postoperative elevations in plasma C-reactive protein, PMN-elastase, IL-6 and IL-8 levels. Duration of mechanical ventilation was significantly lower in patients randomized to pentoxifylline. This study was not powered to detect differences in rare but serious complications.

**REFERENCES**

8. Li JJ, Fang CH. C-reactive protein is not only an inflammatory marker but also a direct cause of cardiovascular diseases. Med Hypotheses 2004;62:499-506.