Methylprednisolone inhibits increase of interleukin 8 and 6 during open heart surgery

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It has been reported that interleukin 8 (IL-8) and interleukin 6 (IL-6) are two of the chemical mediators causing myocardial injury. It is not clear whether treatment with corticosteroids in vitro in these patients can prevent the production of interleukin 8 and 6. This prospective study was conducted to investigate whether methylprednisolone (MP) pretreatment (30 mg · kg⁻¹ before CPB and before declamping of aorta) influenced the production of IL-8 and 6 in the peripheral circulation in 27 patients undergoing elective coronary artery bypass surgery. The IL-8 and IL-6 concentrations were measured by ELISA kit. We also studied the effect of MP pretreatment on postoperative cardiac function. Serum concentration of IL-8 in non-MP-treated patients (37 ± 44 pg · ml⁻¹ preoperatively) increased to 169 ± 86 pg · ml⁻¹ 60 min after declamping of the aorta (P < 0.001). The increase was greater than the increase from 22 ± 8.9 pg · ml⁻¹ to 52 ± 35 pg · ml⁻¹ in the MP-treated patients (P < 0.01). Serum IL-6 concentration in non-MP-treated patients increased from the preoperative value of 59 ± 30 pg · ml⁻¹ to 436 ± 143 pg · ml⁻¹ 60 min after declamping of the aorta (P < 0.001). The increase was greater than the increase from 36 ± 15 pg · ml⁻¹ to 135 ± 85 pg · ml⁻¹ in the MP-treated patients (P < 0.01). Furthermore, postoperative cardiac index in MP-treated patients (3.6 ± 1.1 L · min⁻¹ · m⁻²) was higher than 2.3 ± 0.8 L · min⁻¹ · m⁻² of non MP-treated patients (P < 0.05). The levels of IL-8 max during surgery correlated negatively with postoperative cardiac index (γ = -0.67). These results suggest that methylprednisolone suppresses production of IL-8 and 6.

On a rapporté que l'interleukine 8 (IL-8) et que l'interleukine 6 (IL-6) étaient deux des médiateurs chimiques de la lésion cardiaque. Toutefois, on ne sait pas encore si le traitement aux corticostéroïdes in vivo prévient la production des interleukines 8 et 6. Cette étude prospective vise à déterminer si le prétraitement à la méthylprednisolone (MP) (30 mg · kg⁻¹ avant le CEC et avant le déclampage de l'aorte) influence la concentration de l'IL-8 de l'IL-6 du sang veineux périphérique de 27 patients soumis à une chirurgie réglée de revascularisation myocardique. Les concentrations de l'IL-8 de l'IL-6 sont mesurées avec une trousse Elisa. Nous étudions aussi les répercussions du traitement à la MP sur la fonction cardiaque postopératoire. La concentration sérique de l'IL-8 des patients non traités (37 ± 44 pg · ml⁻¹ en préopératoire) augmente à 169 ± 86 pg · ml⁻¹ 60 minutes après le déclampage de l'aorte (P < 0,001). Cette augmentation est plus importante que l'augmentation de 22 ± 8,9 pg · ml⁻¹ à 52 ± 35 pg · ml⁻¹ notée chez les patients traités à la MP (P < 0,01). La concentration sérique de l'IL-6 chez les patients non traités à la MP augmente de la valeur préopératoire de 59 ± 30 pg · ml⁻¹ à 436 ± 143 pg · ml⁻¹ 60 min après le déclampage de l'aorte (P < 0,001). Cette augmentation est plus importante que celle de 36 ± 15 pg · ml⁻¹ à 135 ± 85 pg · ml⁻¹ survenue chez les patients traités à la MP (P < 0,01). De plus, l'index cardiaque postopératoire des patients traités à la MP (3,6 ± 1,1 L · min⁻¹ · m⁻²) est plus élevé que celui des patients non traités 2,3 ± 0,8 L · min⁻¹ · m⁻² (P < 0,05). Les niveaux maximaux de l'IL-8 sont en corrélation négative avec l'index cardiaque postopératoire (γ = 0,67). Ces résultats suggèrent que la méthylprednisolone supprime la production de l'IL-8 et de l'IL-6.

Key words

HEART: reperfusion injury;
HORMONES: cytokines, interleukins, methylprednisolone;
ANAESTHESIA: cardiac, cardiopulmonary bypass.

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There are many reports that, in reperfusion models, infarct size after myocardial ischaemia may be decreased by inhibiting infiltration of neutrophils into ischaemic myocardium,¹⁻³ and attention has been focused on the possible role of neutrophils in reperfusion injury. The mechanism by which neutrophils cause myocardial ischaemia include the presence of free oxygen radicals, products of arachidonic acid metabolized by the lipooxygenase

pathway, or neutrophil lysosomal enzymes including granulocyte elastase (GEL). These substances are induced after neutrophils are activated, suggesting that post-ischaemic reperfusion injury may be relieved if neutrophil activation were inhibited. Previously, we measured inflammatory cytokines such as IL-8 and IL-6 which are potent activators of neutrophils, during open heart surgery. From 60 min after reperfusion (declamping of aorta), plasma concentrations increased from levels seen before surgery and at 60 min after aortic occlusion, and these increases correlated with GEL and CK-MB,⁴ indicating that neutrophils, activated by the increased production of IL-8 and IL-6, were cytotoxic. In the present study, methylprednisolone, which has been shown to inhibit cytokines *in vitro* and *in vivo*,⁵⁻⁸ was given to patients undergoing open heart surgery, and its inhibitory effect on the increased production of IL-8 and IL-6 during open heart surgery was investigated. In addition, the effects of MP on the postoperative cardiac function were also observed.

Methods

With insituational approval and informed consent, this randomized study was performed in 27 patients undergoing elective coronary artery bypass surgery: Group I, 11 patients underwent standard CPB; Group II, 16 patients received 30 mg · kg⁻¹ MP (Solumedrol®, Upjohn Ltd.) *iv* before CPB and before declamping of the aorta. Preanaesthetic medication included diazepam (0.2 mg · kg⁻¹), hydroxyzine (1 mg · kg⁻¹), meperidine (1 mg · kg⁻¹) and atropine (0.01 mg · kg⁻¹). Anaesthesia was induced with fentanyl (30 µg · kg⁻¹), and tracheal intubation was facilitated with vecuronium (0.15 mg · kg⁻¹). Anaesthesia was maintained using oxygen, and high-dose fentanyl (total 100 µg · kg⁻¹). Ventilation was controlled to maintain PaCO₂ at approximately 40 mmHg.

The perfusion apparatus included a hollow fibre membrane oxygenator (Terumo, Capiox) and nonpulsatile roller pump (Pemco Inc.). A mixture of 20% mannitol, 7% sodium bicarbonate, electrolyte solution, and CPD-added preserved blood was used for priming, and then perfused at a flow of 2.4 L · m⁻² · min⁻¹. Haematocrit concentrations were maintained at 20% or more throughout CPB. Crystalloid and blood cardioplegia was used for cardiac preservation.

The ECG, EEG, and oesophageal and rectal temperatures were monitored continuously. Arterial blood oxygen saturation was monitored continuously with a pulse-oximeter (Datex, Satlite), and end-tidal carbon dioxide concentrations with capnography (Datex, Capnomac). A pulmonary artery catheter was inserted into the internal carotid vein and a catheter was placed in the radial artery to measure arterial pressure directly, and from which

TABLE I Clinical characteristics

Group	Group I	Group II
Patients	<i>n</i> = 11	<i>n</i> = 16
Age (yr)	58 ± 13	58 ± 14
BW (kg)	52 ± 11	52 ± 9.7
EF (%)	58.5 ± 10.9	59.7 ± 13
CPB (min)	181 ± 41	148 ± 50
Ao clamp (min)	87 ± 31	97 ± 34
Cardioplegia (ml)	1993 ± 560	2047 ± 659
	mean ± SD	mean ± SD

Values are mean ± SD BW: body weight; EF: ejection fraction; CPB: cardiopulmonary bypass; Ao.clamp: aortic clamp time.

blood samples were drawn. Six blood samples were drawn after induction of anaesthesia, at the following times: before surgery, immediately before starting CPB, 60 min after aortic occlusion, and 60, 120 and 180 min after declamping of the aorta. In each sample, IL-8, IL-6, GEL, CK and CK-MB concentrations were measured. The IL-8 and IL-6 were measured by ELISA kits (IL-8: R&D systems Minneapolis, MN, USA,⁹ IL-6: Toray Fujibionics Inc, Tokyo, Japan),¹⁰ and GEL by enzyme linked immunosorbent assay as GEL-α₁-PI complex. For statistical analyses, Scheffe's F test was used for multiple comparison, and Student's t test for between-group comparison. Significant difference was defined as *P* < 0.05. Data were presented as mean ± standard deviation (mean ± SD).

Results

Patients from the two groups did not differ in terms of age, body weight, ejection fraction, duration of CPB, aortic clamping time and cardioplegic solution (Table I).

The serum concentration of IL-8 increased at 60, 120, 180 min after reperfusion (declamping of aorta) compared with the value before surgery in both groups (*P* < 0.01). The IL-8 concentration in Group II was less (*P* < 0.01) than that in Group I at each time point after reperfusion (Figure 1). The serum concentration of IL-6 increased 60 min after reperfusion and was maintained at a high concentration until 180 min after reperfusion compared with the value of before surgery in both groups (*P* < 0.01). The IL-6 concentration in Group II was less (*P* < 0.01) than that in group I at each time point after reperfusion (Figure 2). Plasma GEL and serum CK concentrations increased progressively at 60, 120, 180 min after reperfusion compared with the values before surgery (*P* < 0.01, *P* < 0.01, Table II). Serum CK-MB concentration increased at 120, 180 min after reperfusion compared with the value before surgery (*P* < 0.01, Table II). There were no differences between the groups in GEL, CK and CK-MB concentration (Table II). On en-

FIGURE 1 IL-8 concentrations at the different times in patients treated with (Group II) or without (Group I) methylprednisolone. Sampling point (1) before operation (2) pre-CPB (3) 60 min after aortic clamp (4) 60 min after declamping of the aorta (5) 120 min after declamping of the aorta (6) 180 min after declamping of the aorta. Mean $\pm$ SD. $\star P < 0.01$ vs before operation. $\star P < 0.05$ vs Group I (without MP)

FIGURE 2 IL-6 concentrations in serum at the different times in patients treated with (Group II) or without (Group I) methylprednisolone. Mean $\pm$ SD. $\star P < 0.01$ vs before operation. $\star P < 0.05$ vs Group I (without MP)

tering the Intensive Care Unit (ICU) after surgery, the cardiac index was higher in Group II (3.6 ± 1.1 L $\cdot$ min $^{-1}$ $\cdot$ m $^{-2}$) than in Group I (2.3 ± 0.8 L $\cdot$ min $^{-1}$ $\cdot$ m $^{-2}$) ($P < 0.05$) and the pulmonary capillary

wedge pressure (PCWP) was lower in Group II (9.7 ± 3.4 mmHg) than 12.2 ± 3.9 mmHg in Group I ($P < 0.05$). Cardiac index at the entrance of ICU was correlated negatively with the IL-8 maximum during surgery in Group II ($\gamma = 0.67$, $P < 0.05$, Figure 3).

Doses of catecholamine used after cardiac surgery in ICU were not different between groups. (Group I: dobutamine 7.62 ± 11.1 μ g $\cdot$ kg $^{-1}$ $\cdot$ min $^{-1}$, dopamine 3.77 ± 1.6 μ g $\cdot$ kg $^{-1}$ $\cdot$ min $^{-1}$; Group II: dobutamine 10.69 ± 4.2 μ g $\cdot$ kg $^{-1}$ $\cdot$ min $^{-1}$, dopamine 5.0 ± 2.0 μ g $\cdot$ kg $^{-1}$ $\cdot$ min $^{-1}$).

Discussion

Free oxygen radicals have been considered to play an important role in post-ischaemic reperfusion injury as a direct cytotoxic factor. However, recent reports showed that monoclonal antibodies of adhesion molecules decrease reperfusion injury and indicate that an interaction between neutrophils and the vascular endothelium may be an important pathogenic factor in post-ischaemic reperfusion injury.¹¹⁻¹³ Adhesion molecules are expressed on the membrane surface of neutrophils and endothelial cells, and this is followed by their adhesion and activation, which produce various cytotoxic effects. Further, inflammatory cytokines (IL-2, TNF- α , IL-6, IL-8, etc.), which are produced from monocyte, macrophages or endothelial cells, play an important role in the interaction between neutrophils and vascular endothelium.^{14,15} These cytokines stimulate neutrophils and endothelial cells to express various adhesion molecules on their membrane surface and, accordingly, activate them directly or indirectly.

In our previous study, IL-8, IL-6 and TNF- α were determined in patients undergoing open heart surgery with cardiopulmonary bypass. The results showed that changes in TNF- α , were minimal throughout the peri-operative period, but that concentrations of IL-8 and IL-6 increased at 60, 120 and 180 min after reperfusion compared with levels before surgery and 60 min after aortic occlusion. In addition, the changes correlated with the CK-MB and duration of aortic occlusion. These results suggested that the production of IL-8 and IL-6 in the endothelium due to ischaemia was involved in reperfusion injury.⁴ In the present study, methylprednisolone was given to similar patients, on the assumption that its inhibitory effect on the increased production of IL-6 and IL-8 might prevent or suppress reperfusion injury and other post-surgical complications, including low output syndrome (LOS). Methylprednisolone is known to inhibit the release of free oxygen radicals,¹⁶ in addition to its anti-shock and membrane-stabilizing effect.¹⁷ It has also been reported recently that methylprednisolone inhibits IL-1, IL-2, IL-6 and TNF- α . Imamura *et al.* have shown *in vitro* a dose-related reduction in the ability of periph-

TABLE II Concentrations of plasma granulocyte elastase (GEL), serum creatine phosphokinase (CK), CK-MB in each period

		Sampling points					
Group		1	2	3	4	5	6
GEL ($\mu\text{g} \cdot \text{L}^{-1}$)	Group I	164 $\pm$ 47	158 $\pm$ 36	422 $\pm$ 325	927 $\pm$ 446*	1195 $\pm$ 648*	1189 $\pm$ 198*
	Group II	168 $\pm$ 71	206 $\pm$ 98	413 $\pm$ 353	1059 $\pm$ 517*	1134 $\pm$ 453*	1062 $\pm$ 467*
CK ($\text{IU} \cdot \text{L}^{-1}$)	Group I	161.6 $\pm$ 116	229.3 $\pm$ 124	246.9 $\pm$ 73	428.6 $\pm$ 130*	519 $\pm$ 240*	592 $\pm$ 179*
	Group II	167 $\pm$ 100	198 $\pm$ 119	210 $\pm$ 73	502 $\pm$ 187*	609 $\pm$ 287*	621 $\pm$ 274*
CK-MB ($\text{IU} \cdot \text{L}^{-1}$)	Group I	0.6 $\pm$ 0.7	0.7 $\pm$ 0.9	0.71 $\pm$ 1.1	4.1 $\pm$ 3.2	6.8 $\pm$ 3.2*	10.8 $\pm$ 6.8*
	Group II	0.8 $\pm$ 1.3	0.8 $\pm$ 1.8	0.4 $\pm$ 1.0	6.6 $\pm$ 8.9	11.7 $\pm$ 12.2*	16.3 $\pm$ 12.5

Sampling times (1) before operation (2) pre-CPB (3) 60 min after aortic clamp (4) 60 min after declamping of the aorta (5) 120 min after declamping of the aorta (6) 180 min after declamping of the aorta. Mean $\pm$ SD. * $P < 0.01$ vs before operation (1).

FIGURE 3 Correlation between cardiac index and the maximum level of interleukin 8 during surgery.

eral monocytes macrophages from patients with multiple sclerosis receiving methylprednisolone to produce cytokines (TNF- α , IL-1, IL-2, IL-6).¹⁸ However, there is no evidence that it inhibits the production of IL-6 or IL-8 *in vivo*. We found that MP was effective in suppressing the increased production of cytokines since the concentrations of IL-8 and IL-6 in MP-treated patients were less than those in non-MP-treated patients at each time point after reperfusion. It has been reported that IL-6 levels increase considerably in patients with acute myocardial infarction.¹⁹ Youker *et al.*²⁰ suggested that the expression of ICAM-1 (intercellular adhesion molecule-1) on cardiac myocytes was induced by IL-6 and adhesion of myocytes to leukocytes was potentiated by IL-6, and in this respect was involved in reperfusion injury. Moreover, Finkel *et al.*²¹ found that IL-6 inhibited myocardial contractility through production of nitric oxide (NO), and suggested that the production of IL-6 might be a pathogenic factor in the stunned myocardium. Whereas, IL-8 has been shown to be chemotactic to neutrophils *in vitro*, and to show various other biological activities including neutrophil activation. Activated neutrophils have

been known to induce the release of lysosomal enzymes^{22,23} and the production of leukotriene B₄²⁴ and 25 HETE. They have also been shown to potentiate the expression of CR-1, Mac-1 and other factors associated with cell adhesion, and thus to increase the adhesion of neutrophils to unstimulated vascular endothelial cell.^{14,15} It was found recently that IL-8 was produced in tissue hypoxaemia related to ischaemia *in vitro*,²⁵ suggesting a possible role of IL-8 in post-ischaemic reperfusion injury, myocardial infarction and multiple organ failure (MOF). This evidence strongly suggests that IL-6 and IL-8 are involved in organ damage and the demonstration that two doses of methylprednisolone at 30 mg $\cdot$ kg⁻¹ inhibit the rise in cytokines during open heart surgery may be of clinical importance.

During surgery, serum CK concentration increased at 60, 120, 180 min after reperfusion in both groups. The CK-MB also increased in both groups at 120, 180 min after reperfusion. It is known that peak concentrations of CK-MB appear 4 to 12 hr after cell injury, and intraoperative changes remained within the normal range in the present study, suggesting that it is difficult to discuss the protective effect of methylprednisolone on the myocardium, if the discussion is only based on its intraoperative levels. Consequently, we evaluated post-surgical cardiac function. As a result, in MP-treated patients, post-surgical cardiac index was higher and PCWP was lower than those in non-MP-treated patients, nevertheless doses of total catecholamine used after cardiac surgery in ICU were not different between groups. Furthermore, cardiac index correlated negatively with maximum concentration of IL-8 during surgery, suggesting that MP pretreatment may improve post-surgical cardiac function by suppressing increased production of IL-8.

In summary, the increased production of IL-6 and IL-8 during open heart surgery with cardiopulmonary bypass was lower in MP-treated patients than in non-MP-treated patients.

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