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Original research

Hepatic ischemia reperfusion injury: A systematic review of literature and the role of current drugs and biomarkers

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ABSTRACT

Hepatic ischemia reperfusion injury (IRI) is not only a pathophysiological process involving the liver, but also a complex systemic process affecting multiple tissues and organs. Hepatic IRI can seriously impair liver function, even producing irreversible damage, which causes a cascade of multiple organ dysfunction. Many factors, including anaerobic metabolism, mitochondrial damage, oxidative stress and secretion of ROS, intracellular Ca^{2+} overload, cytokines and chemokines produced by KCs and neutrophils, and NO, are involved in the regulation of hepatic IRI processes.

Matrix Metalloproteinases (MMPs) can be an important mediator of *early* leukocyte recruitment and target in acute and chronic liver injury associated to ischemia. MMPs and neutrophil gelatinase-associated lipocalin (NGAL) could be used as markers of I-R injury severity stages.

This review explores the relationship between factors and inflammatory pathways that characterize hepatic IRI, MMPs and current pharmacological approaches to this disease.

1. Introduction

Different liver surgical options applied for intrahepatic lesions or liver transplantation require a period of ischemia and the Pringle maneuver (inflow control) or total vascular exclusion are the most common procedures [1–4]. When the blood flow is restored, injury on already ischemic liver could occur. This phenomenon is called ischemia-reperfusion injury (IRI) [5] and remains a main cause of liver dysfunction or functional failure following liver surgery. Hepatic IRI includes both warm and cold IRI - two entities that share similar pathophysiological processes [6]. The factors and cells implicated in the hepatic IRI process are anaerobic metabolism, mitochondria, oxidative stress, intracellular calcium overload, liver Kupffer cells (KCs) [7–9] and neutrophils, cytokines and chemokines [10–12].

Recently, several studies have shown the strong correlation between inflammation, neutrophils and Matrix Metalloproteinases (MMPs) activation on both vascular diseases, including chronic venous ulcers [13–15] and non-vascular disorders, such us carotid body tumors and their hemodynamic correlations [16,17]. MMPs are proteolytic enzymes that engage the extracellular matrix (ECM) and regulate the immunity; neutrophil gelatinase-associated lipocalin (NGAL) is an acute-phase protein and its expression is up-regulated under different conditions; it also cooperates with MMPs in ECM degradation [18].

The liver is an organ with a several function in metabolic homeostasis, detoxification, and immunity and it is frequently exposed to various injuries, which can cause cell death and hepatic

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dysfunction [19]. Normal degradation of ECM components is an important feature of tissue repair and remodeling, but alteration of ECM turnover contributes to a variety of liver diseases [20]. In this way, it has been documented that MMPs are significantly involved in IRI in the lung, heart, brain, kidney, post-ischemic revascularization of lower limbs and liver [21–23].

Although there are numerous evidences on the administration of drugs with a protective action on the liver in animals [24–27], even today there are few evidences about the use of these substances on human IRI [28].

A better understanding of the mechanisms in the development of IRI will provide insights into improving the treatment regimen for IRI and an effective method for preventing or minimizing hepatic IRI during liver surgery is urgently needed [29].

The purpose of this systematic review is to examine the pathophysiology of hepatic IRI, the prognostic stratification and the therapeutic approaches in the light of recent scientific evidences.

2. Materials and methods

PubMed and ScienceDirect databases were searched for articles using the terms: hepatic ischemia/reperfusion injury, liver resection and transplantation, pharmacological/therapeutic approaches, inflammation, biomarkers.

Only publications in English were included. Titles and abstracts were screened by 3 authors (R. M., C. M., Z. A) to identify potentially relevant studies. Reference lists of retrieved articles were also searched for relevant publications.

Clinical Trial, Meta-Analysis, Systematic Reviews and Case Reports were included. Studies were excluded if performed in no English languages, if the cohort was defined by the presence of Hepatic Ischemia/Reperfusion Injury and an additional confounding disease process (eg, chronic renal failure or other vascular diseases) or if Hepatic Ischemia/Reperfusion Injury specific results could not be distinguished from those of a larger population consisting of individuals without disease. Studies were excluded when the primary focus was arterial disease and inflammatory diseases.

3. Results

3.1. Study selection

Initial database searches yielded 4720 studies from PubMed and 1262 from ScienceDirect. We evaluated 867 eligible full text articles and 197 studies were included in qualitative synthesis (Fig. 1).

The epidemiology of hepatic IRI and its natural history, the factors that characterized its pathogenesis, the recent features for pharmacological treatment and the possible new the role of MMPs as biomarkers is given below.

3.1.1. Resection and liver transplantation

Hepatic IRI is the main cause of morbidity and mortality in liver surgery and transplantation [30–34]. The liver has a dual-blood inflow supply via the portal vein and the hepatic artery. Physiologically, the portal vein is responsible for supplying most of the blood to the non-tumorous part of the liver (75–85%), with the hepatic artery providing only a supportive role (20–25%). In order to minimize blood loss, many methods of hepatic vascular control have been introduced to control intraoperative blood loss clamping of the portal triad (inflow occlusion).

In 1908, for the first time, Pringle applied inflow vascular occlusion technique (*the Pringle maneuver*) [35] at the hepatic hilar, due to total compression of the hepatoduodenal ligament. Actually this technique is the most used and easier method for controlling afferent blood flow but the risk of IRI is increased [36,37]. In patients with chronic liver diseases, the *Pringle maneuver* increases the risk of liver ischemic lesions and intestinal congestion, which is accentuated by a prolonged period of vascular inflow occlusion [38,39].

Bergoc et al. proposed a main portal vein inflow occlusion technique to control bleeding during liver resection: the arterial inflow and oxygen supply to the liver is maintained. This resective technique was performed mostly for benign and malignant liver tumors, especially for hepatocellular carcinoma and has been shown a possible curative treatment option in patients with carcinoma on early stage [40,41].

In 1987, Bismuth and Makuuchi proposed a hemihepatic vascular occlusion (HHO) technique to reduce the severity of visceral congestion and total liver ischemia, especially for the remaining liver [42,43]. This technique interrupts the arterial and venous inflow to the right or left hemiliver and therefore avoids both splanchnic blood stasis and ischemia or IRI to the liver [44,45]: the technique can reduce intraoperative bleeding and postoperative liver functional disturbances [46]. A limit of this method is visceral congestion, because substantial portal blood flow is preserved and only portions of the liver are anoxic [47]. Moreover, portal vein and artery dissection to perform selective clamping is time consuming and may results in another blood loss [48]. Furthermore, reperfusion of the remnant liver after declamping of the portal triad causes additional damage to its parenchymal and non-parenchymal cells with consequences of the functional integrity and consecutive hepatic failure [49,50].

Evidences have shown that the liver ischemia induced by the clamping of hilum vessels cause severe liver damage due to the activation of KCs [51,52]. Although the underlying protective mechanisms of Ischemic Preconditioning (IP) are still not fully understood, some studies have shown that the activation of KCs, leucocytes and the release of cytotoxic mediators on reperfusion may lead to a substantial breakdown of the hepatic microcirculation, an event which seems to play a key role following warm and cold ischemia [53–60]. On the other hand, in healthy livers, a balanced portal vein (PV) and hepatic artery (HA) inflow are significantly dependent on the arterial buffer response, an autoregulation system which influences the whole blood supply to the liver at the level of the hepatic arterioles and portal venules, and which is assumed to be predominantly the result of adenosine action [61,62].

During reperfusion, additional liver injury is added to damage already sustained during ischemia. Consequences of this injury can include liver failure, systemic inflammatory reaction syndrome (SIRS) and multiple organ failure (MOF), both of which have high rates of morbidity and mortality [63–66].

Liver transplantation is a curative option in patients with end-stage liver disease and hepatic tumors [67,68]. Thanks to recent innovations, the indications for organs donor from older, steatotic, or non-heart-beating donors were extended, as well as organs that have been subjected to prolonged periods of warm and cold storage [69]. However, these new “accepted” organs are particularly susceptible to IRI as a result of damage during procurement, preservation and surgery [70–73]. The ‘warm’ IRI starts at the level of the hepatic cell, develops in situ during liver transplantation surgery or during various forms of shock or trauma; the ‘cold’ IRI is initiated by hepatic sinusoidal endothelial cells and is usually coupled with warm IRI during liver transplantation surgery [74,75].

The hepatic parenchyma is physiologically designed to compensate the hemodynamic alterations that characterize the liver resection (LR): hepatic cells assure its functions and maintain its regeneration capacity [76]. Decrease in parenchymal volume results in a hyper perfusion of the liver, with sinusoids dilation, hemorrhagic infiltration, shear stress, centro lobular necrosis, and