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Kawasaki Disease: Immune Globulin Alone or Associated with Aspirin?

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Kawasaki disease (KD) is one of the most common vasculitis diseases of childhood. It causes fever and manifestations of acute inflammation lasting for an average of 12 days without therapy. But, because KD may cause coronary artery (CA) aneurysm, resulting in significant morbidity or even mortality, all patients are treated with immune globulin (IVIG) plus aspirin.

The treatment can be start between 7 to 10 days of illness but seems that the risk of CA aneurysm reduce when we use IVIG before 5 to 6 days of the illness.

The recommended initial therapy includes intravenous IVIG: 2 g/kg administered as a single infusion over 8 to 12 hours and aspirin: initial dose of 30 to 50 mg/kg daily divided into four doses.

Randomized, controlled studies and meta-analyses have confirmed that IVIG plus aspirin, compared with aspirin alone reduces the risk of CA aneurysms. Aspirin alone does not appear to reduce aneurysm formation.

On the other hand, IVIG appears to have a generalized anti-inflammatory effect, modulating cytokine levels and production, increasing T cell suppressor activity, down-regulating antibody synthesis and providing anti-idiotypic antibodies.

The prevalence of CA aneurysms in the first month after the diagnose of KD, reduce from 28% with aspirin alone, to 4% with IVIG dose of 2 g/kg plus aspirin.

In the literature, we have only one controlled study comparing IVIG therapy alone with combined IVIG plus aspirin therapy as an antiplatelet agent, prescribed 24 to 48 hours following resolution of fever. In this study, fever resolved within 24 hours after IVIG therapy in 80% of patients with KD. Coronary artery aneurysm was formed in 3 percent of patients whose fever normalized within 24 hours of completing IVIG therapy. These results are comparable with those seen in studies of children treated initially with both IVIG and aspirin in anti-inflammatory dose (around 4 %).

Aspirin, with his anti-inflammatory action don't avoid to have CA aneurysm. But IVIG alone can reduce the risk. Why we use both together?

We all use IVIG in several situations: immune thrombocytopenia purpura, Guillain-Barré syndrome, multiple sclerosis among others.

The etiology of KD remains unknown. The major debate concerns whether a single, heretofore unidentified agent causes KD or rather is it caused by an immunologic response to a variety of triggers. KD is a systemic, inflammatory illness that particularly affects medium-sized arteries, especially the coronary arteries. The destruction of elastin and collagen fibers and loss of structural integrity of the arterial wall lead to dilatation and aneurysm formation. Inflammatory cells infiltrating the coronary arteries can include neutrophils, T cells (particularly CD8 T cells), eosinophils, plasma cells (particularly IgA producing), and/or macrophages.

In other diseases mentioned above using IVIG, the mechanism are similar. The most common cause of thrombocytopenia due to platelet destruction is an immune-mediated process. Autoantibodies, drug-dependent antibodies, or alloantibodies mediate platelet destruction through interaction with platelet membrane antigens or by forming immune complexes, which can bind to reticuloendothelial cell

Fc receptors leading to platelet clearance from the circulation. IVIG as a first-line choice, particularly when a rapid rise in platelet count is desired. In this case aspirin is not recommended. The Guillain-Barré syndrome (GBS) is an acute monophasic illness. It is thought to result from an immune response to a preceding infection that cross-reacts with peripheral nerve components because of molecular mimicry. The immune response can be directed towards the myelin or the axon of peripheral nerve, resulting in demyelinating and axonal forms of GBS. The mechanism of improvement with IVIG is uncertain, but it is thought to involve suppression of inflammatory and immune-mediated processes. The cause of multiple sclerosis (MS) remains unknown. The most widely accepted theory is that MS begins as an inflammatory immune-mediated disorder characterized by autoreactive lymphocytes. Inflammatory T cells, B cells, and macrophages are typically seen on histopathologic examination of MS lesions. We can find also IgG (and IgM) oligoclonal bands in the cerebrospinal fluid (CSF). Approximately one-half of patients with MS have a specific serum IgG autoantibody directed against the inwardly rectifying potassium channel Kir4.1, which is expressed by oligodendrocytes and perivascular astrocytic processes in the central nervous system. IVIG can also be given in this setting and in the occasional patient who fails to respond to glucocorticoids. In these two last diseases, we don't use aspirin associated with IVIG.

The only meaning of using aspirin in KD is the anti-platelet dose, after stop the fever that occurs in most cases 24 - 48 hours with IVIG therapy. More trials need to be done to confirm and support that IVIG alone is effective in KD and don't need any anti-inflammatory dose of aspirin at the same time.

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