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Research Article

**EFFECTS OF DEXAMETHASONE ON EARLY COGNITIVE  
DECLINE AFTER CARDIAC SURGERY: A RANDOMIZED  
CONTROLLED TRIAL**<sup>1</sup>Dr Ruqaya Bashir, <sup>2</sup>Dr Ahmad Kamal, <sup>3</sup>Dr Raina Amin.<sup>1,3</sup>MBBS, King Edward Medical University, Lahore.<sup>2</sup>MBBS, University College of Medicine and Dentistry, University of Lahore, Lahore**Article Received:** June 2020**Accepted:** July 2020**Published:** August 2020**Abstract:**

After cardiac surgery, post-operative cognitive decline is a well known and common complication. POCD is characterized by the impaired functions of memory and intellectual ability of a person linked to health care resources. The focus of the investigators has been upon the potential factor like inflammation owing to a surgical procedure that is involved in the POCD pathogenesis.

A randomized controlled study was carried out on prophylactic dexamethasone where it was used to attenuate the inflammatory response and its impacts upon lowering the risk for the POCD. The duration of this trial was from January 2016 to January 2017 and total 170 patients were added, out of which 161 were added in the analysis. Patients were randomized and intravenous bolus of 0.1 mg/kg dexamethasone was given 10 hours before surgery.

In comparison to the placebo group, the dexamethasone group showed significant POCD reduction and systematic inflammation. Post operative S100 $\beta$  levels were also found lower in the dexamethasone group.

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## INTRODUCTION:

About 30 to 65% incidence rate of postoperative cognitive decline after the cardiac surgery has remained same in patients after discharge from the hospital, despite the declining ratio of complications in the surgery. The incidence of POCD varies widely depending upon their definitive criteria like evaluation method, the assessment time, patient characteristics, and the type of surgery. A super sensitive neuropsychological test battery is often used for POCD detection as its symptoms are subtle. <sup>1, 2</sup> With memory decline, decrease psychomotor speed and attention, POCD predominantly manifests. The presence of POCD is linked with reduced quality of life, high mortality ratio, early resignation from the work and depending upon health care resources. <sup>3, 4</sup> It is found that after cardiac surgery, POCD occurs due to systematic inflammatory responses induced by the use of cardiopulmonary bypass (CPB) and the surgery itself. Following this, the latter causes like cerebral inflammation and blood-brain barrier also play a significant role. Several factors like activation of an immune system, contact between blood and artificial bypass circuit material owing to ischemia reperfusion injury, or complement activation following CPB, contribute to the ubiquity inflammatory response to CPB. It has been also found that circulation of several inflammatory markers after surgery were similar independently of the CPB usage during surgery. One proposed possible elaboration is that during CPB, cerebral microemboli originates which are responsible for POCD. However, several studies fail to explain the positive effect of avoiding the CPB usage. <sup>5, 6</sup>

It is hypothesized that if inflammation triggers POCD then suppression of inflammation can reduce the risk of POCD occurrence and corticosteroids might can play a significant role here. In this context, dexamethasone is found as an effective drug with long duration action and is a potent synthetic glucocorticoid.

In systemic inflammation, C-reactive protein (CRP) is an acute phase reactant and it began to increase within a few hours of surgery and continue increasing until 3<sup>rd</sup> postoperative day. But if other inflammatory markers are absent, it began to decline automatically to preoperative levels. <sup>7</sup> The S100 $\beta$  protein is a marker of brain injury and BBB disruption. This protein concentration shows that either it was elevated for some time after CPB observed after surgery of the heart.

The purpose of this study is to assess the dexamethasone effects after heart surgery on cognitive outcomes.

## METHODS:

### • Study Design and Participants

A double blind, randomized, placebo- controlled, parallel arm study based trial was conducted at the University Hospital in Lahore between January 2016 to January 2017. Approval from Ethical Committee was taken along with the consent from all the 170 patients after complete provision of the information. 161 patients were finally added for analysis after the exclusion criteria.

Patients with age between 40 to 80 years who were scheduled for coronary artery bypass graft surgery, heart valve surgery without or with CPB were added. Any cerebrovascular incident in the last 3 years like mental illness, hearing or visual issues with disease requiring steroid administration more than 7 days in the previous years, alcohol or drug usage, previous carotid or cardiac surgery, adrenal gland disease, WBC less than 4 or above  $10 \times 10^9 l^{-1}$ , additional corticosteroid treatment, preoperative stroke, and left ventricular ejection fraction of less than 35% were set as exclusion criteria.

Patients were randomized so that they can receive intravenous bolus of 0.1mg/kg dexamethasone or same placebo volume 10 hours before surgery. All the physicians, biochemists and other staff were blind to the treatment allocation of the patients.

### • Surgery

The surgery started for all the patients at the same time 8:00. Anesthesia was administered and its level was maintained as per guidelines of the surgery. Heparin was administered to achieve an activated time of clotting more than 280s, and equivalent dose of protamine sulphate was administered at the time of decannulation to reverse the effect of heparin.

Patients with CPB, non pulsatile roller pump equipped with microporous oxygenator membrane integrated with 40- $\mu$ M arterial line filters and heparin coated circuits was performed. A constant level of perfusion flow rate of 2.4 l min<sup>-1</sup> m<sup>-2</sup> was used. In patients without CPB distal anastomoses were performed with the aid of octopus tissue stabilizer. During beating heart surgery, the principles of neutralization and heparinisation were used. Forced warm blanket and oesophageal probe was used to maintain the core temperature near normothermia.

### • Outcome

#### ➤ Primary Outcome Measure

The primary outcome measure of the endpoint of this analysis was observed on the 6<sup>th</sup> day of surgery on the incidence of POCD. In order to study these outcomes team opted the Ottens et al procedure for comparative evaluation. The Jacobson and Traux

Reliable Change Index was calculated for each patient in the placebo and dexamethasone group. RCI was the main score of 8 main variables. Greater RCI showed higher cognitive performance. POCD in the patient was defined as an RCI equal to or less than value -1.96.<sup>8</sup>

#### ➤ Secondary Outcome Measure

In both the groups, the incidence of SIRS or systemic inflammatory response system was observed. SIRS means the presence of any of the 4 criteria in patients after surgery: heart rate greater than 90 bpm, body temperature above 38 °C or below 36 °C, WBC count above 12 or below  $4 \times 10^9 \text{ l}^{-1}$ , and respiratory rate greater than 20 bpm or arterial carbon dioxide tension below 4.26 kPa (32 mmHg).

On 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> post-operative days CRP level was measured in both the groups after 12 hours of surgery. Turbidity method was used to assess serum CRP. S100 $\beta$  levels were determined after 6 to 30 hours at the end of CRP. Their levels were assessed using electrochemiluminescence 'sandwich' immunoassay method. An S100 $\beta$  level more than 0.12  $\mu\text{g l}^{-1}$  was considered to be pathologically increased.<sup>11,12</sup>

#### ➤ Cognitive Outcome Measure

On the 6<sup>th</sup> day after surgery, 9 out of 80 patients in the dexamethasone group and 22 out of 81 patients in the placebo group completed the POCD diagnostic criteria. The statistically significant difference was found between both the groups (relative risk =RR, 0.43; 95% CI, 0.21 to 0.89;  $P = 0.02$ ). Neuropsychological test analysis showed that the RCI was  $0.85 \pm 1.5$  in the dexamethasone group and  $0.25 \pm 1.0$  in the placebo group ( $P = 0.01$ ).

### DISCUSSION:

The randomized trial of 170 patients out of which 161 were added for final analysis, showed positive outcomes of the dexamethasone administration on the early incidence of POCD in comparison to the placebo group. This trial also showed significantly lower SIRS and post-operative CRP levels in the dexamethasone group.

In the recent years, multiple studies have depicted the negative impacts of steroids on mortality after cardiac surgery. In the SIRS study, cumulative dose of 500 mg of methylprednisolone were given intra-operatively, whereas in the DECS trial, single dose of 1 mg/kg of dexamethasone was given. Both the trials failed to show positive effects of steroids. Moreover, Ottens *et al*<sup>8</sup> found no significant effect of intra-operative administration of high dose of dexamethasone on POCD incidence after 1 or 2

months of surgery. But as we have examined only early POCD so direct comparison can not be made. This current study showed a statistically positive difference between the placebo group and dexamethasone group in the incidence of POCD on the 6<sup>th</sup> day of surgery. The incidence of POCD was lower.<sup>9,10</sup> Furthermore, strict definition of POCD was applied stating that RCI level equal to or less than -1.96 on at least one test. Analysis of neuropsychological test battery showed significant difference in the MMSE score and simple reaction time between both the groups. The MMSE values of the dexamethasone group showed preservation of global cognitive status after surgery. The simple reaction time and SDMT results of the dexamethasone group suggested reasonable influences of dexamethasone on the domains of information processing speed and psychomotor speed. As the S100 $\beta$  levels in the dexamethasone group were lower than in placebo group, so it also showed less neuronal damage.<sup>13</sup>

The strength of this study can be evaluated from the fact that no patient was left behind to follow up on the 6<sup>th</sup> day after surgery, except only 8 patients. This made the current study satisfactory in comparison to other studies reporting on cognitive outcomes after cardiac surgery.

In conclusion, this randomized double blind trial study, 170 cardiac surgical patients was added, the early POCD risk and inflammation incidence were reduced with the administration of dexamethasone. Therefore, upon the trial basis, it is believed that the result of this study can help in further investigation of the positive outcomes of dexamethasone administration on cognitive decline after cardiac surgery.

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