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Original Article

Effect of postconditioning and atorvastatin in preventing remote intestinal reperfusion injury

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ABSTRACT

Objective: To evaluate the capacity of ischemic postconditioning and atorvastatin in prevent or minimize reperfusion injury in small bowel of rats subjected to ischemia and reperfusion by abdominal aorta clamping.

Methods: 41 Wistar norvegic rats were distributed into 5 groups: ischemia and reperfusion, ischemic postconditioning, postconditioning + statin, statin and Sham. After anesthesia, laparotomy and dissection of the infra-renal abdominal aorta were performed; except the Sham group, all others were subjected to aorta clamping for 70 min (ischemia) and withdrawal of clamp for 70 min (reperfusion). In the IPC and IPC + S groups, four cycles of postconditioning were performed between the phases of ischemia and reperfusion lasting 30 s each. In IPC + S and S groups, 3.4 mg/day of atorvastatin was given for seven days per gavage; 1 cm of the ileum were removed for histological study and the results were subjected to statistical treatment considering significant $p < 0.05$.

Results: The average of intestinal lesion was 2 in the I/R group, 0.66 in the IPC group, 0 in the IPC + S group, 0 in the S group, and 0 in the SHAM group.

Conclusion: The ischemic postconditioning and atorvastatin were capable of minimizing intestinal reperfusion injury, either alone or in combination.

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Efeito do pós-condicionamento e da atorvastatina na prevenção de lesão de reperfusão intestinal remota

Palavras-chave:
Isquemia
Reperfusão
Pós-condicionamento isquêmico
Hidroximetilglutaril-CoA redutase, inibidores da
Intestino delgado

RESUMO

Objetivo: Avaliar a capacidade do pós-condicionamento isquêmico e da atorvastatina para prevenir ou minimizar a lesão de reperfusão no intestino Delgado de ratos submetidos à isquemia e reperfusão por pinçamento de aorta abdominal.

Métodos: 41 ratos noruegueses Wistar foram distribuídos em 5 grupos: isquemia e reperfusão, pós-condicionamento isquêmico, pós-condicionamento + estatina, estatina e simulacro. Depois da anestesia, procedeu-se à laparotomia e dissecação da aorta abdominal infrarrenal; exceto no grupo de simulacro, todos os demais grupos foram submetidos ao pinçamento da aorta durante 70 minutos (isquemia) e à retirada do pinçamento também durante 70 minutos (reperfusão). Nos grupos PCI e PCI + E, foram efetuados quatro ciclos de pós-condicionamento entre as fases de isquemia e de reperfusão, com duração de 30 segundos cada. Nos grupos PCI + E e E, foram administrados 3,4 mg/dia de atorvastatina durante 7 dias por gavagem; procedemos à remoção de 1 cm do íleo para o estudo histológico, e os resultados foram estatisticamente tratados. Consideramos $p < 0,05$ como estatisticamente significativo.

Resultados: As médias para as lesões intestinais foram 2 no grupo I/R, 0,66 no grupo PCI, 0 no grupo PCI + E, 0 no grupo E, e 0 no grupo S.

Conclusão: O procedimento de pós-condicionamento e atorvastatina demonstraram capacidade de minimizar a lesão de reperfusão intestinal, tanto isoladamente como em conjunto.

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Introduction

Reperfusion is a fundamental step in the treatment of ischemia. However, clinical and experimental evidence shows that the main events leading to cell and tissue dysfunction are related to reperfusion.[1]

The ischemia and reperfusion (IR) injury is a pathophysiological event common to several diseases of daily clinical practice. The intestine may be the target of IR injury directly, as in mesenteric ischemia, or be reached at a distance, as in cases of shock or reperfusion injury in other organs, such as aortic clamping, used in aneurysm surgeries.[2]

Increasing evidence is emerging that the gut can be affected by remote reperfusion injury, since toxic reactive oxygen species (ROS) act systemically. In surgeries with temporary aortic occlusion, intestinal vascular involvement is a frequent complication, with a multifactorial etiology, including reperfusion injury.[3]

Regardless of where ischemia occurs, when reperfusion happens, there is a systemic impairment to a greater or lesser extent. IR is associated with the production of tumor necrosis factor (TNF). Injury of the intestinal mucosa by IR allows the release of endotoxin into the portal circulation, inducing the production of TNF by liver macrophages. Increased TNF in the systemic circulation is capable of leading to inflammatory lung injury, characterized by the accumulation of neutrophils. This sequence of events was demonstrated by Caty et al.[4] in a model of IR by temporary occlusion of the superior mesenteric artery in rats. After reperfusion, endotoxin levels in portal venous blood and TNF were increased in the systemic circulation. In parallel, there was accumulation of neutrophils in the lungs and increased pulmonary capillary permeability.

Some techniques for protection against reperfusion injury have already been tried and tested, and among them, ischemic postconditioning (IPC), which consists of one or more short cycles of reperfusion, followed by one or more short cycles of ischemia, immediately after the ischemic phase and before permanent reperfusion occurs. Although IPC has already demonstrated a protective effect in many organs submitted to IR as well as in distance protection,[5] its efficacy in the prevention of remote intestinal lesion is still very early.[6]

Much has been studied about the pathophysiology of reperfusion injury and some mechanisms have already been well evidenced such as the role of free radicals, vascular endothelial dysfunction, and neutrophil-mediated injury.[1] Recently, there has been an increase in interest in statins, drugs known for their anti-dyslipidemic effect, this time due to its pleiotropic effect, which is characterized by anti-inflammatory properties, immunomodulatory, antithrombogenic and endothelial function.[7] Recent experimental studies[8] have shown promising results with the use of statins demonstrating their role in the protection against IR injury, a fact that led us to inquire about its benefits in the face of reperfusion injury, the objective of this study being to evaluate the capacity of IPC and statins in reducing intestinal injury, alone and in combination.

Considering the lack of studies on the protective effect of postconditioning on remote intestinal reperfusion injury, as well as the potential protective effect of statins, which have not yet been tested in a model similar to the one presented

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