Effect of dexamethasone on perioperative renal function impairment during cardiac surgery with cardiopulmonary bypass

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Background. In cardiac surgery with cardiopulmonary bypass (CPB), corticosteroids are administered to attenuate the physiological changes caused by the systemic inflammatory response. The effects of corticosteroids on CPB-associated renal damage have not been documented. The purpose of this study was to evaluate the effects of dexamethasone on perioperative renal dysfunction in patients undergoing cardiac surgery with CPB.

Methods. Renal damage was prospectively studied in 20 patients without concomitant morbidity undergoing coronary artery surgery with CPB. Patients were randomized in a double-blind fashion to receive dexamethasone or placebo. Markers of glomerular function (creatinine clearance) and damage (microalbuminuria), and markers of tubular function (fractional excretion of sodium and free water clearance) and damage (N-acetyl-β-D glucosaminidase (NAG)) were evaluated in addition to plasma and urinary glucose levels. Plasma and urinary specimens were obtained at the following time periods: (1) baseline, during the 12 h before surgery; (2) skin incision before heparinization; (3) from heparinization until the end of CPB; (4) during the 2 h following weaning from CPB; (5) in the intensive care unit from 2 to 6 h after weaning of CPB; (6) and from 36 to 60 h after weaning of CPB.

Results. CPB was associated with an increase in markers in the placebo group, which returned to baseline during the second postoperative day, demonstrating a transient impairment of glomerular and tubular renal function. Similar patterns were observed in patients treated with dexamethasone. While postoperative glycosuria was significantly higher in the dexamethasone-treated group, no other differences between groups were observed.

Conclusion. Dexamethasone administration before CPB has no protective effect on perioperative renal dysfunction in low-risk cardiac surgical patients.

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Perioperative renal dysfunction in cardiac surgery contributes to postoperative morbidity, mortality, and prolonged hospital stay.¹ In particular, a transient decline in renal function is observed in patients with normal preoperative renal function during surgery involving cardiopulmonary bypass (CPB).² The mechanism underlying this decline in renal function during CPB is thought to be multifactorial in origin, and related to hypoperfusion, loss of pulsatile perfusion, haemolysis, and a systemic inflammatory response.³ The systemic inflammatory response is induced by contact of cellular and humoral blood components with the extracorporeal circuit. In addition, complement activation and cytokine release triggered by CPB causes endothelial adherence of leucocytes followed by margination, degranulation, and ultimately tissue destruction.⁴,⁵ It is recognized that the activation and degranulation of neutrophils is an important pathway in pathogenesis of the systemic inflammation after cardiac surgery with CPB.

The administration of corticosteroids before the institution of CPB has been advocated to attenuate the inflammatory response in the postoperative period.⁶ High-dose systemic corticosteroids reduce chemotactic sensitization of neutrophils and subsequent tissue sequestration. In addition, corticosteroids inhibit the activation of cytokines.⁷

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Nevertheless, the effect of corticosteroids on the CPB-associated renal function loss has not yet been documented. In a prospective randomized double-blind study, we examined the effects of dexamethasone on perioperative renal dysfunction in low-risk patients undergoing coronary artery bypass graft surgery with CPB. The injury to glomerular and tubular structures was assessed by measurement of sensitive markers of glomerular and tubular dysfunction and damage.

**Patients and methods**

**Patients**

The study was approved by the hospital ethics committee. Patients undergoing coronary artery bypass graft surgery first time were screened prospectively according to the entry criteria. After informed consent, patients with normal renal function as assessed by a serum creatinine of less than 120 µmol litre\(^{-1}\) and normal urinalysis were included. All patients had coronary artery disease but normal cardiac (ejection fraction more than 45%), cerebral and hepatic function. None of the patients received ACE inhibitors or diuretics. Patients with diabetes, recent myocardial infarction, hypertension, unstable angina, or recent use of radiocontrast media were excluded, as these conditions are associated with increased baseline levels of the urinary markers used in this study.

**Anaesthetic management**

Patients \((n=20)\) were randomized in a double-blind fashion to receive either dexamethasone or a placebo. A baseline serum glucose sample was obtained after overnight fasting. In the treatment group, patients received dexamethasone 1 mg kg\(^{-1}\) before induction of anaesthesia and 0.5 mg kg\(^{-1}\) 8 h later. Patients in the control group received a placebo. Anaesthesia was provided according to a fixed protocol. Pre-medication consisted of oral diazepam 10–15 mg 2 h before the operation. After insertion of peripheral venous and radial arterial cannulae under local anaesthesia, general anaesthesia was induced with sufentanil 2.5 µg kg\(^{-1}\) and midazolam 0.1 mg kg\(^{-1}\). Tracheal intubation was achieved with pancuronium 0.1 mg kg\(^{-1}\) and the lungs were ventilated with air and oxygen \((F_{\text{IO}_{2}}=0.4)\). A flow-directed pulmonary artery catheter was inserted into the right internal jugular vein, and an indwelling bladder catheter was used for urine collection. Rectal temperature was measured continuously in the first 24 postoperative h. Anaesthesia was maintained with sufentanil, midazolam, and pancuronium. Cefuroxime 1.5 g was administered after induction. Hydroxyethyl starch 6% solution and lactated Ringer’s solution were used to obtain a mean arterial pressure (MAP) of more than 60 mm Hg to maintain filling pressures and cardiac output. Transfusions of packed cells were given if the haemoglobin fell below 5.0 g dl\(^{-1}\). According to our standard practice, i.v. insulin was started at a serum glucose of more than 10 mmol litre\(^{-1}\). In the intensive care unit, inotropic support with dopamine was started at a cardiac index of less than 2.2 litre min\(^{-1}\) m\(^{-2}\). Diuretics, mannitol, or aprotinin were not administered during the study period. Patient characteristics and perioperative variables were recorded prospectively.

**Cardio-pulmonary bypass**

Non-pulsatile CPB was performed with a roller pump and membrane oxygenator (Cobe Optima; Cobe Laboratories, Lakewood, CO). The extracorporeal circuit was primed with 500 ml hydroxyethyl starch 6% and 1000 ml lactated Ringer’s solution. Flow during CPB was maintained at 2.2 litre min\(^{-1}\) m\(^{-2}\) during moderate hypothermia (32°C) with \(\alpha\)-stat regulation of blood pH. Cold St Thomas solution was infused into the aortic root to maintain cardioplegia during aortic cross clamping. During CPB, the MAP was allowed to vary between 60 and 90 mm Hg. Deviations beyond this range were corrected with phenylephrine or nitroglycerine.

**Renal markers**

Glomerular function was determined by measuring creatinine clearance, while tubular function was assessed from fractional excretion of sodium and free water clearance. In addition, urinary albumin excretion was used as an index of glomerular capillary damage, while tubular damage was determined by measurement of excreted urinary N-acetyl-\(\beta\)-d-glucosaminidase (NAG). Plasma and urinary osmolality, serum concentrations of sodium and creatinine and urinary concentrations of glucose, sodium, creatinine, microalbumin, and NAG were measured at six time points:

1. baseline, during the 12 h before surgery;
2. after skin incision before systemic heparinization;
3. from heparinization until the end of CPB;
4. during the 2 h after weaning from CPB;
5. in the intensive care unit from 2 to 6 h after weaning from CPB; and
6. from 36 to 60 h after weaning from CPB.

For each interval, the fractional excretion of sodium, free water clearance, creatinine clearance, urinary excretion of microalbumin, and urinary NAG excretion were calculated.

**Laboratory methods**

Urine samples were stored at \(-20°C\) for the determination of glucose, sodium, creatinine, osmolality, albumin, and NAG. Plasma samples were transported to the laboratory immediately and glucose, sodium, creatinine, and osmolality were determined using a Vitros analyzer (Ortho Clinical Diagnostics, Beere, Belgium) and Osmomat analyser (Gonotec, Salm and Kipp, The Netherlands), respectively. Urine microalbumin was determined by a nephelometric method according to the instructions of the manufacturer (DADE-Behring, Leusden, The Netherlands). Individual urinary NAG levels were determined by means of a modified
enzyme assay according to Lockwood at pH 4.5 and corrected for non-specific conversion (HaemoProbe, Groningen, The Netherlands).

Statistical analysis

Results are presented as mean (SD) or median (range). Measurements of microalbumin and NAG are expressed as a ratio of the creatinine concentration to correct for changes in urinary flow. The results were analysed using repeated measures analysis of variance, Student’s t-test, Mann–Whitney test, and χ² test. Statistical significance was accepted at P<0.05. A power analysis, based on previous studies of NAG levels in this population suggested that 20 patients would need to be studied to detect a 30% difference between the two groups.

Results

Twenty patients were randomized into two equal groups, and all patients completed the study. The following complications were observed: repeat surgery for bleeding (n=2); perioperative myocardial infarction (n=1); atrial fibrillation (n=1); and nosocomial pneumonia (n=1). Six patients in the dexamethasone group and one patient in the placebo group received insulin to regulate serum glucose in the postoperative period (P<0.05). Seven patients in the dexamethasone group and two patients in the placebo group received dopamine less than 5 µg kg⁻¹ min⁻¹ because of a low cardiac index (P=0.025). In the first 24 postoperative h, rectal temperature was higher in the placebo group (dexamethasone-treated: 37.2 (0.3)°C, placebo 37.9 (0.8)°C, P=0.02). Further patient characteristics and operative data are shown in Table 1. Mean age and BMI were slightly higher in the dexamethasone-treated group compared with placebo.

Table 1 Patient characteristics and periopeative data. No.=number

<table>
<thead>
<tr>
<th></th>
<th>Dexamethasone</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient, No.</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Male/female sex, No.</td>
<td>9/1</td>
<td>8/2</td>
<td></td>
</tr>
<tr>
<td>Age, yr (range)</td>
<td>67.7 (58–76)</td>
<td>59.6 (47–76)</td>
<td>0.03</td>
</tr>
<tr>
<td>BMI, kg m⁻²</td>
<td>27.4 (3.0)</td>
<td>24.7 (1.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Preoperative creatinine, µmol litre⁻¹</td>
<td>87.5 (16.3)</td>
<td>95.5 (15.2)</td>
<td>0.30</td>
</tr>
<tr>
<td>Duration of CPB, min</td>
<td>116 (28)</td>
<td>96 (24)</td>
<td>0.11</td>
</tr>
<tr>
<td>Duration of operation, min</td>
<td>258 (63)</td>
<td>232 (54)</td>
<td>0.33</td>
</tr>
<tr>
<td>Aorta cross-clamping, min</td>
<td>75 (22)</td>
<td>61 (18)</td>
<td>0.17</td>
</tr>
<tr>
<td>Distal anastomoses, No.</td>
<td>2.9 (0.7)</td>
<td>3.3 (0.7)</td>
<td>0.22</td>
</tr>
<tr>
<td>Units of blood transfused, No.</td>
<td>2.2 (3.9)</td>
<td>1.3 (1.6)</td>
<td>0.51</td>
</tr>
<tr>
<td>Serum glucose, baseline mmol litre⁻¹</td>
<td>6.9 (1.7)</td>
<td>6.2 (1.7)</td>
<td>0.32</td>
</tr>
<tr>
<td>Highest postoperative glucose</td>
<td>11.1 (1.4)</td>
<td>9.1 (2.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>Highest rectal temperature, °C</td>
<td>37.2 (0.3)</td>
<td>37.9 (0.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Creatinine day 1, µmol litre⁻¹</td>
<td>90.0 (23.3)</td>
<td>95.0 (12.3)</td>
<td>0.57</td>
</tr>
<tr>
<td>Length of stay in ICU (days)</td>
<td>1.2 (0.4)</td>
<td>1.1 (0.3)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Marked blood loss occurred in one patient in the dexamethasone group, who received 13 units of blood more than 6 h after bypass. As this would affect only time point 6 of the study, this patient is included in the analysis.

There was no clinical or laboratory evidence of postoperative renal dysfunction in either group. Urine output during surgery and in the postoperative period did not differ between groups (Fig. 1).

The time course of glomerular function is shown in Figure 2. At baseline, glomerular variables were similar and within the normal range in both groups. Both groups showed a similar increase in creatinine clearance in the first 2 h after weaning from CPB, albeit not significantly (point 4), which returned to baseline values by the second postoperative day. During the entire observation period, no differences in creatinine clearances between the groups were found. Urinary microalbumin excretion increased in both groups with a peak at the end of CPB (P=0.007 and P=0.005 in the placebo and dexamethasone group compared with baseline values, respectively, point 3 in Fig. 2), and returned to baseline by the second postoperative day.

The time course of tubular variables is given in Figure 3. At baseline, no differences between variables were found. Fractional excretion of sodium increased in both groups after the start of bypass (P=0.013 and P=0.007 in the placebo and dexamethasone group compared with baseline values at time point 4, respectively), and returned to baseline values by the second postoperative day, with no differences observed between groups. Free water clearance decreased during heparinization then increased during CPB in both groups and returned by baseline on the second postoperative day.

In the intensive care unit (point 5), free water clearance was decreased in both groups compared with baseline values (P=0.028 and P=0.022 in the placebo and dexamethasone group compared with baseline values, respectively). The urinary excretion of NAG increased during the operative period and returned to baseline levels by the second postoperative day.

Fig 1 Urine output in the two groups (mean (SEM)) at six time points: (1) baseline, during the 12 h before surgery; (2) after skin incision before systemic heparinization; (3) from heparinization until the end of CPB; (4) during the 2 h after weaning from CPB; (5) in the intensive care unit from 2 to 6 h after weaning from CPB, and (6) from 36 to 60 h after weaning from CPB. There was no difference between the two groups at any time point.
postoperative day in both groups (P=0.007 and P=0.005 in the placebo and dexamethasone group compared with baseline values, respectively, at time points 3 and 4). In patients treated with dexamethasone, glycosuria was more marked than in the placebo group (Table 2). In the intensive care unit, glycosuria in the dexamethasone group returned towards baseline values as a result of insulin therapy.

**Discussion**

In this randomized, double-blind study we demonstrated that dexamethasone does not exert an obvious protective effect on the transient perioperative renal dysfunction that occurs in cardiac surgical patients undergoing CPB. While the release patterns of several sensitive markers clearly demonstrate a transient impairment of glomerular and tubular renal function, these patterns were similar in the perioperative period in both placebo and dexamethasone-treated patients and returned to baseline levels within 3 days. The transient subclinical renal damage observed in low-risk cardiac surgical patients undergoing CPB is in accordance with previous investigations.2 9–11

With respect to the effects of corticosteroids on renal function in cardiac surgical patients, limited information is available. Nonoyama and colleagues studied the effect of a massive dose of dexamethasone on renal function and suggested that the drug had a protective renal effect as evidenced by an increase in urinary output from a solute diuresis. However, no difference in creatinine clearance was observed.12 To our knowledge, our study is the first randomized double-blinded study evaluating the effect of dexamethasone on perioperative renal function by assessing functional variables and levels of specific markers related to glomerular and tubular function. In every patient, the time course of renal markers was studied into the postoperative period, and demonstrated reproducible elevations in patients who underwent CPB. As both time course and multiple

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**Table 2** Urinary glucose (mmol litre$^{-1}$). Data median (range) sample period: see legend to Figure 1. *,# = significant increase over baseline levels, P<0.01 and P<0.05, respectively

<table>
<thead>
<tr>
<th>Sample period</th>
<th>Dexamethasone</th>
<th>Placebo</th>
<th>P-value between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.4 (17.4)</td>
<td>0.5 (3.3)</td>
<td>0.85</td>
</tr>
<tr>
<td>2</td>
<td>0.6 (108.6)</td>
<td>0.8 (2.8)</td>
<td>0.63</td>
</tr>
<tr>
<td>3</td>
<td>1.4 (78.4)*</td>
<td>1.0 (4.5)</td>
<td>0.63</td>
</tr>
<tr>
<td>4</td>
<td>4.9 (49.0)*</td>
<td>0.4 (4.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>5</td>
<td>16.2 (64.7)*</td>
<td>0.8 (28.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>6</td>
<td>1.5 (203)*</td>
<td>0.8 (55.5)#</td>
<td>0.36</td>
</tr>
</tbody>
</table>
markers were studied, a substantial beneficial effect of dexamethasone on renal impairment should have been detected despite the limited patient numbers, as we found previously in patients undergoing beating heart surgery. \(^2\)

How does one explain the absence of any effect from dexamethasone? First, the dexamethasone dosage may have been inadequate. This explanation seems unlikely, in view of the marked temperature and diabetogenic effect observed in the dexamethasone-treated patients. A second explanation may be that dexamethasone does not adequately prevent the sensitization of neutrophils and their subsequent tissue sequestration. Indeed, Gu and colleagues demonstrated recently that dexamethasone \(1 \text{ mg kg}^{-1}\) did not stabilize neutrophils, and that priming and sensitization of neutrophils occurred before commencing CPB. \(^3\) Yet the contribution of the inflammatory response to transient renal dysfunction during CPB is still unclear. It was suggested recently that leukodepletion during cardiac surgery with CPB may offer some renal protection, as demonstrated by Tang and colleagues. \(^4\) A third explanation, related to neutrophil activation, may be the inability of dexamethasone to mitigate complement activation. It has been demonstrated that corticosteroids do not prevent the perioperative increase in blood levels of C3a in patients undergoing cardiac surgery with CPB. \(^5\) \(^6\) \(^7\) Alternatively, the transient renal dysfunction observed in CPB may be caused by other factors that are probably unaffected by dexamethasone, such as non-pulsatile flow or hypoxia.

Controversy exists about the beneficial effect of corticosteroids in patients undergoing cardiac surgery with CPB. \(^7\) Beneficial effects of corticosteroids have been reported in several clinical investigations, including improved hemodynamics (increased CI, decreased SVR) and increased pulmonary compliance. \(^8\) \(^9\) \(^10\) The effect of dexamethasone on pro- and anti-inflammatory cytokine responses during coronary artery bypass grafting with CPB has been studied by El Azab and colleagues. \(^11\) Dexamethasone \(100 \text{ mg}\) before induction of anaesthesia changes the circulating cytokine profile in an anti-inflammatory direction, and results in a more stable cardiovascular postoperative course and a shorter stay in the intensive care unit. In contrast, Chaney and colleagues reported that administration of corticosteroids demanded increased haemodynamic support and a prolonged intubation time, while Mayumi and colleagues found increased blood glucose levels. \(^12\) \(^13\) \(^14\) \(^15\) \(^16\) Furthermore, in a study by Niazi and colleagues, patients were randomized into three groups to receive, before CPB, methylprednisolone \(30 \text{ mg kg}^{-1}\), dexamethasone \(6 \text{ mg kg}^{-1}\), or placebo therapy. \(^17\) In this study, no differences in perioperative variables were found between the dexamethasone and the placebo group. In our study, we did not observe an overall beneficial effect from dexamethasone treatment. However, patients in the dexamethasone group received a low dose of dopamine significantly more often. In addition, dexamethasone-treated patients tended to have longer aorta cross-clamping time and a lower number of grafts compared with placebo patients although the differences did not reach statistical significance (Table 1). The difference in inotropic support may therefore be explained by surgery-related factors, including less favourable coronary artery anatomy or less effective myocardial protection. Alternatively, dexamethasone treatment may have impaired cardiovascular performance requiring additional inotropic support. Nevertheless, despite increased inotropic support, the ICU stay of dexamethasone-treated patients was not extended. Furthermore, the postoperative serum glucose level was significantly higher in the dexamethasone group, resulting in pronounced glycosuria with a need for insulin administration. It has been reported that pronounced hyperglycaemia may lead to complications in critically ill patients. \(^18\) Van de Berghe and colleagues demonstrated that normalization of blood glucose with intensive insulin therapy reduces morbidity and mortality among critically ill patients in the surgical intensive care unit. \(^19\) Taken together, these observations suggest that corticosteroids offer no overall clinical benefit in low-risk patients undergoing cardiac surgery with CPB.

A number of studies have investigated release patterns of markers of renal dysfunction in cardiac surgery patients undergoing CPB. \(^20\) \(^21\) \(^22\) While creatinine clearance is of limited value, a number of additional markers display a transient increase during the bypass and ICU period, and normalize during the first postoperative week. \(^23\) \(^24\) \(^25\) \(^26\) \(^27\) While this generally holds true for NAG activity, its activity at specific time points is difficult to compare between studies because of differences in sampling methodology and the assay method used, resulting in large variations in NAG activity. Specifically, this applies to the secondary NAG peak found by assessing urinary levels of specimens obtained 48 h after surgery in CPB patients. \(^28\) In our current and previous study, \(^2\) which used a sampling period from 36 to 60 h after surgery, this secondary peak was not identified.

A limitation of the current study is that, despite randomization, patients in the dexamethasone group were slightly older and hence the possibility of confounding exists. However, its impact seems limited, as baseline values of sensitive markers were similar in both groups and no correlation was found between age and the baseline levels of renal markers or their increase during CPB. The similarity of the patient groups is likely a result of the inclusion of low-risk patients without concomitant co-morbidity. Further, in the present study, a small beneficial effect of dexamethasone administration compared with placebo may have gone unnoticed. However, such a possible effect seems clinically irrelevant in view of the major protection from renal damage by off-pump surgery in a similar patient population. \(^2\)

In conclusion, in this study, transient subclinical renal damage was demonstrated in low-risk patients undergoing coronary artery bypass grafting with CPB. Dexamethasone administration before CPB was without beneficial effect. More importantly, dexamethasone did not display any
protective effect on the transient impairment of renal function, which occurs during cardiac surgery.

References