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ORIGINAL ARTICLE

The Protective Effect of Orally Administered Amlodipine against Intestinal Ischemia-Reperfusion Injury in Rats

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Keywords:
Amlodipine;
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Abstract

Objective- This study investigated the effect of amlodipine on intestinal ischemia-reperfusion injury in rats

Design- Experimental study

Animals- Fifteen male Sprague-Dawly rats weighing 200-220g

Procedure- Rats were randomly divided into 3 groups: IR group (operation with clamping), sham group (operation without clamping), and IRA group (operation with clamping and 5mg/kg amlodipine pretreatment). Intestinal ischemia-reperfusion was performed by occlusion (clamping) of the arteria mesenterica anterior for 60 min, followed by 60 min reperfusion. Levels of superoxide dismutase (SOD), glutathione peroxidase (GPx) and malondialdehyde (MDA) were determined in intestinal tissue of rats. Intestinal tissues were also investigated histopathologically.

Results- Pretreatment with amlodipine impeded the increase in lipid peroxidation and mitigated GPx and SOD levels. Amlodipine also prevented I/R cellular damage and histological alternations in intestinal tissue. The levels of MDA ($P<0.006$) was significantly increased in the intestine of IR group rats. Intestinal GPx and SOD levels were decreased significantly ($p<0.001$) after I/R.

Conclusion and clinical relevance- The findings of this study suggest that amlodipine has a preventive activity on I/R-induced intestine injury. The observed preventive effects of amlodipine in the present study can possibly be mediated by means of its well-known antioxidant and anti-inflammatory potential. Therefore, we suggest that amlodipine may be a novel approach to therapy for protective intestinal I/R injury.

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1. Introduction

Intestinal ischemia reperfusion injury (IIRI) takes place as a result of a quick decrease in the intestinal blood flow following specific clinical conditions such as the surgery of abdominal aortic aneurysm, the transplantation of small bowel, the bypass of heart and lungs, and the necrosis during infancy. Moreover, it may happen due to strangulated hernias, entercolitis, hemorrhagic, traumatic or septic shock, or even severe burns.[1,2] The disturbance of blood circulation causes an ischemic lesion. Nonetheless, the recovery of the blood flow results in more cell injury which is named reperfusion injury.

Research has shown that the oxidative stress (OS), which is related to the superfluous of reactive oxygen species (ROS), comprises the basic pathological process of I/R injury.[3,4] A large number of studies have indicated the intensified concentration of intracellular calcium ion concentration in ischemic tissues.[5] Intensified concentration of intracellular calcium ion results in the instigation of pathological events in the cells like apoptosis.

Based on these findings, the anti-oxidative and anti-inflammatory drugs, and those that inhibit calcium channels before or after reperfusion may avert the I/R damage and its complocations.[6,7,8]

Amlodipine is classified as a third-generation dihydropyridine-type blocker of calcium channel which has antioxidant activity and vascular selectivity. Research has shown that, it prevents lipid peroxidation, escalates the production of GPx and the activity of SOD, and decreases the process of oxidizing the low-density lipoproteins.[9] A number of studies have indicated that amlodipine has preserved some I/R organs like the brain,[10] heart,[11] and liver.[12] These successful results for amlodipine in various systems of organs motivated us to utilize it in the model of I/R injury of rat intestine.

To the best of our knowledge, there is not any information in regard to the effects of amlodipine on intestine I/R injury.

Consequently, we decided to conduct an experimental study to determine the effects of amlodipine on a number of biochemical parameters including Glutathione peroxidase (GPx), superoxide dismutase (SOD) and malondialdehyde (MDA). Moreover, we tried to gauge the capability of amlodipine as an antioxidant which results in histopathologic changes in experimental I/R injury in rat intestine.

2. Materials and Methods

Animals

In this study, 15 adult male Sparaque-dawly rats (9 to 10 weeks of age) were utilized. The weight of these rats ranged between 200 and 220 g. These animals were habituate in our laboratory for 1 week before the beginning of the experiment. The housing condition was standardized to supply 12-h light and dark cycle, temperature of 22 ±2˚C and relative humidity of 60%. The procedures were performed according to the guidelines of the Ethics Committee of the International association for the study of pain [11]. The university Research Council accepted all experiments. Rats were randomly divided into 3 groups: IRC group (operation with clamping), sham group (operation without clamping), and IR+amlodipine group (operation with clamping and 5mg/kg amlodipine pretreatment). Intestinal ischemia-reperfusion was carried out by occlusion (clamping) of the superior mesenteric artery (SMA) for 1 hour, followed by 1-hour reperfusion. In the IR+ amlodipine group, 45 min before I/R 5mg/kg amlodipine was administered orally. Anesthetic overdose was used to euthanize the rats. Levels of superoxide dismutase (SOD), glutathione peroxidase (GPx) and malondialdehyde (MDA) were determined in intestinal tissue of rats. Intestinal tissues were also investigated histopathologically.

Technique of intestinal I/R

An intramascular injection of 80mg/kg Ketamine 5% (Alfasan, Woerden, Netherlands) and 10 mg/kg Xylazine 2% (Alfasan, Woerden, Netherlands) was used for anesthesia in each animal. Before the anesthesia induction, 5mg/kg amlodipine 5 (Aria company, Tehran, Iran) was administered orally by means of a catheter to the rats in IR+ amlodipine group, distilled water was administered in an equal amount through the identical procedure as a solvent in rats in the sham an IR groups. Intestinal I/R was induced as follows: The rats were situated in the supine position and secured in the dissection tray. The abdominal region was shaved and cleansed by means of antiseptic solutions. Midline laparotomy was employed to reach the intestinal region. SMA was subjected with care and occluded with an atraumatic microvascular clamp. Therefore, intestinal ischemia created in 1-hour ischemia was determined by the existence of pulseless or pale color of the intestine. Then, the abdominal region was closed.

After, ischemia, the clamp was removed and 1-hour reperfusion was induced. The restoration of the pulses and the return of the pink color were presumed to be reperfusion of the intestine. At the end of reperfusion, the jejunal segment was removed, and anesthetic overdose was used to euthanize the animals.[13]

Biochemical assays

Assay of protein concentration

Protein concentration was assayed in the intestinal homogenate according to the method of Bradford.[14]

Assay of lipid peroxidation

Lipid peroxidation was determined in the intestinal homogenate by measuring malondialdehyde (MDA) based on the thiobarbituric acid reactive substance (TBARS) method.[15]

Assay of glutathione peroxidase

To measure cytosolic enzyme activity, the testis samples were homogenized in 1.15% KCL solution. Glutathione peroxidase (GPx) activity was measured according to Paglia and Valentine[16] using Randox (United Kingdom).

Assay of Superoxide dismutase (SOD)

Tissue superoxide dismutase (SOD) was assayed by a spectrophotometric method on the basis of the prevention of a superoxide-induced decreased nicotinamide adenine dinucleotide (NADH) oxidation according to Paoletti et al.[17]

Histopathological examination

The intestine of each animal was fixed in 10% neutral buffered formalin, dehydrated in graded ethanol series, cleared in xylol, embedded in paraffin wax and serial sections were taken at about 5-6 µm. The sections were mounted on slides, stained with hematoxylin and eosin (H&E) and examined by light microscopy. Histopathological changes were evaluated on basis of the grading system described previously by Chiu and colleagues[18] with some modifications as shown in Table 1.

Statistical analysis

Analysis was carried out by means of Graph Pad Prism, Version 5.05 (Graph Pad software, sndiego, USA). Analysis of parametric data were carried out by One-Way ANOVA and repeated measure test Followed by Tukey Post-test (parametric methods); and Kruskal-Wallis multivariate analysis, followed by Dunns post-test (non-parametric methods). Results were expressed as mean ± SD. P-Values less than 0.05 were considered statistically significant.

Table 1. Histological scoring system of intestinal damage in tissue samples of rats, as proposed by Chiu et al. with some modifications.

Score	Microscopic characteristics
0	normal mucosa
1	formation of subepithelial detachments at the tip of the villi with mild capillary congestion
2	subepithelial detachments exerted a moderate amount of upward push on the mucosa epithelium with moderate capillary congestion
3	large subepithelial detachments exerted a massive amount of upward push on the mucosa epithelium along the villi and few denuded villus tips with severe capillary congestion and mild hemorrhage
4	the villi were denuded to the level of lamina propria and dilated congested capillaries with moderate hemorrhage
5	presence of ulceration, disintegration of lamina propria, and severe hemorrhage

3. Results

Biochemical

The values of the tissue MDA levels, SOD and GPx activities, and statistical differences of these measurements are shown in Table 2. Intestinal I/R significantly increased the tissue MDA levels ($p<0.006$) and decreased the activities of the antioxidant enzyme (SOD $p<0.001$, GPx $p<0.001$).

Amlodipine treatment significantly ($p<0.05$) decreased the elevated tissue MDA levels and increased the reduced GPx and SOD ($p<0.002$) enzyme activities in the intestine tissues.

Table 2. Tissue MDA levels and SOD and GPx enzyme activities in all the groups*

	Experimental groups		
	Sham	I/R group	I/R + amlodipine group
MDA (nmol/mg protein)	0.16±0.02	0.32±0.14[a]	0.23±0.03[b]
SOD (U/mg protein)	7.08±0.35	4.56±0.43[a]	5.88±1.2[b]
GPx (U/mg protein)	3.73±0.56	2.23±0.49[c]	3.2±0.51[d]

Histopathological findings

Histopathological examination of the intestine was performed according to Chiu's scoring system with some modifications which presented in Figure 1 and showed significant differences between different experimental groups (P<0.05). Sham-operated rats (as negative control) showed normal intestinal architecture associated with normal mucosa and mild capillary congestion in some cases. However, in I/R group (as positive control) was found moderate to severe histopathological lesions including mucosal erosions, ulcers and necrosis, inflammatory cell infiltration, hemorrhage, and capillary congestion (Figure 2). Interestingly, amlodipine treatment group demonstrated moderate to mild histopathological injury which was showed significant differences with sham (P=0.004) and I/R (P=0.002) groups (Figure 2).

4. Discussion

The results of the study clearly show that pretreatment by means of orally administered amlodipine significantly attenuated intestinal I/R injury in rats. Research has indicated that a number of antioxidants are efficient for the treatment of I/R-induced intestinal injury by means of scavenging ROS.[19] The preventive effect impact of amlodipine on induced tissue lesion because of antioxiant and anti-inflammatory actions has been reported previously in several experimental models which may expound on their mitigation of I/R injury.[20,21] Nevertheless, it is not clear whether short-term administration of amlodipine at the beginning of ischemia will inhibit or mitigate the I/R injury. As an index of the anti-oxidative defense system, we measured the activities of SOD and GPX and the levels of MDA. MDA is one of the last products of lipid peroxidation. MDA can be administered in both tissue and blood. The concentration of MDA is directly proportional to the cell damage caused by free radicals [21]. Antioxidant enzymes, including GPx and SOD, safeguard tissues against reperfusion injury by destroying ROSz[22]. These measurements can be made on tissue, blood, and other fluids [23]. Pergel A. et al, reported that intestinal I/R injury upregulated the MDA content. Furthermore, infliximab administration remarkably downregulated the MDA content. Moreover, SOD and GPx activities showed that infliximab treatment upregulated the intestinal reperfusion injury. [13]

In this study, the level of MDA significantly increased in I/R rats. Nonetheless the amlodipine treatment decreased it in the intestine tissue. In these results, increased MDA levels may be attributed to the high production of free radicals by an I/R injury. The capability of amlodipine to decrease lipid perxidation in the rats which received

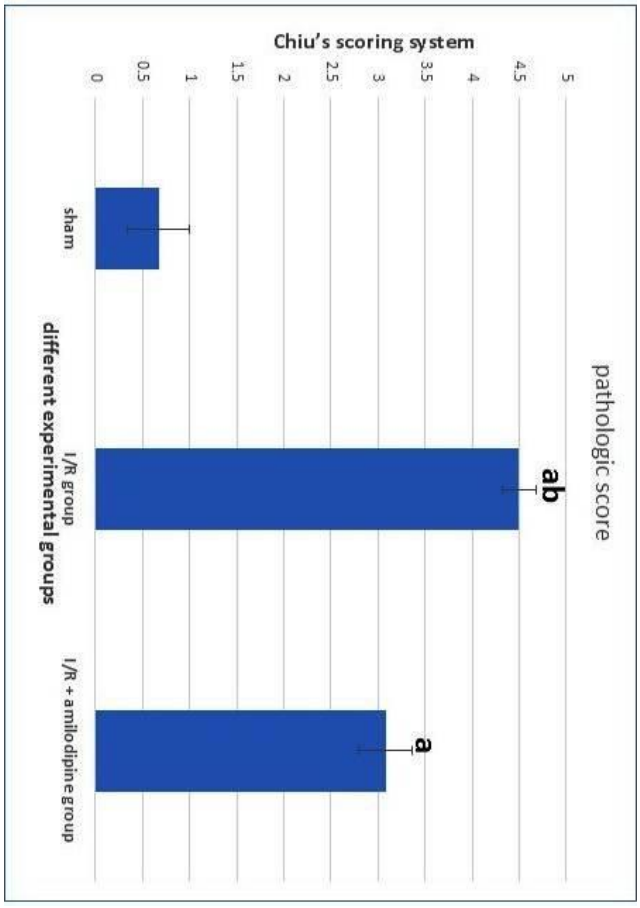

Figure 1. Histological scoring of intestinal pathological lesions (mean ± SEM) in tissue samples of rats according to Chiu's scoring system with some modifications in different experimental groups. I/R: ischemia/ reperfusion; a: significant difference with sham group (P<0.05); b: significant difference between I/R group and I/R+ amlodipine group (P<0.05).

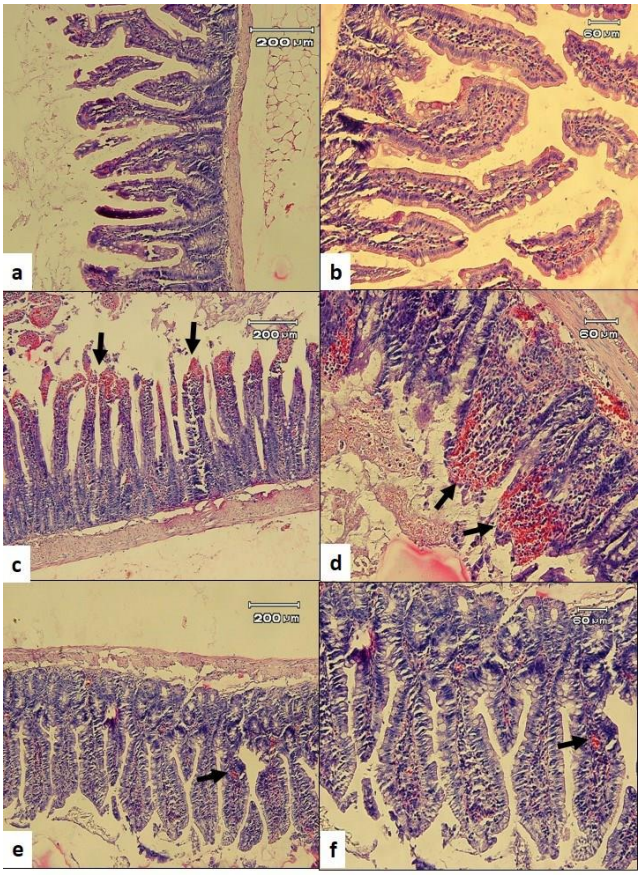

Figure 2. Intestine, rat. a and b: sham group with normal intestinal structure; c and d: severe pathological lesions including hemorrhage, necrosis, ulcer and inflammatory cell infiltration (*arrows*) associated with shortening of the intestinal villi after I/R; e and f: all pathological lesions such as capillary congestion and inflammatory cell infiltration (*arrows*) attenuated after treatment with amlodipine in I/R injury. H&E.

amlodipine may be link to its calcium channel blocking effect it may prevent tissue from oxidative and inflammatory injury by means of calcium. Research has shown that, intracellular calcium is increased by I/R injury.[24] The escalation in intracellular calcium activates cytosolic protease which is related to calcium.[25] Furthermore, intracellular calcium changes the dehyrogenases into xanthine oxidase which has a major role in the production of reactive oxygen radicals.[26] Moreover, Amlodipine alleviated ischemia injury by means of its antioxidative and GPx and SOD-stimulatory activities.[27] Our finding in regard to the significant increase in GPx and SOD levels in intestine tissue of rats in I/R amlodipine group supports the previous studies.[28,29] For instance, Zekai Halici. et al, reported that both 3 and 5 mg/kg doses of amlodipine administered before ischemia and I/R treatments significantly increased the activity of SOD to 98.1 and 100.3 mmol/min/mg tissue and 97.7 and 99.2 mmol/min/mg tissue, respectively, in the rat's ovary.[30] It is well known that histopathological examination is one of the most important methods for the evaluation of intestinal damage following ischemia–reperfusion and the Chiu scoring system has been introduced as the most widely used histological method for this purpose. On basis of this method, in IR group there were moderate to severe necrosis, erosions and ulcer in mucosa, severe hemorrhage and capillary dilation and congestion associated with polymorphonuclear inflammatory cell infiltration in intestinal submucosa. Moreover, separation of intestinal apical cells, shortening of the intestinal villi and capillary congestion of muscularis mucosa were observed. By contrast, pathological lesions significantly reduced in rats with I/R treatment by amlodipine. However, according to the author's knowledge, there was no information on the beneficial effect of amlodipine treatment on I/R-induced intestinal injury in rats. The same pathological results have been reported in treatment by another component on basis of Chiu's scoring system. Recent studies reported that the treatment by infliximab and berberine in intestinal I/R injury can attenuate the pathological lesions with marked reduction in Chiu's score.[13,31] Moreover, in both mentioned treatments were observed the lesser edema, inflammation and cell infiltration in intestinal submucosa which is in agreement with the present findings. In conclusion, the present microscopic results suggest that treatment by amlodipine before ischemia–reperfusion in the intestine can markedly attenuate the severity of intestinal pathological I/R injury.

Finally, the findings of this study suggest that amlodipine has a preventive activity on I/R-induced intestine injury. The observed preventive effects of amlodipine in the present study can possibly be mediated by means of its well-known antioxidant and anti-inflammatory potential. Therefore, we suggest that amlodipine may be a novel approach to therapy for protective intestinal I/R injury. Nonetheless, there is a need for further studies to examine the mechanism by which amlodipine performs these functions.

Conflict of interest

None declared.

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چکیده

اثر محافظتی آملودیپین خوراکی در برابر آسیب ایسکمی-پرفیوژن مجدد روده در رت‌ها

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هدف- هدف از این مطالعه بررسی اثرات محافظتی آملودیپین بر آسیب‌های روده پس از پیچش / رفع پیچش در موش صحرایی بود.

طرح مطالعه- مطالعه تجربی

حیوانات- ۱۵ سر رت نر نژاد اسپاراگو با وزن ۲۲۰-۲۰۰ گرم

روش کار- رت‌ها به‌طور تصادفی به ۳ گروه: گروه IR (کلامپ رگ)، گروه شم (بدون کلامپ رگ) و گروه IRA (کلامپ رگ و ۵ میلی‌گرم/کیلوگرم پیش‌داروی آملودیپین). ایسکمی-رپرفیوژن روده‌ای با بستن شریان مزانتریک قدامی به مدت ۶۰ دقیقه و سپس ۶۰ دقیقه رپرفیوژن انجام شد. سطوح سوپراکسید دیسموتاز (SOD)، گلوتاتیون پراکسیداز (GPx) و مالون دی آلدئید (MDA) در بافت روده موش صحرایی تعیین شد. بافت روده همچنین ازنظر هیستوپاتولوژیک مورد بررسی قرار گرفتند.

نتایج- پیش درمانی با آملودیپین مانع افزایش پراکسیداسیون لیپیدی و کاهش سطح GPX و SOD شد. آملودیپین همچنین باعث آسیب سلولی و تغییرات بافت‌شناسی در بافت روده گروه ایسکمی-رپرفیوژن شد. سطح MDA به‌طور معنی‌داری در روده موش صحرایی گروه IR افزایش یافت ($P<0.006$). سطوح GPx و SOD پس از القای IR به‌طور معنی‌داری کاهش یافت ($p<0.001$).

نتیجه‌گیری و کاربرد بالینی – یافته‌های مطالعه حاضر نشان داد که آملودیپین دارای اثرات پیشگیرانه در آسیب‌های روده‌ای ناشی از ایسکیمی-رپرفیوژن است. اثرات پیشگیرانه آملودیپین می‌تواند به دلیل خاصیت آنتی‌اکسیدانی و ضدالتهابی شناخته‌شده آن باشد. لذا، به نظر می‌رسد آملودیپین یک راهکار برای درمان آسیب‌های روده‌ای ناشی از ایسکمی-رپرفیوژن باشد.

واژه‌های کلیدی - آملودیپین، ایسکمی-رپرفیوژن، روده، موش صحرایی