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Opinion Article

The Regulatory Role of Dexamethasone Prophylaxis in Pediatrics

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DESCRIPTION

Cardiopulmonary Bypass (CPB) procedures during cardiac organ surgery produce systemic effects, particularly in younger children. The contact of cellular and humoral blood elements with biocompatible artificial material of extracorporeal circuit provokes a Systemic Inflammatory Response (SIR) involving blood cell and epithelial tissue cell activation and cytokine release, which leads to myocardial, renal, and pulmonary dysfunctions and includes a negative impact on the postoperative clinical course [1,2]. Different anti-inflammatory methods have been used to minimize the CPB-related organ dysfunctions, as well as steroid prophylaxis. Though Glucocorticoid (GC) administration before CPB has been found to lead to a reduced inflammatory response, the advantages of glucocorticoids on clinical outcomes of adult and pediatric patients are debated.

Pentraxins are a superfamily of macromolecules belonging to the humoral arm of natural immunity and including the classical short pentraxins (C Reactive Protein (CRP) and serum amyloid P component in human and mice, resp.) and long pentraxins. CRP, a prototype of the short pentraxin family, is an acute-phase macromolecule in humans [1]. It's made within the liver in response to inflammatory signals, preponderantly IL-6, it interacts with totally different ligands, and it's concerned with innate resistance to totally different pathogens. Long Pentraxin PTX3 may be a novel inflammatory marker, a prototype of the long pentraxin family, made by innate immune cells and tube-shaped structure cells in response to proinflammatory.

PTX3 may be a multifunctional macromolecule and plays complex, nonredundant roles *in vivo* , recognizing a various range of pathogens, modulating complement activity, and facilitating pathogen recognition by macrophages and nerve fibre cells. Many evidence link PTX3 and cardiovascular diseases: PTX3 production by smooth muscle cells excited by atherogenic beta-lipoprotein, localization in arteriosclerosis lesions, and high expression level observed within the heart of pediatric patients throughout inflammatory reactions. PTX3 levels increase speedily in pediatric patients with Acute Myocardial Infarction (AMI), rising as the only independent predictor of mortality. Additionally, PTX3 plasma levels are elevated in pediatric patients with unstable angina and in patients undergoing stenting, suggesting that PTX3 may be a candidate for being a new prognostic marker in ischemic heart disorders [2,3]. However, besides the role of PTX3 as a cardiovascular biomarker related to inflammatory reactions, recent *in vivo* and *in vitro* data to a protective cardiovascular role of PTX3 through a regulatory role on inflammation. In this respect, accumulated levels of PTX3 could reflect a protecting response of the host.

Soluble protein receptor release could represent a mechanism to counterbalance inflammatory responses. IL-1 is a key cytokine in inflammation and represents an important target of GC-mediated immunosuppressive activities. GC suppresses IL-1 production however augments cell surface expression of IL-1 Receptor (R) II with consequently increased release of the soluble form of the receptor itself. IL-1 RII has no signaling properties, and acts as a "decoy" target for IL-1, binding with high affinity to IL-1 and preventing its binding to the signaling IL-1RI.

Here we've analyzed the influence of dexamethasone prophylaxis in pediatric patients undergoing CPB on blood levels of PTX3, IL-1 RII, and alternative inflammatory parameters. This demonstrates for the first time that dexamethasone prophylaxis in pediatric patients undergoing internal organ bypass for heart surgery is related to considerably increased plasma levels of the long pentraxin PTX3 at totally different time points [4]. This result was obtained from the study of a homogenous patient group selected within the clinical trial. Proof for the potent medicinal drug results of dexamethasone was obtained from laboratory studies; patient clinical analysis pointed to a useful effect of steroid prevention on the postoperative outcome that failed to reach applied statistical significance.

Steroid prophylaxis throughout CPB on inflammation and clinical operative recovery has been investigated in several studies with opposite results. These discrepancies are also associated with the age of patients and the dosage, timing and type of steroid administered. PTX3 was found to be accumulated also in control patients not receiving dexamethasone. However, (i) PTX3 levels were considerably higher in dexamethasone-treated versus dexamethasone-untreated patients and (ii) increased and returned to baseline values earlier within the former than in the

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latter group. IL1-RII is an IL-1 decoy receptor endowed with anti-inflammatory activity. We tend to find increased serum levels of IL-1RII in glucocorticoid-treated patients but failed to reach statistical significance.

Dexamethasone was previously found to inhibit the lipopolysaccharide-induced PTX3 production in myeloid DC. In distinction, in fibroblasts and epithelial tissue cells, dexamethasone alone induced and, under inflammatory conditions, increased PTX3 production. The divergent result of glucocorticoid on PTX3 regulation is likely due to variations within the practicality of their receptor in several cell populations [5]. Glucocorticoid receptors might act as ligand-dependent transcription factors through direct deoxyribonucleic acid-binding (dimerization-dependent), or as factor transcription repressers through protein-protein interference with the action of another signalling pathway (dimerization-independent). In non haematopoietic cells the stimulation of PTX3 gene expression and production is dimerization dependent; on the contrary, suppression of PTX3 production in cells of haematopoietic process origin is dimerization independent and mediated by interference with alternative signalling pathways, possibly the NF-kB and AP-1 pathways. Therefore the increased PTX3 levels observed within the present investigation could be in part due to the restrictive role exerted by glucocorticoids on PTX3 expression.

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