Gut permeability and myocardial damage in paediatric cardiac surgery

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CHAPTER 1

INTRODUCTION

The use of steroids has attracted considerable attention in several areas of acute medicine, including acute septic shock and cardiopulmonary bypass. There are remarkable similarities in the pathophysiology of these two events, and after nearly forty years, the use of steroids for both indications remains highly controversial. Steroids have proven to be beneficial in only a few specific pathologies, bacterial meningitis in children[1], meningitis in adults[2], severe typhoid fever[3], late acute respiratory distress syndrome[4], *Penumocystis carinii* pneumonia in acquired immunodeficiency syndrome[5] and adrenal insufficiency.[6]

Cardiopulmonary bypass (CPB) induces a systemic inflammatory response syndrome (SIRS) in patients following cardiac surgery that can lead to major organ injury and postoperative morbidity. Initiation of CPB sets in motion an extremely complex and multifaceted response involving complement activation along with activation of platelets, neutrophils, monocytes and macrophages. These changes initiate the coagulation, fibrinolytic and kallikrein cascades, increasing blood levels of various endotoxins, cytokines and increasing endothelial cell permeability.

The physiological insults caused by CPB have been associated with major postoperative morbidity, including neurological, pulmonary and renal dysfunction, and/or haematological abnormalities. Additional clinical manifestations associated with the SIRS include increased metabolism (fever), fluid retention, myocardial oedema and detrimental haemodynamic changes.

The use of steroids began in the mid 1960s, following reports of their beneficial effects in septic shock. In 1974, Weitzman and Berger[7] systematically reviewed 32 original clinical investigations published between 1950 and 1971 that addressed the use of corticosteroids in bacterial infections. Of the 12 studies involving septic shock, nine advocated the use of corticosteroids and three concluded that steroids were not beneficial.

Two years later, Schumer[8] published a report that demonstrated very impressive reductions in mortality in patients with septic shock treated with corticosteroids. Mortality rates of 11.6% and 9.3% were reported for patients treated with methylprednisolone (30 mg/kg iv) and dexamethasone (3 mg/kg iv) respectively, versus 38.4% for patients receiving placebo. Based on this report, it became standard practice in the late 1970s and early 1980s to administer high-dose corticosteroids at the onset of septic shock.

In the 1980s there were several well-designed single centre studies as well as two large multicentre clinical trials. In an open label trial, Sprung and colleagues[9] randomized 59 patients to receive methylprednisolone, 30 mg/kg iv, dexamethasone 6 mg/kg iv or placebo. Objective criteria for septic shock closely approximated current consensus criteria, and outcome measures were well established. They demonstrated more rapid shock reversal as well as improved survival at 6 days after drug administration with corticosteroids. This survival benefit disappeared, however, when patients were followed up beyond 10 days. In another single centre study, Luce and colleagues[10] found no improvement in survival or ARDS in a double blind comparison of methylprednisolone versus placebo in 75 patients with septic shock.

The results of two large multicentre clinical trials of steroids in sepsis were published in 1987. In the Veteran Administration trial,[11] 233 patients were randomized to receive methylprednisolone (30 mg/kg iv) or placebo within three hours of diagnosis. No difference in 14-day mortality or complications was demonstrated. In the largest clinical trial, Bone and colleagues[12] randomized 381 patients to receive methylprednisolone (30 mg/kg iv) or placebo. Patients who received methylprednisolone had a higher mortality rate than those in the placebo group. As a result of these multicentre trials, the use of corticosteroids for septic shock fell out of favour. Reviews and critical care textbooks in the 1990s have generally cautioned against the use of supraphysiological doses of corticosteroids in septic shock.

In 2003, critical care and infectious disease experts representing 11 international organizations developed management guidelines for the use of corticosteroid therapy in patients with sepsis and septic shock that would be of practical use for the bedside clinician.[13] *Among their recommendations it is clearly stated that the use of corticosteroids in high doses is strongly discouraged*.

Interestingly, the use of steroids in cardiac surgery developed in a similar pattern to that in sepsis. Following animal studies carried out in the 1960s, methylprednisolone became the drug of choice because of its anti-inflammatory potency and minimal tendency to induce sodium and water retention. An intravenous dose of 30 mg/kg was at that time considered optimal because this had been shown to be beneficial in clinical shock studies,[14] yet caused no detrimental systemic effects when administered to a small group of healthy volunteers.[15]

A seminal study published in 1970 by Dietzmanand and colleagues[16] reported that methylprednisolone (30 mg/kg) was effective in treating the low output syndrome in dogs and humans following cardiac surgery. Specifically, in 98 dogs, methylprednisolone administration decreased systemic vascular resistance, increased cardiac index, improved tissue perfusion, and increased survival from 22 to 65%. In 19 humans following cardiac valve replacement the same beneficial haemodynamic effects were observed.

In the early 1980s the pivotal role that complement activation played in the basic physiological insults caused by CPB was demonstrated. This triggered a number of investigations focusing on the effect of steroids on post-bypass complement activation and cytokines production. An overwhelming number of these studies demonstrated that the use of steroids was associated with a considerable reduction of proinflammatory cytokines production in the postoperative period.

However we had to wait another decade to see investigators moving away from biochemical parameters and focusing on clinical outcome. Tassani and colleagues[17] showed in 1999 that patients given methylprednisolone had better haemodynamic parameters in the postoperative period although extubation time was not affected. More recently Yared and colleagues[18] reported, in a study involving more than 200 patients, that giving dexamethasone before CPB started was associated with earlier tracheal extubation than the placebo group. In contrast to these two previous studies Chaney and colleagues[19,20] demonstrated in two prospective randomized trials that the use of methylprednisolone was associated with delayed tracheal extubation and was not associated with any haemodynamic improvements.

In paediatric cardiac surgery the use of steroids has not been investigated to the same extent as in adults, and its use is as controversial. Lindberg and colleagues[21] considered that it was unethical not to use dexamethasone in children weighing less than 10 kg scheduled for cardiac surgery. Schroeder and colleagues[22] accept that the lack of a control group without methylprednisolone is a limiting factor in their study. According to them it is standard practice to use steroids in these patients. Dexamethasone appears to reduce postoperative troponin I production.[23] It has also been shown to reduce the production of C-reactive protein without any effect on the release of protein S100B and Von Willebrand factor.[21] The concentration of proinflammatory cytokines decreases when steroids are used before CPB starts.[24] The reduction is even more remarkable if steroids are given before and during CPB.[22]

Oxygen delivery and cardiac output improve faster when steroids were used in an animal model.[25] Even the timing of the administration seems to be relevant.[26] However, when clinical end points have been used to test the benefits of steroids the results are not so impressive.[27]

Our aim in this thesis was to investigate how dexamethasone could influence the side effects associated with CPB in two organs, the small intestine and the heart. To that purpose we chose two surrogate markers, gut permeability and cardiac troponin T production.

The dual sugar permeability test to assess gut permeability was introduced in the 1970s to overcome the problems associated with the use of single markers. After thirty years it has stood the test of time and remains in use for clinical and research purposes. Gut permeability had not been investigated in paediatric patients undergoing cardiac surgery. Before examining the effect of dexamethasone on gut permeability we first had to evaluate the changes in intestinal permeability during the perioperative period in patients undergoing surgery with and without cardiopulmonary bypass. This study is presented in chapter two.

Proinflammatory cytokines have a deleterious effect on the intestinal barrier when studied *in vitro*.[28] In the same *in vitro* model, when the intestinal mucosa is exposed to anti-inflammatory cytokines, the gap between the epithelial cells of the intestinal mucosa improves.[29] Animal studies have shown that steroids accelerate the maturation and stimulate the growth of the intestinal mucosa in ex-premature animals and it has long been accepted that steroids given to the pregnant mother reduce the risk of necrotizing enterocolitis in the premature baby.

Chapter three describes the effect of dexamethasone on gut permeability when administered during induction of anaesthesia in paediatric patients undergoing cardiac surgery with cardiopulmonary bypass. The results of this study confirm what has been already shown in *in vitro* studies; although the mechanism is not clear, dexamethasone reduces gut permeability when given before CPB starts.

Neonates with a hypoplastic left heart syndrome undergoing stage I of the Norwood operation are at higher risk of intestinal ischaemia in the perioperative period. In these patients the systemic and pulmonary circulations depend on one functioning ventricle.

This can expose the patient to periods when there is an imbalance between the systemic and pulmonary circulations, with excessive pulmonary flow to the detriment of mesenteric perfusion. The surgical procedure requires a period of circulatory arrest, adding an extra insult to the mesenteric circulation. Necrotizing enterocolitis is relatively uncommon in paediatric patients undergoing cardiac surgery, however mortality is nearly 100% in patients with HLHS.[30] It has been common practice in our institution to use steroids in these occasions only. We felt that preoperative and intraoperative insults to the intestinal mucosa in this group of patients warranted a separate investigation. The results are presented in chapter four.

Sometimes research produces totally unexpected results. Rhamnose is one of the saccharides used in the dual sugar permeability test. For the last thirty years it has been assumed that rhamnose was an inert sugar, which did not undergo any metabolism in humans. However we found increased concentrations of rhamnitol, a metabolite of rhamnose, in the urine of patients undergoing the DSPT. This is evidence that rhamnose is indeed metabolized by the human body and the results are presented in chapter five.

Cardiac troponin T (cTnT) is a specific marker of myocardial infarction.[31] It is also a reliable marker of myocardial injury in the paediatric population.[32] Before we investigated the effect of dexamethasone on postoperative release of cTnT another issue had to be addressed.

The anaesthetic agent used during the surgical procedure could influence cTnT concentrations postoperatively. Several studies have demonstrated that sevoflurane and other volatile anaesthetics reduce the postoperative production of cardiac troponin I when compared to other anaesthetic agents in adult patients undergoing coronary graft surgery.[33,34]

The theoretical explanation for this benefit can be found in the process of anaesthetic preconditioning. Exposing the adult myocardium to brief periods of ischaemia and reperfusion induces greater tolerance to a subsequent, more prolonged ischaemic insult, a phenomenon known as ischaemic preconditioning (IP). Animal experiments have shown that inhalational anaesthetics, morphine, and possibly other opioids mimic the effects of ischaemic preconditioning. This is often referred to as anaesthetic preconditioning. The results of our study and further discussion over the subject are presented in chapter six.

A possible consequence of the SIRS related to the use of CPB is myocardial damage. This can manifest itself as a low output syndrome with a need for high inotropic support in the postoperative period. cTnT concentrations rise up to three fold postoperatively in children undergoing cardiac surgery when compared to adults undergoing coronary bypass surgery.[35]

Human and animal studies have shown a reduction in cardiac troponin I concentrations after CPB related to the use of steroids.[36,37] The explanation for this is not totally clear. The use of cardiac troponin I in paediatric cardiac surgery is limited by the fact that for up to two years after birth in infants with congenital heart disease and for up to nine months after birth in healthy infants, troponin I is produced not only by myocardial muscle but also by skeletal muscle. Slow twitch skeletal muscle troponin I is expressed in variable amounts in these infants.[38]

When cTnT was used as an end point to test the effect of dexamethasone on myocardial protection, patients receiving dexamethasone before CPB had lower concentrations of cTnT in the postoperative period. However, these changes were short-lived and 24 h after admission to the intensive care unit there were no differences between the two groups. The subject is further discussed in chapter seven. In the same study we have shown that dexamethasone did not improve morbidity. Sixty-eight patients were needed to demonstrate a 50% reduction in the postoperative use of inotropic support or an 18 hours reduction in ventilator hours. However, the use of dexamethasone was not associated with any changes in postoperative ventilator hours or the amount of inotropic support needed in the postoperative period.

As one could expect this thesis provides no definitive answer to the use of dexamethasone (1 mg kg^{-1}) before CPB starts. On the one hand dexamethasone does not seem to provide any benefits in terms of lowering postoperative morbidity. On the other hand it does clearly reduce gut permeability in the postoperative period. Since intestinal complications in this group of patients are relatively rare, a sufficiently powered study to test the benefits of dexamethasone using intestinal complications as an end point would be difficult, if not impossible. However, mortality related to intestinal complications in this setting is so high that it is perhaps unethical to even consider further research.

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