Colchicine and Neutrophils in Testicular Ischemia/Reperfusion Injury

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We read the interesting and notable paper written by Gozukara KH et al[(1)] about the protecting role of colchicine in an experimental murine model of testicular ischemia/reperfusion injury. Although to date the emergent restoration of blood flow represents the primary therapeutic approach for testicular torsion treatment in order to prevent tissue damage, different drugs and physical therapies have been proposed as adjuvant treatment in decreasing cellular damage following testicular ischemia/reperfusion injury[(2)]. In this regards, restoration of blood flow after testicular detorsion leads to a more severe damage than that induced by ischemia due to a paradoxic cascade of events, including excessive production of reactive oxygen species (ROS), intracellular calcium overload, lipid peroxidation, protein denaturation, apoptosis activation[(3)]. On these bases, antioxidants, modulators of inflammations, platelet inhibitors, calcium channel blockers have been experimentally and, sometimes, clinically evaluated in the attempt to solve the adverse effects of post-ischemic reperfusion critical testicular damage. However, so far, some agents have proven to be clinically ineffective, others are not currently used in clinical practice[(3)]. For this reason, current therapeutic strategies for testicular/reperfusion injury are merely palliative, actually failing to improve the underlying condition. In a recent paper, Gozukara KH et al[(1)] documented that complementary per-operative and short-term post-operative usage of colchicine in experimental testicular detorsion has a significant anti-inflammatory and anti apoptotic effect. Even if the mechanism of action of colchicine has not been clearly elucidated in ischemia/reperfusion injury, it has been supposed that colchicine inhibits neutrophil action in testicular ischemia/reperfusion injury. It has been previously shown that neutrophils play a key role during reperfusion damage. In particular, hypoxia as a consequence of ischemia leads to an over-production of metabolic intermediates and ROS [(5)]. While ROS production during a short period of ischemia can be counteracted by free radicals and antioxidants such as nitric oxide (NO), a relative long period of ischemia can cause irreversible effects which are amplified upon reperfusion due to an immediate re-oxygenation of ischemic tissue. As a consequence of this mechanism, the excessive production of ROS results in inflammatory response, it switches-off NO production, it impairs the endothelial barrier releasing ROS into extracellular matrix and, so, increasing adhesion molecules expression that mediate neutrophils recruitment[(6)]. Neutrophils are involved in primary cellular response to ischemic/reperfusion injury, being able to infiltrate the damaged tissue within minutes of activation. These cells block capillaries preventing tissue reperfusion, exacerbating tissue necrosis and immune response. Moreover they secret themselves proinflammatory cytokines and chemokines promoting a positive feedback loop of neutrophil recruitment and activation[(7)]. While a lot of emphasis has been placed on potential protective molecules (i.e. antioxidants, modulators of inflammations, platelet inhibitors), it has been rarely pointed out the role of cells and, in particular, the role of neutrophils in testicular ischemia/reperfusion injury. It has been supposed that colchicine is able to block neutrophil cell division in the G2/M phase by disrupting microtubules polymerization to tubulin dimers. This pathway is considered a keystone in cell migration, secretion of cytokines, and maintenance of the cytoskeleton and cell shape [(8)]. Therefore colchicine seems to decrease the cytoplasmic Ca+2 release in neutrophils[(9)], reducing the oxygen radicals produced by mitochondria. We believe that the actual advantages of the use of colchicine in testicular ischemia/reperfusion injury are at least two: firstly, colchicine interacts with neutrophils, which are involved in the initial phase of inflammatory response and apoptotic pathway; secondly, the clinical effects of colchicine have been already evaluated and its use approved for human beings.
In conclusion, we would like to congratulate with Authors for the intuitive idea[(1)], however the effect of colchicine in testicular ischemia/reperfusion injury needs to be investigated in further randomized controlled studies.

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REPLY BY AUTHOR

I would like to thank the author for providing this encouraging and admirable comprehensive summary. There are no words left by the author to add in molecular aspect for this reply.

Since colchicine is one of the oldest known therapeutic molecules, and being a molecule approved for human usage in our age, it allows us to do such a study.

As shown by many studies in different tissues, colchicine acts as a molecule that can be used to control the 'immune storm' at the beginning.

As a clinician's point of view, the necessity of acting fast in testicular torsion and the prompt start of immune modulation effect of colchicine from the first hours after application is like a key-lock unison. Indeed, the effect of long-term colchicine use on reproductive capacity is well studied. It will be useful for future torsion studies to focus on this short postoperative period and the 'going-on's inside the testicle so that the early victory gained by surgery can be accomplished.

Although it is used in a variety of diseases through this feature, I still do not think we truly realize and use its real potential. As an indicator of this potential, we read Colchicine-based studies have been initiated to reduce or prevent organ damage in the COVID 19 pandemic, which we have recently witnessed and been a victim of.

'So novels never end when its last page is read. It's over when you stop dreaming it.'

Kind regards.