**Cyclosporine before Coronary Artery Bypass Grafting does not prevent postoperative decreases in renal function: A randomized clinical trial.**

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Supplementary Appendix CiPRICS Trial

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## Table S1. Markers of myocardial damage

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Markers of myocardial damage** | | **Placebo (N=79)** | **Cyclosporine (N=75)** | **p** |  |
|  |  |  |  |  |  |
| Plasma Troponin T (ng/L) | |  |  | 0.279\* |  |
| Day -1 | | 43 ± 123 | 35 ± 126 |  |  |
| 4 hours | | 381 ± 202 | 334 ± 164 |  |  |
| 8 hours | | 390 ± 184 | 366 ± 204 |  |  |
| 12 hours | | 332 ± 176 | 361 ± 331 |  |  |
| 24 hours | | 269 ± 189 | 286 ± 294 |  |  |
| Day 2 | | 251 ± 223 | 330 ± 900 |  |  |
| Day 3 | | 222 ± 213 | 327 ± 1153 |  |  |
| Day 4 | | 221 ± 271 | 313 ± 1094 |  |  |
|  | |  |  |  |  |
| Plasma CK-MB (µg/L) | |  |  | 0.412\* |  |
| Day -1 | | 2.7 ± 1.7 | 2.81 ± 3.0 |  |  |
| 4 hours | | 14.9 ± 6.0 | 14.6 ± 5.4 |  |  |
| 8 hours | | 15.5 ± 9.4 | 15.7 ± 9.9 |  |  |
| 12 hours | | 15.7 ± 15.8 | 16.1 ± 15.9 |  |  |
| 24 hours | | 14.4 ± 18.1 | 14.0 ± 21.1 |  |  |
| Day 2 | | 6.8 ± 8.2 | 7.3 ± 17.3 |  |  |
| Day 3 | | 3.2 ± 2.7 | 3.6 ± 8.0 |  |  |
| Day 4 | | 2.6 ± 2.3 | 2.3 ± 2.3 |  |  |
|  | |  |  |  |  |
|  | |  |  |  |  |
| CK-MB AUC (µg\*h/L) | | 780.9 ± 667.3 | 793.3 ± 1137.6 | 0.699\*\* |  |
|  | |  |  |  |  |
| Troponin-T AUC (ng\*h/L) | | 24614 ± 18030 | 30377 ± 68508 | 0.206\*\* |  |

Table S1. Markers of myocardial damage expressed as mean ± SD. Day -1 illustrates the day before surgery, usually the same as admission day. Day 0 surgery day, Day 1 the day after surgery etc. Hours means hours after study drug administration. \*Testing with Linear Mixed Model. **T**roponin and CK-MB log transformed before testing.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Marker of cerebral damage** | **Placebo (N=79)** | **Cyclosporine (N=75)** | **p** |  |
|  |  |  |  |  |
| Serum S100B (µg/L) |  |  | 0.677\* |  |
| Day -1 | 0.07 ± 0.08 | 0.06 ± 0.03 |  |  |
| Day 1 | 0.16 ± 0.17 | 0.16 ± 0.07 |  |  |
| Day 2 | 0.14 ± 0.15 | 0.13 ± 0.06 |  |  |

## Table S2. Marker of cerebral damage

Table S2. Marker of cerebral damage expressed as mean ± SD. Day -1 illustrates the day before surgery, usually the same as admission day. Day 0 surgery day, Day 1 the day after surgery etc. \*Testing with Linear Mixed Model. S100B log transformed before testing.

## Table S3. SAE listing according MedRa classification

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | Placebo | Cyclosporine |
|  |  | n (%) | n (%) |
| SAE | | 14 (53.8) | 12 (46.2) |
|  | Postoperative wound infection | 0 (0.00) | 1 (8.33) |
|  | Atrial fibrillation | 0 (0.00) | 1 (8.33) |
|  | Cardiac arrest, Myocardial infarction, Pulmonary oedema | 1 (7.14) | 0 (0.00) |
|  | Cardiac disorder | 1 (7.14) | 0 (0.00) |
|  | Cardiac failure | 0 (0.00) | 1 (8.33) |
|  | Chest pain, Nausea, Vomiting | 1 (7.14) | 0 (0.00) |
|  | Colon gangrene | 0 (0.00) | 1 (8.33) |
|  | Deep vein thrombosis | 1 (7.14) | 0 (0.00) |
|  | Gastrointestinal bleeding | 1 (7.14) | 0 (0.00) |
|  | Gastrointestinal bleeding, Cardiac arrest | 0 (0.00) | 1 (8.33) |
|  | Hydronephrosis, Ureteral stricture | 1 (7.14) | 0 (0.00) |
|  | Infection | 1 (7.14) | 0 (0.00) |
|  | Mediastinitis | 1 (7.14) | 0 (0.00) |
|  | Non-cardiac chest pain | 1 (7.14) | 0 (0.00) |
|  | Pericardial effusion | 1 (7.14) | 1 (8.33) |
|  | Pleural effusion | 0 (0.00) | 3 (25.00) |
|  | Pneumonia | 1 (7.14) | 1 (8.33) |
|  | Postpericardiotomy syndrome | 1 (7.14) | 0 (0.00) |
|  | Raised liver function tests | 0 (0.00) | 1 (8.33) |
|  | Stroke | 2 (14.29) | 0 (0.00) |
|  | Vascular graft occlusion, myocardial infarction | 0 (0.00) | 1 (8.33) |

Table S3. SAE listing according MedRa classification

## Table S4. Safety biochemistry.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Safety Chemistry** | | **Placebo (N=79)** | **Cyclosporine (N=75)** | **p** |  |
|  |  |  |  |  |  |
| Plasma Potassium (mmol/L) | |  |  | 0.007\* |  |
| Preoperatively | | 4.1 ± 0.3 | 4.1 ± 0.3 |  |  |
| Day 1 | | 4.5 ± 0.3 | 4.6 ± 0.3 | 0.290\* |  |
| Day 2 | | 4.1 ± 0.4 | 4.3 ± 0.3 | <0.001\* |  |
| Day 3 | | 4.1 ± 0.3 | 4.1 ± 0.3 | 0.978\* |  |
| Day 4 | | 4.2 ± 0.4 | 4.2 ± 0.4 | 0.867\* |  |
|  | |  |  |  |  |
| Plasma Mg (mmol/L) | |  |  | 0.696\* |  |
| Preoperatively | | 0.8 ± 0.1 | 0.8 ± 0.1 |  |  |
| Day 1 | | 1.1 ± 0.2 | 1.1 ± 0.2 |  |  |
| Day 2 | | 0.9 ± 0.1 | 0.9 ± 0.2 |  |  |
| Day 3 | | 0.9 ± 0.1 | 0.9 ± 0.3 |  |  |
| Day 4 | | 0.9 ± 0.1 | 0.9 ± 0.2 |  |  |
|  | |  |  |  |  |
| Plasma CK (µkat/L) | |  |  | 0.635\* |  |
| Preoperatively | | 1.7 ± 1.2 | 1.7 ± 1.3 |  |  |
| Day 1 | | 10.3 ± 6.5 | 9.1 ± 6.3 |  |  |
| Day 2 | | 11.8 ± 11.7 | 10.7 ± 9.8 |  |  |
| Day 3 | | 8.1 ± 9.1 | 7.6 ± 9.1 |  |  |
| Day 4 | | 4.6 ± 4.7 | 4.6 ± 5.0 |  |  |
|  | |  |  |  |  |
| Plasma Bilirubin (µmol/L) | |  |  | 0.933\* |  |
| Preoperatively | | 8.4 ± 4.3 | 7.6 ± 3.8 |  |  |
| Day 1 | | 12.2 ± 5.3 | 13.5 ± 7.0 |  |  |
| Day 2 | | 11.0 ± 4.7 | 12.7 ± 8.0 |  |  |
| Day 3 | | 9.8 ± 4.9 | 11.1 ± 6.6 |  |  |
| Day 4 | | 9.9 ± 5.1 | 10.8 ± 5.6 |  |  |
|  | |  |  |  |  |
| Plasma ASAT (µkat/L) | |  |  | 0.722\* |  |
| Preoperatively | | 0.5 ± 0.3 | 0.7 ± 0.4 |  |  |
| Day 1 | | 0.8 ± 0.4 | 0.9 ± 0.8 |  |  |
| Day 2 | | 0.7 ± 0.4 | 1.0 ± 3.3 |  |  |
| Day 3 | | 0.6 ± 0.3 | 1.3 ± 6.1 |  |  |
| Day 4 | | 0.7 ± 1.0 | 0.9 ± 2.7 |  |  |
|  | |  |  |  |  |
| P-ALAT (µkat/L) | |  |  | 0.532\* |  |
| Preoperatively | | 0.7 ± 0.5 | 1.0 ± 1.0 |  |  |
| Day 1 | | 0.6 ± 0.6 | 0.9 ± 0.8 |  |  |
| Day 2 | | 0.5 ± 0.4 | 1.1 ± 3.8 |  |  |
| Day 3 | | 0.5 ± 0.3 | 1.3 ± 5.9 |  |  |
| Day 4 | | 0.7 ± 1.3 | 1.1 ± 4.5 |  |  |
|  | |  |  |  |  |
| Plasma GT (µkat/L) | |  |  | 0.856\* |  |
| Preoperatively | | 1.2 ± 2.1 | 0.9 ± 0.9 |  |  |
| Day 1 | | 0.9 ± 1.4 | 0.7 ± 0.7 |  |  |
| Day 2 | | 0.8 ± 1.3 | 0.7 ± 0.6 |  |  |
| Day 3 | | 1.0 ± 1.5 | 0.8 ± 0.8 |  |  |
| Day 4 | | 1.3 ± 1.7 | 1.0 ± 1.1 |  |  |
|  | |  |  |  |  |
| P-ALP (µkat/L) | |  |  | 0.824\* |  |
| Preoperatively | | 1.4 ± 0.7 | 1.4 ± 0.6 |  |  |
| Day 1 | | 1.0 ± 0.4 | 1.0 ± 0.5 |  |  |
| Day 2 | | 1.0 ± 0.4 | 1.1 ± 0.4 |  |  |
| Day 3 | | 1.1 ± 0.5 | 1.2 ± 0.7 |  |  |
| Day 4 | | 1.3 ± 0.9 | 1.5 ± 1.2 |  |  |
|  | |  |  |  |  |
| Plasma CRP (mg/L) | |  |  | <0.001\* |  |
| Preoperatively | | 6.1 ± 9.0 | 4.0 ± 6.1 |  |  |
| Day 1 | | 63.4 ± 27.8 | 59.0 ± 33.0 | 0.286 |  |
| Day 2 | | 171.8 ± 67.9 | 196.7 ± 75.5 | 0.002 |  |
| Day 3 | | 185.5 ± 73.2 | 223.7 ± 82.9 | <0.001 |  |
| Day 4 | | 141.2 ± 73.6 | 175.4 ± 74.2 | <0.001 |  |
|  | |  |  |  |  |
| Blood Leukocytes (109/L) | |  |  | 0.032\* |  |
| Preoperatively | | 7.7 ± 1.8 | 7.5 ± 1.7 |  |  |
| Day 1 | | 11.8 ± 3.5 | 13.5 ± 3.5 | <0.001 |  |
| Day 2 | | 11.8 ± 2.8 | 13.5 ± 3.3 | <0.001 |  |
| Day 3 | | 11.1 ± 2.7 | 12.0 ± 2.5 | 0.002 |  |
| Day 4 | | 9.7 ± 2.5 | 10.1 ± 2.2 | 0.033 |  |
|  | |  |  |  |  |
| Blood Haemoglobin (g/L) | |  |  | 0.046\* |  |
| Preoperatively | | 137.8 ± 15.8 | 135.6 ± 13.7 |  |  |
| Day 1 | | 111.8 ± 13.1 | 108.9 ± 12.4 | 0.326 |  |
| Day 2 | | 103.2 ± 12.8 | 101.8 ± 11.4 | 0.826 |  |
| Day 3 | | 104.1 ± 11.9 | 99.1 ± 11.1 | 0.023 |  |
| Day 4 | | 105.7 ± 12.4 | 101.5 ± 10.9 | 0.064 |  |
|  | |  |  |  |  |
| Blood Thrombocytes (109/L) | |  |  | 0.019\* |  |
| Preoperatively | | 237.5 ± 60.6 | 242.3 ± 63.2 |  |  |
| Day 1 | | 186.0 ± 47.0 | 187.5 ± 53.0 | 0.979 |  |
| Day 2 | | 169.3 ± 46.0 | 164.9 ± 44.3 | 0.108 |  |
| Day 3 | | 183.2 ± 47.8 | 173.5 ± 47.5 | 0.012 |  |
| Day 4 | | 225.2 ± 56.8 | 210.4 ± 55.1 | 0.006 |  |
|  | |  |  |  |  |

Table S4. Safety biochemistry expressed as mean ± SD. Outcome in terms of safety related clinical chemistry. Day -1 illustrates the day before surgery, usually the same as admission day. Day 0 surgery day, Day 1 the day after surgery etc. Mg = Magnesium, ASAT = Aspartate Aminotransferase, ALAT = Alanine Aminotransferase, ALP = Alkaline Phosphatase, GT = Gamma-glutamyl Transferase, CRP = C-Reactive Protein, CK = Creatine Kinase. \* Linear Mixed Model. All variables (besides potassium and haemoglobin) log transformed before testing.

## Table S5. Diuretics

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Diuretics** | | **Placebo (N=79)** | **Cyclosporine (N=75)** | **p** |  |
|  |  |  |  |  |  |
| Furosemide (mg) | |  |  |  |  |
| Day 0 | | 0 (0‒0) | 0 (0‒10) | 0.185 |  |
| Day 1 | | 85 (60‒120) | 100 (80‒133) | 0.077 |  |
| Day 2 | | 80 (40‒90) | 80 (80‒120) | 0.002 |  |
| Day 3 | | 40 (0‒80) | 80 (40‒80) | 0.007 |  |
| Day 4 | | 20 (0‒40) | 40 (0‒80) | 0.053 |  |
|  | |  |  |  |  |
| Amilorid (mg) | |  |  |  |  |
| Day 0 | | 0 (0‒0) | 0 (0‒0) | 0.970 |  |
| Day 1 | | 5 (0‒5) | 5 (5‒5) | 0.203 |  |
| Day 2 | | 5 (0‒5) | 5 (0‒5) | 0.242 |  |
| Day 3 | | 0 (0‒5) | 5 (0‒5) | 0.004 |  |
| Day 4 | | 0 (0‒5) | 5 (0‒5) | 0.011 |  |
|  | |  |  |  |  |

Table S5: Administration of diuretics (intravenous and orally combined) in the two groups. Median (IQR). All testing with Mann-Whitney U-test.