THE EFFECT OF CARVEDILOL ON POST-ISCHEMIC SPLANCHNIC TISSUE INJURY

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Abstract

The objective of the current work aimed to investigate whether carvedilol is an effective antishock agent in the well established in vivo ischemia/reperfusion model of splanchnic artery occlusion shock. Also, to investigate the mechanism of this protection, such as antioxidant properties, preservation of endothelial function, and inhibition of neutrophil accumulation and adhesion. For this study, 36 rats weighing 120-200gm were selected. They were classified into 4 groups; control, splanchnic ischemia-reperfusion (SI/R), SI/R rats injected by 0.5mg/kg carvedilol and SI/R rats injected by 1.0 mg/kg carvedilol. Each group was formed of 9 rats. The results obtained showed that; hematocrite, tissue malondialdehyde (MDA), and tissue myeloperoxidase (MPO) were significantly increased ($p<0.001$) while plasma MDA and anti MPO were non-significantly increased in ischemic-reperfusion group compared with the control group. Comparative study of injected groups versus non-injected SI/R group, the result showed that; significant decrease of hematocrite ($p<0.01$), tissue MDA ($p<0.001$) and MPO ($p<0.001$) while plasma MDA and anti MPO were non-significantly changed in SI/R rats injected with 1.0 mg/Kg carvedilol. Mean while, SI/R rats injected with 0.5mg/Kg carvedilol showed non significant changes of all studied biochemical parameters when compared with the non-injected SI/R rats.

We could conclude that; carvedilol pretreatment leads to amelioration of the adverse effects of SI/R shock by scavenging oxygen free radicals, counteracting the increased microvascular permeability and inhibiting the adhesion and activation of neutrophils in this model of splanchnic ischemia/reperfusion.

Introduction

Ischemia and reperfusion of the splanchnic circulation resulting from vascular occlusion, hemorrhage, or trauma are critical in the

development of shock states, since, this region appears to play a major role in promoting lethality ***(Hayward and Lefer, 1998)***.

Gut ischemia-reperfusion injury is a serious condition in intensive care patients. Activation of immune cells within the huge endothelial surface area of gut microcirculation may initiate a systemic inflammatory response with secondary injury to distant organs ***(Schwarz et al., 1999)***.

Splanchnic ischemia and reperfusion results in the accumulation of neutrophils in the splanchnic visceral organs where they mediate their injurious effects ***(Hayward and Lefer, 1998)***.

MPO is a heme-containing enzyme secreted by human phagocytes after activation by respiratory burst stimulants. MPO has 2 major activities: halogenation and peroxidation. During the halogenation activity of MPO, hydrogen peroxide (H_2O_2) reacts with native MPO to form the redox intermediate which oxidizes halides to hypophalous acids (HOCI) via a 2-electron oxidation. HOCL is the major strong oxidant generated by the MPO system of stimulated phagocytes at physiological concentrations of halide ions. MPO also oxidizes a number of organic substrates (RH) to free radical intermediates by a classical peroxidase cycle ***(Carr et al., 2000)***.

During reperfusion, gut injury may be amplified by increased production of oxygen radicals and exhaustion of endogenous antioxidant defense mechanisms ***(Schwarz et al., 1999)***.

Recent studies have demonstrated that carvedilol is a vasodilating beta-blocker and antioxidant approved for treatment of mild to moderate hypertension, angina, and congestive heart failure ***(Lysko et al., 2000; Cargoni et al., 2000 and Kurz et al., 2000)***.

However, the effect of carvedilol on post ischemic/reperfusion of the splanchnic area needs to be clarified.

Aims of the work

The objective of the current work aimed to investigate whether carvedilol is an effective antishock agent in the well established in vivo ischemia/reperfusion model of splanchnic artery occlusion (SAO) shock. Also, to investigate the mechanism of this protection, such as antioxidant properties, preservation of endothelial function, and inhibition of neutrophil accumulation and adhesion.

Material and methods

Experimental animals:

Thirty six male albino rats of local strain, weighing from 120-200gm were used without previous preparation.

Experimental design and animal groups:

The animals were subdivided into four equal groups. Each consisting of nine rats. All groups were fasted for 12-18 hours with free access to water.

Group I: Served as control group.

Group II: Subjected to acute splanchnic ischemia and reperfusion shock (SI/R).

Group III: Received carvedilol (0.5mg/kg/day) aqueous suspension by intraperitoneal injection for five successive days, then subjected to acute splanchnic ischemia and reperfusion shock.

Group IV: Received carvedilol (1mg/kg/day) aqueous suspension by intraperitoneal injection for five successive days, then subjected to acute splanchnic ischemia and reperfusion shock.

The above two doses used were consistent with the plasma levels of the drug attained in patients on doses of 25-50 mg/day ***(Ruffolo and Feuerstein, 1997).***

Methods:

A-Induction of acute splanchnic ischemia/ reperfusion shock *(Christopher et al., 1995)*:

The rats were anaesthetized with urethane in a dose of (0.6 m1/100 gm) of 25% freshly prepared solution injected intraperitoneally (I.P). The abdomen was opened via midline incision. The superior mesenteric artery (SMA) was isolated from the surrounding connective tissue near its aortic origin. Acute splanchnic ischemia-reperfusion shock was induced using total occlusion of the SMA with non-traumatic ligation. Thirty minutes later, the ligation was removed from the SMA followed by observing the rat for additional 60 min. of reperfusion.

B-Preparation of the intestinal tissues and blood samples:

The abdomen was opened and part of jejunum was taken (about 1.0gm) in a clean dry tube. Also, the thorax was opened and a blood sample was taken by intracardiac heparinized syringe (200 µl heparin/2 ml blood). The blood sample was divided into two parts. The first part, was drawn in a fine capillary tube for hematocrite determination. The second part was centrifuged at 3000 r.p.m for 15 min. The supernatant plasma was collected in a dry clean tube for determination of malondialdehyde and antimyeloperoxidase autoantibodies. The small intestinal tissues were homogenized for determination of myeloperoxidase and malondialdehyde.

C-Biochemical Analysis:

1.Estimation of hematocrite % ***(Thompson and Briton, 1977)***.

2.Estimation of malondialdehyde in plasma ***(Draper and Hadley, 1990)***.

3.Estimation of malondialdehyde in tissue homogenates ***(Draper and Hadley, 1990)***.

4.Estimation of myeloperoxidase in tissue homogenates ***(Bradly et al., 1982)***.

5.Estimation of antimyeloperoxidase autoantibodies in plasma ***(Hagen et al., 1993)***.

Statistical analysis:

The obtained results-were tabulated and statistically analyzed using student's t-test. p values < 0.05 were considered significant while p values > 0.*05* were insignificant ***(Budneck,1987).***

Results & Discussion

Table (1): Mean, ±SE, and p values of hematocrite, plasma malondialdehyde (MDA), tissue MDA, tissue myeloperoxidase (MPO) and plasma antimyeloperoxidase (anti MPO) in SI/R group compared with the control group.

Groups / **Parameters**	**Group I (control) n=9**	**Group II (SI/R) n=9**	**P values**
Hematocrite (%)	42.16±0.94	49.29±0.88	p1<0.001
Plasma MDA (nmol/ m1)	7.31±0.47	8.09±0.78	NS
Tissue MDA (nmol/ml/h)	4.27±0.32	8.65±0.29	p1<0.001
Tissue MPO (U/dl/100mg tissues)	0.126±0.023	1.205±0.163	p1<0.001
Plasma antiMPO (U/ml)	7.31±0.47	5.914±0.076	NS

NS: Non significant (p>0.05).
p<0.05 : significant
p1 : probability versus control group.

Table (2): Mean, ± SE, and p values of hematocrite, plasma (MDA), , tissue MDA, tissue (MPO) and plasma (anti MPO) in SI/R group pretreated with 0.5 mg/kg carvedilol compared with SI/R group.

Groups / Parameters	Group I (SI/R) n=9	Group II (SI/R+carvedilol 0.5 mg/kg) n=9	P values
Hematocrite (%)	49.29±0.88	47.92±1.48	NS
Plasma MDA (nmol/ m1)	8.09±0.78	6.82±0.75	NS
Tissue MDA (nmol/ml/h)	8.65±0.29	7.89±0.26	NS
Tissue MPO (U/dl/100 mg tissues)	1.205±0.163	0.980±0.105	NS
Plasma anti MPO (U/ml)	5.914±0.076	5.985±0.082	NS

NS: Non significant ($p>0.05$).
$p<0.05$: significant

Table (3): Mean, ± SE, and P values of hematocrite, plasma (MDA), , tissue MDA, tissue (MPO) and plasma (anti MPO) in SI/R group pretreated with 1.0 mg/kg carvedilol compared with SI/R group.

Groups / **Parameters**	**Group I (SI/R) n=9**	**Group II (SI/R + carvedilol 1.0 mg/kg) n=9**	**P values**
Hematocrite (%)	49.29±0.88	45.16±0.69	p2<0.001
Plasma MDA (nmol/ m1)	8.09±0.78	6.52±0.25	NS
Tissue MDA (nmol/ml/h)	8.65±0.29	6.58±0.23	p2<0.001
Tissue MPO (U/dl/100mg/tissues)	1.205±0.163	0.460±0.045	p2<0.001
Plasma anti MPO (U/ml)	5.914±0.076	6.096±0.099	NS

NS: Non significant (p>0.05).
p<0.05 : significant
p2 : probability versus (SI/R) group.

DISCUSSION

Occlusion followed by reperfusion of the major vessels which supply blood to the abdominal viscera, primarily the intestine is well known to produce a severe from of circulatory shock that leads to death. Some of the mechanisms involved in this shock state include parenchymal and microvascular damage that leads to increased microvascular permeability and intravascular fluid loss ***(Haglund and Lundgren, 1978)***.

The results of this work revealed that splanchnic ischemia reperfusion shock significantly increased the hematocrite value (Table 1) compared with the control group while pretreatment with (0.5 mg/kg) of carvedilol showed non significant decreases (Table2). However, carvedilol in a dose of (1.0 mg/kg) significantly decreased the hematocrite value ($p<0.01$) when they compared with SI/R group (Table 3).

These findings are consistent with the observations of ***Christopher et al., (1995)*** who reported that hematocrite value increased in SI/R shock rats, however carvedilol-treated rats displayed significantly less haemoconcentration. These findings indicate that carvedilol curtailed the increase in hematocrite value, an indirect measure of loss of fluid from the vascular compartment in this model of SI/R shock.

Also, pretreatment with carvedilol was found to protect against endothelial damage that could exacerbate the systemic shock state by increasing microvascular permeability and aggravating mesenteric ischemia with subsequent decrease of Hematocrite ***(Christopher et al., 1998)***.

The present findings, showed that plasma MDA was non significantly increased in SI/R group compared with the control group

(Table I). Also pretreated groups showed non significant decreases of plasma MDA compared with SI/R group (Tables 2 &3).

However, there was no previous reports about plasma MDA level in SI/R shock of rats or those treated by carvedilol but compatible studies in SI/R shock of dogs and patients with coronary artery disease ***(Matsuda et al., 2000)*** and those with ischemic heart failure ***(Lysko et al., 2000)***.

While,***Lysko et al.,(2000)*** found that; plasma MDA level was non-significantly changed between treated and non-treated groups ***Matsuda et al., (2000)*** found that long term therapy with carvedilol produced a significant decrease of plasma MDA level in patients with coronary artery disease due to its antioxidant effect. It is clear that the cause of discrepancy between these results and the present results may be referred to the use of different species, the site of ischemia and the duration of therapy with carvedilol.

Moreover, the present study revealed that tissue MDA level was markedly increased in splanchnic ischemia/reperfusion compared with the control group ($p<0.001$) (Table 1). Carvedilol pretreatment (0.5mg/kg) non significantly decreased the tissue MDA level (Table 2) while carvedilol in a dose (1.0 mg/kg) significantly decreased it ($p<0.001$) (Table 3)when compared with SI/R group.

The above results may be due to the inhibition of oxygen free radicals mediated lipid peroxidation inside the cells and tissues ***(Lysko et al., 2000).*** Also, these results suggested that the protective effect of carvedilol may be closely related to its antioxidant effect ***(Christopher et al., 1995)***. So, it is effective against SI/R shock model which is associated with a burst of oxygen free radicals production, thus it inhibits the lipid peroxidation ***(Yue et al., 1994a)***.

In (1998), Tadolini and Franconi suggested the molecular mechanism of carvedilol action. It may inhibit lipid peroxidation by

binding the Fe^{+3} generated during the oxidation of Fe^{+2} by lipid hydroperoxides in the substrate. Therefore, the antioxidant potency of carvedilol can be ascribed to its ability to bind Fe^{+3} that is a catalyst of the process and to its lipophilic nature that concentrates it in the membranes where Fe^{+3} is generated by a site specific mechanism.

Also, Noguchi et al., (2000) concluded that the antioxidant effect of carvedilol against lipid peroxidation, may be due to prevention of ferric ion induced oxidation by sequestering ferric ion.

Although, the model of splanchnic ischemia/reperfusion was used to induce free radial, there were no reports estimated the tissue MDA level except of ***Aydin et al., (1998)***. They found a significant increase of intestinal tissue MDA & serum MDA in experimental dogs using the same model of SMA legation. Also, they concluded that plasma MDA levels are valuable marker of diagnosis in intestinal ischemia.

There are different models, used to generate free radicals either by ischemia ***(Yue et al., 1995b; Krammer and Weglick, 1996; and Lysko et al., 2000)*** or by non-ischemic measures such as chemicals e.g. phorbol ester and/or dihydrofumaric acid ***(Yue et al., 1992b)***, vitamin C/Fe^{+2} ***(Yue et al., 1992a)*** and enzymatically using xanthine and xanthine oxidase ***(Yue et al., 1994b)***. All these models revealed that carvedilol acts as an oxygen free radical scavenger which are nearly the same results of our findings.

In the present work, SI/R shock was associated with a significant increase of MPO activity ($p<0.001$) (Table 1) compared with the control group. On the other hand, pretreatment with (0.5mg/kg) carvedilol only slightly decreased MPO activity (Table 2) while pretreatment with (1.0 mg/kg) of carvedilol induced a significant decrease in MPO activity ($p<0.001$) (Table 3) when they compared with SI/R group.

It was clear that rats subjected to splanchnic artery occlusion developed significant increase in tissue MPO activity, and a marked injury to the distal ileum ***(Cuzzocrea et al., 2000)***.This can be explained by the fact that polymorph nuclear leukocytes (PMNs) play an important role in tissue injury associated with ischemia and reperfusion ***(Mullane, 1991)***. Also PMNs-endothelial adhesive interaction can be rapidly induced by a burst of free radical generation at the onset of reperfusion ***(Mc-Ever, 1990)***.

By scavenging free radicals generated after reperfusion, carvedilol prevented PMNs accumulation in ischemic-reperfused tissue and significantly attenuated the increase in MPO activity and therefore protect tissues from PMNs induced injury ***(Christopher et al., 1995)***.

Yue et al., (1995a) demonstrated that carvedilol inhibited the adhesion of neutrophil to damaged or activated endothelial cells through suppressing intracellular adhesion molecue-1 (ICAM-1) which is involved in the attachment of neutrophil to endothelial cells and smooth muscle cells thereby, limiting neutrophil induced tissue injury.

The present results were in agreement with that of ***Christopher et al., (1998)*** who found that both carvedilol as well as its hydroxylated metabolite were effective against post-ischemic splanchnic tissue injury. The high MPO activity demonstrated in the ischemic ileal tissue showed significant decrease on treatment with either the metabolite or carvedilol, at a dose 1.0 mg/kg. However, treatment with 0.5mg/kg carvedilol resulted in a slight decrease in MPO activity. These results suggested that carvedilol as well as its metabolite retarded accumulation of neutrophils in intestinal tissues following SI/R shock.

Additionally, the present results were in parallel with other studies used the same model of ischemia/reperfusion on hearts of different animal species: minipigs ***(Bril et al., 1992)*** and Rabbits ***(Brunvand et al.,***

1998). The net results revealed that carvedilol and/or its metabolite produced a significant reduction of MPO activity. So, carvedilol exerted a protective effect through its antioxidant properties in myocardial ischemia/reperfusion studies ***(Feuerstein et al., 1998)***.

On the other hand , plasma anti MPO showed non-significant changes in the all studied groups (Tables 1, 2,3).

From the present results, it can be observed that neither SI/R nor carvedilol pretreatment produced significant change in plasma anti MPO level. These results indicated that carvedilol can not induce the formation of antibodies against neutrophil which react with the cytoplasmic constituents of neutrophil to produce attenuation in myeloperoxidase level.

This expectation depends on the findings of ***Iwahori et al., (1998)***, who reported that treatment with antineutrophil antibody such as (RP_3) selectively and sufficiently depleted the circulating neutrophil, markedly reduced myeloperoxidase and attenuated ischemia/reperfusion injury in skeletal muscles. However, ***Fabian and Kent, (1999)*** demonstrated that superoxide anion production during reperfusion is reduced by antineutrophil antibody treatment after prolonged cerebral ischemia.

The above mentioned results indicated that carvedilol did not induce the formation of antineutrophil cytoplasmic autoantibodies or (Anti-MPO) and this provides further evidence that carvedilol leads to inhibition of the inflammatory response to ischemic injury and reduction in infiltration of activated neutrophils into the ischemic tissue ***(Bril et al., 1992 and Ma et al., 1996)***.

Thus, we could conclude that; carvedilol may ameliorate the adverse effects of SI/R shock by scavenging oxygen free radicals, counteracting the increased microvascular permeability and inhibiting the

adhesion and activation of neutrophils in this model of ischemia/reperfusion.

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الملخص العربى

تأثير دواء "كارفيدلول على إصابة أنسجة الأحشاء بعد الإحتشاء فى الفئران

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قسمى الكيمياء الجيوية*والفارماكولوجى-كليتى طب بنها والمنوفية

جامعتى الزقازيق والمنوفية

يتسبب نقص سريان الدم للأحشاء أو الإحتشاء الذى يعقبه عودة سريان الدم فى حدوث صدمة دموية يصحبها زيادة فى معدل الوفاة. تعددت الأسباب لهذه الظاهرة ولكن بعد العديد من التجارب تبين أن عناصر الأكسجين الحرة تعتبر من أهم العوامل فى حدوث مثل هذه الصدمة.لذلك صممت هذه الدراسة لإيضاح تأثير دواء"كارفيدلول" على إصابة أنسجة الأمعاء بعد الإحتشاء ومحاولة التعرف على كيفية حدوث هذا التأثير مثل دوره كمعاكس لعناصر الأكسجين الحرة والحفاظ على خصائص النسيج المبطن للأمعاء ومنع تجمع والتصاق كرات الدم البيضاء بالأنسجة المصابة. و لهذه الدراسة تم إستخدام 36 من ذكور الفئران البيضاء وقسمت إلى أربع مجموعات متساوية وهى مجموعة ضابطة والثانية تم تعريضها لصدمة الإحتشاء (نقص سريان الدم للأحشاء لمدة 30 دقيقة يعقبها عودة سريان الدم لمدة 60 دقيقة) والثالثة والرابعة تم حقنهم بدواء "كارفيدلول" 5و. مجم، 1 مجم/كجم على التوالى لمدة 5 أيام.وقد أوضحت نتائج هذه الدراسة وجود زيادة ذات دلالة إحصائية فى مستوى الهيماتوكريت والمالونديالدهايد والمايلوبيروكسيديز داخل الأنسجة بينما وجد أن مستوى المالونديالدهايد والمايلوبيروكسيديز بالبلازما لاتوجد لهما زيادة إحصائية ودلك فى مجموعة الإحتشاء عند مقارنتها بالمجموعة الضابطة. عند عمل دراسة مقارنة بين المجموعتين اللتين تم حقنهما بمجموعة الإحتشاء، تشير الدراسة إلى وجود نقص ذات دلالة إحصائية فى مستوى الهيماتوكريت والمالونديالدهايد و المايلوبيروكسيديز داخل الأنسجة بينما وجد أن مستوى المالونديالدهايد والمايلوبيروكسيديز بالبلازما لاتوجد لهما زيادة إحصائية وذلك فى مجموعة الإحتشاء والتى تم حقنها بجرعة مقدارها 1 مجم/كجم. أما التى تم حقنها بمقدار 5و0 مجم/كجم فلا يوجد لها أى تأثير على جميع المواد البيوكيميائية التى تم قياس مستواها سواء داحل الأنسجة أو بالبلازما.

مما سبق يمكننا إستنتاج أن إعطاء دواء "كارفيدلول" يخفف من الآثار السلبية لصدمة الإحتشاء وذلك عن طريق معاكسة تأ ثير عناصر الأكسجين الحرة والتغلب على زيادة نفاذية

الأوعية الدموية الدقيقة ومنع تجمع والتصاق كرات الدم البيضاء بالأنسجة المصابة فى هــذا النوع من الإحتشاء.