

# Peran kurkumin sebagai penghambat stres oksidatif akibat cedera iskemia reperfusi pada pasien tetralogi fallot yang menjalani operasi koreksi = The role of curcumin as an inhibitor of oxidative stress caused by ischemic reperfusion injury in tetralogy of fallot patients undergoing corrective surgery

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## Abstrak

### [<b>ABSTRAK</b><br>

Latar Belakang: Penggunaan mesin pintas jantung paru (PJP) selama operasi koreksi pada pasien tetralogi Fallot (TF) dapat menyebabkan respons inflamasi yang intensif. Kombinasi pemberian kardioplegia dan penglepasan spesies oksigen reaktif selama fase reperfusi juga menyebabkan cedera iskemia reperfusi miokardium. Kurkumin diketahui sebagai scavenger beberapa spesies oksigen reaktif. Selain itu, kurkumin juga meningkatkan aktivitas antioksidan seperti glutathione (GSH) dan menekan fosforilasi nuclear factor-kappa B (NF- $\kappa$ B) dan c-Jun N-terminal kinase (JNK). Inhibisi NF- $\kappa$ B dan regulasi jalur bawah JNK merupakan mekanisme yang penting untuk menekan respons inflamasi.

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Tujuan: Untuk mengevaluasi efek proteksi kurkumin sebagai antioksidan pada pasien TF yang menjalani operasi koreksi dengan menilai konsentrasi MDA dan GSH dalam serum, protein aktif NF- $\kappa$ B, JNK dan kaspase-3 di miokardium, serta luaran klinis pascabedah.

Metodologi: Pasien TF usia 1-6 tahun yang direncanakan menjalani operasi koreksi dirandomisasi secara acak ke dalam kelompok kurkumin atau plasebo. Kurkumin (45 mg/hari) diberikan peroral selama 14 hari prabedah. MDA dan GSH dinilai pada fase pra-iskemia, iskemia, reperfusi, dan 6 jam pasca-klem silang aorta dilepas. Pada saat operasi spesimen darah diambil dari atrium kanan pada fase pra-iskemia dan 6 jam pasca-klem silang aorta dilepas, sedangkan dari sinus koronarius diambil pada fase iskemia dan reperfusi. Untuk menilai NF- $\kappa$ B, JNK, dan kaspase-3, spesimen jaringan otot jantung diambil dari infundibulum pada fase pra-iskemia, iskemia, dan reperfusi. NF- $\kappa$ B dan JNK dianalisis dengan metode enzyme-linked immunosorbent assay (ELISA), sedangkan kaspase-3 dengan teknik imunohistokimia. Parameter hemodinamik dan fungsi ventrikel dicatat saat 6 jam, 24 jam, 36 jam, dan hari ke-5 pascabedah.

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Hasil: Selama periode Juli 2012 - Juli 2013, terdapat 45 orang pasien yang direkrut (22 kurkumin dan 23 plasebo). Tidak ada perbedaan konsentrasi MDA dan GSH pada tiap fase pengamatan pada kedua kelompok. Tidak ada beda bermakna aktivitas protein aktif NF- $\kappa$ B di antara ketiga fase pengamatan pra-iskemia, iskemia, atau reperfusi. Tetapi pada kelompok kurkumin aktivitas protein aktif JNK menurun dari fase pra-iskemia ke fase reperfusi. Ekspresi kaspase-3 pada fase pra-iskemia dan reperfusi pada kedua kelompok tidak berbeda. Namun pada kelompok kurkumin terdapat penurunan ekspresi kaspase-3 yang bermakna pada fase iskemia. Hasil klinis menunjukkan terdapat penurunan suhu lebih rendah dan fungsi ventrikel kanan dan kiri yang lebih baik pada kelompok kurkumin secara bermakna, meskipun tidak ada beda dalam waktu pemakaian ventilasi mekanis dan lama perawatan pada kedua kelompok.

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Simpulan: Efek kardioproteksi kurkumin pada cedera iskemia reperfusi pascabedah koreksi TF menghambat jalur JNK dan kaspase-3 yang terjadi pada kardiomiosit, terutama pada fase iskemia. Kurkumin juga memperbaiki fungsi ventrikel kanan dan kiri, serta menurunkan suhu perioperatif.

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Background. Cardiopulmonary bypass (CPB) during tetralogy of Fallot (TF) corrective surgery has been associated with an intense inflammatory response. The cardioplegia used during surgery and the extraburst of reactive oxygen species (ROS) generated during reperfusion contributes to myocardial ischemia and reperfusion injury. Curcumin has been known as a potent scavenger of several types of ROS. It also enhances the activity of antioxidant, such as glutathione (GSH), and suppresses phosphorylation of nuclear factor-kappa B (NF- $\kappa$ B) and c-Jun N-terminal kinase (JNK). Inhibition of NF- $\kappa$ B and down regulation of the JNK pathway could be potential mechanisms for controlling inflammatory responses and apoptosis, respectively.

Objectives. To evaluate the protective effects of curcumin as an antioxidant in patients undergoing TF corrective surgery by evaluating the blood levels of MDA and GSH, activity of NF- $\kappa$ B and JNK, the presence of caspase-3 (C-3) in the myocardium, and post-operative clinical outcomes.

Methods. TF patients aged 1-6 years who were scheduled for elective corrective surgery were randomized double blind to receive either curcumin (45 mg/day) or placebo orally for 14 days prior to surgery. MDA and GSH levels were evaluated during the pre-ischemia, ischemia, and reperfusion phases, as well as 6 hours after aortic clamping off. Blood specimens were taken directly from the right atrium for the pre-ischemia data and for the 6 hours after aortic clamping off data; and from the coronary sinus for the ischemia and reperfusion data. To assess NF- $\kappa$ B, JNK, and C-3, tissue specimens were taken from the infundibulum during the pre-ischemia, ischemia, and reperfusion phase. NF- $\kappa$ B and JNK were measured by an enzyme-linked immunosorbent assay (ELISA) methods, and C-3 was measured by an immunohistochemical technique. Hemodynamic parameters and ventricular functions were monitored at 6-, 24-, and 48-hours post-surgery, and day 5 post-surgery.

Results. During July 2012-July 2013, 45 patients were included, 22 in the curcumin and 23 in the placebo groups. In the 4 observation phases, MDA and GSH concentrations were similar between treatment groups. Also, there was no significant difference in NF- $\kappa$ B activity between the groups for 3 observations. However, in the curcumin group, JNK activity significantly decreased from the pre-ischemia to reperfusion phases compared to the control group. C-3 expression in both the pre-ischemia and reperfusion phases was not significantly different between groups. However, C-3 expression in the curcumin group was significantly lower than placebo in the ischemia phase. Patients in the curcumin group had lower temperature and better right and left ventricular functions, but there were no significant differences in mechanical ventilation, or length of hospital or ICU stay in the two groups.

Conclusion. Cardioprotective effects of curcumin on ischemia reperfusion injury after TF corrective surgery may include inhibition of the JNK pathway and C-3 in cardiomyocytes, particularly in an ischemia phase.

Curcumin also improves right and left ventricular functions and lower perioperative temperature.

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