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The Beneficial Effect of Using Prostacyclin on Ischemia Reperfusion Injury of Horse Jejunum

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Abstract: In this study, effect of prostacyclin on ischemia reperfusion injury, that was performed in the jejunum of horse was investigated. In 12 horses total arterio venous occlusion was performed in 25 cm of a jejunal segment. In all cases, 1h reperfusion was performed after 2 h of no flow ischemia. Twelve horses were assigned into two equal groups, one as a control (1) group and the other as a prostacyclin (2) group. In the 2 nd group, 1 Lısotonic NaCl solution including diluated PGI_2 was administrated into the jugular vein for five minutes before the occlusion at a rate of 5 ng/kg/min and increased to 25 ng/kg/min during the occlusion and decreased to 5 ng/kg/min for first five minutes of the reperfusion and continued during the remaining reperfusion period. In all cases tissue samples and photographs of the jejunum were obtained 15 min before the occlusion, 10 minutes before the reperfusion and at the end of reperfusion for TEM and gross pathology. Blood samples were collected from the facial artery in order to measure TNF α and IL-6, 15 min before the occlusion, 10 min before the reperfusion and at the end of reperfusion in all cases. In the control group, while the dark muddy brown appearance of Ischemic Strangulative Obstructioned (ISO) segments were constant after the reperfusion; in the PGI_2 group moderately anemic appearance, that was caused via ischemia, was back to normal after the reperfusion. After the reperfusion, irregular microvilli and excesive mitochondrial cristalysis were observed in the control group; and short but regular microvilli and many mitocondria with cristae were observed in the PGI_2 group. During the experiment period, serum TNF α values were increasing in the control group and were decreasing in the PGI_2 group. IL-6 levels could not be detected in many cases. In conclusion, prostacyclin has been found useful to decrease the ischemia reperfusion injury of horse jejunum according to the results of TEM and macroscopic pathology and the level of TNF α.

Key words: Intestinal ischemia reperfusion injury, prostacyclin, iloprost, PGI_2, horse

INTRODUCTION

Intestinal ischemia-reperfusion injury is a common condition of acute abdominal disease in the horse (Blikslager *et al*., 1997; Moore, 1997). Such injury has been documented in experimental animals (Chiu *et al*., 1970; Katırcıoğlu *et al*., 1996). Recent studies have shown that reperfusion after intestinal ischemia triggers a complex inflammatory response that includes activation of the complement system, aggregation and margination of polymorph nuclear neutrophyls and release of a number of toxic metabolites including oxygen-derived free radicals, eicosanoids (leucotrienes, prostaglandins), (PAF+ lysophosphatidylcholine+arachidonic acid) and lysosomal proteases (Moore, 1997; Moore *et al*., 1995). It has revealed that intestinal ischemia and subsequent reperfusion cause microvascular distant organ injuries. Toxic mediators released from ischemic reperfused areas also impair organ metabolism Katırcıoğlu *et al*., 1996.

Dabareiner *et al*. (1993), have documented that 70 min of arteriovenous occlusion in the equine jejunum resulted in a disrupted intramural vascular pattern with distribution away from the mucosa and to a lesser extend the serosa and reported that the jejunum is more sensitive to vascular compromise than the large colon. Dabareiner *et al*. (1995), in a different study, have indicated that ischemia reperfusion of the equine jejunum caused a significant increase in microvascular permeability by evaluating results of Light Microscopy (LM) and Transmission Electron Microscopy (TEM).

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Although Dimethyl Sulfoxide (DMSO), a hydroxyl radical scavenging solvent known as one of the agents to attenuate ischemic intestinal injury in laboratory animals (Carati *et al*., 1988) is not effective to prevent equine jejunal injury (Arden *et al*., 1989; 1990). Another study (Moore *et al*., 1995) showed that DMSO, allopurinol, 21 Aminosteroid U- 743896 and $MnCl_2$ had no beneficial effect on colonic mucosal injury associated with low flow ischemia reperfusion in horses either. In the other study (Moore *et al*., 1998), the usage of platelet activating factor antagonist L 691, 880 was ineffective in diminshing the reperfusion injury of large colon in horses. Although pretreatment with nonspesific phospholipase A2 inhibitors (methylprednisolon, dexamethasone or quinacine) were not succesful in preventing intestinal reperfusion injury in the dog (Boros *et al*., 1993), Campbell and Blikslager (2000) have shown that COX2 inhibition via etodolac may have beneficial effects on repairing ischemic-injured intestine and the tissues treated with etodolac have significant elevations in PGE_2 and PGI_2. Blikslager *et al*. (1977) have shown reductions in mucosal permeability in ischemic injured tissues treated with PGE_2 and PGI_2 (prostacyclin) in porcines.

It is shown that $_{PGI2}$ which is a metabolite of cyclooxygenase pathway inactivates leucocytes, inhibits the toxic metabolites of arachidonic acid such as leucotriens (Katırcıoğlu *et al*., 1992) and protects microcirculation of ischemic tissue from reperfusion injury (Katırcıoğlu *et al*., 1996). It is known that prostacyclin has powerful cytoprotective, antiagregative and vasodilatatory effects (Grylewski, 1987). Öztamur (2002) has reported that PGI_2 infusion was effective in the reduction of experimentally induced Ischemia Reperfusion (IR) injury in the equine small intestine by evaluating results of LM. However equine studies on PGI_2 are limited with evaluating it's hemodynamic effects in conscious ponies (Moore *et al*., 1982) and cardiopulmoner effects in anesthetized horses (Trim *et al*., 1985).

Iloprost, a synthetic analogue of prostacyclin, added to the cardioplegic solutions improves myocardial performance, inhibits the toxic mediator release from endothelium leucocyte interaction and reduces the severity of IR injury on dogs (Katırcıoğlu *et al*., 1998). Another study (Katırcıoğlu *et al*., 1997) revealed that intravenous prostacyclin reduced the severity of intestinal reperfusion injury occuring at the early period of reperfusion by inhibiting the release of the toxic mediators as Tumor Necrosis Factor (TNF), thus decreasing distant organ injury on rabbits. It was reported that TNF and indirectly IL-6 can cause shock and distant organ injury in endotoxemia which can evolve following strangulations and obstructions of small intestines in horses (Morris, 1991). Hovewer Moore *et al*. (1995) did not observed measurable TNF ve IL-6 activity in horses during low flow ischemia and reperfusion of the large colon.

The purpose of the this study was to determine the effects of prostacyclin on severity of equine jejunal mucosal IR injury by evaluating the results of TEM, TNFα and IL-6 levels as well as compairing previously used doses on other experimental animal studies.

MATERIALS AND METHODS

This project was performed with approval and under the guidelines of ethics commite of Ankara University, Faculty of Veterinary Medicine.

Experimental preparation: Twelve healthy mixed breed horses ranging from 3 to 15 years old and from 250 to 450 kg of body weight were studied. Food, but not water, was withheld for 24 h prior to the study. All experiments were conducted on horses under general anaesthesia, followed by euthanasia at the completion of each experiment. A 14 gauge cathater was inserted into the left jugular vein for administration of polyionic isotonic fluids, anaesthetic drugs and iloprost (group 2). Horses were sedated by xylazine hydrochlorure (1.1 mg kg^{-1} body weight) and anaesthetized with a bolus of ketamine hidroclorure (2.2 mg/kg/body weight) administered iv to effect on positioned in dorsal recumbency, intubated and maintained on halothane vapourised in 100% O_2. Arterial blood pressure was monitored via a catheter placed in the facial artery and the mean arterial pressure was maintained at the 70 mm Hg or above by altering isotonic fluid infusion rates and infusing dobutamine hydroclorid (dobutrex 250-0.5-5microgram/kg/min). All experiments were heparinized (500 IU/kg/h) and lactated ringer solution was administered iv at 10 mL/kg/h rate. All horses were positioned in dorsal recumbency and a ventral midline celiotomy was performed and jejenum was exteriorized. A 25 cm long jejunal ISO (ischemic strangulation obstruction) segment was created (Sullins *et al*., 1985). Artery and vein supply of ISO segment was ligated with umblical cotton tape (Ethıcon) and umblical cotton tapes were placed at the ends of ISO segment to prevent flow of ingesta through the intestinal lumen and blood through the serosal vessels. All horses underwent 2 h of no flow ischemia and subsequent 1 h of reperfusion.

Experimental design: Twelve horses were assigned to 2 groups of 6 horses each as control and prostacyclin groups. In horses of group 2, PGI_2 (Sigma, P-6188) diluted

in 1 L ısotonic NaCl solution was administered into the jugular vein over a 5 min before the occlusion at a rate of 5 ng/kg/min, increased to 25 ng/kg/min during occlusion and decreased to 5 ng/kg/min for the first 5 min of reperfusion and then continued during the remaining of the reperfusion period (Öztamur, 2002; Katırcıoğlu *et al*., 1997). In all cases tissues samples and photographs of jejunum were obtained 15 min before the occlusion, 10 min before reperfusion and at the end of reperfusion for TEM and gross pathology. Blood samples from facial artery were collected for measurement of TNF α and IL-6, 15 min before occlusion, 10 min before reperfusion and at the end of reperfusion in all of experiments.

Specimen evaluation: A 2×4 cm full thickness jejunal specimens were obtained and fixed in phosphate buffer (pH 7.4) containing 2.5% glutaraldehyde for TEM. These mocosa samples were fixed in 1% osmium tetroxide and dehydrated in 50, 60, 70,80,90 and 96° series of alcohol. After exposing propylene oxide (10 min), the specimens were embedded in araldite-dodeceyl succinic anhydride (DDSA) and benzy 1.5 dimethylamine (BDMA). These samples were incubated at 40 and 60° for 24 and 48 h, respectively. Semi-thin sections were cut perpendicular to the superficial surface at mucosa and they were stained with toluidine blue and examined. Following staining of the ultra-thin sections with uranyl acetate and lead citrate, the samples were examined under TEM (EM 900 Carl Zeiss TEM). TEM centered on characteristics of the villus epithelium and mitochondrium.

TNF α and IL-6 assays: TNF α and IL-6 levels were measured by use of a solid phase sandwich ELISA kits (Biosource International Inc. California 93012 USA). TNF α standards ranging from 0-1000 pg mL were prepared from a standart solution of TNF α at a concentration of 5000 pg mL^{-1}. IL-6 standards ranging from 0-500 pg mL^{-1} were prepared from a standard solution of IL-6 at a concentration of 2500 pg mL^{-1}. Results were obtained with the use of the standred currve.

Statistical analysis: The significant differences between values obtained from the TNF α and IL-6 analyses were determined using the Mann Whitney U and Vilcoxin paired tests (Kutsal., 1990). The level of significance was set at $p<0.05$.

RESULTS

Macroscopic pathology: Over 2 h of ischemia period, ISO segments became to thicken and appeared between the dark muddy brown and the dark red colour and oedematous (Fig. 1 A and B) in the control group. These pathologic signs did not change over 1 h of reperfusion period in the control group. Over 2 h of ischemia period, ISO segments revealed moderately anaemic appearance (Fig. 2) in the prostacyclin group and this condition was corrected at the end of 1 h reperfusion period (Fig. 3).

TEM evaluation: TEM revealed normal mucosal appearance with normal ephitelial cells, tightly packed and long microvilli which have electron dense of mitochondrions with many cristae in both groups before ischemia (Fig. 4). At the end of the ischemia, irregular microvilli and mitocondrial cristalysis, swelling and intracytoplasmic vacuolisation were observed (Fig. 5) in control group, whereas after reperfusion irregular microvilli and excessive cristalysis but not

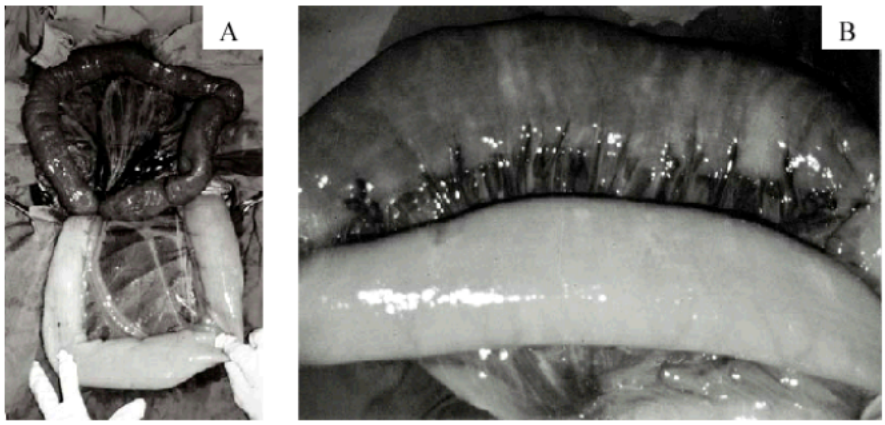

Fig. 1 A, B: Appearance of ISO segment at the end of ischemia at the control group

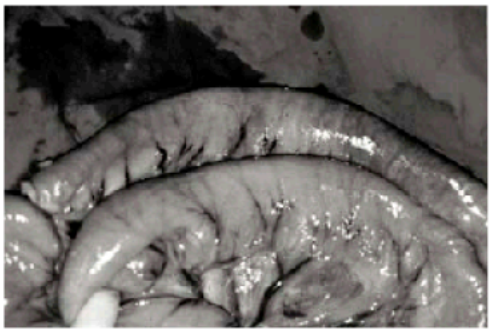

Fig. 2: Appearance of ISO segment at the end of ischemia at the prostacyclin group

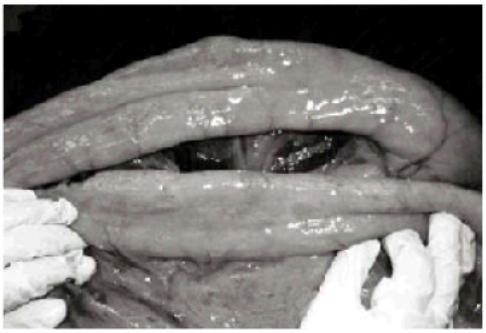

Fig. 3: Appearance of ISO segment after 1 h reperfusion at the prostacyclin group

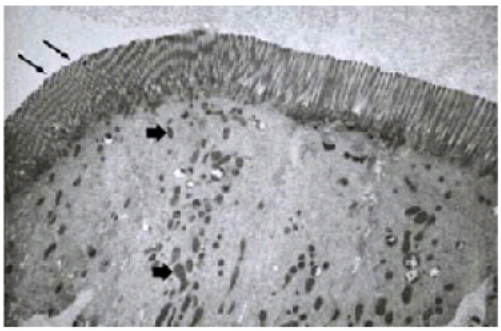

Fig. 4: Transmission electron micrograph of jejunum before occlusion in the control group. Epithelialcells were seem to be normal. Microvilli were tightly packed and long (thin arrows), mitocondrions had electron dense and they were with normal cristae (thick arrows). Uranyl acetate-lead citrate X 9000

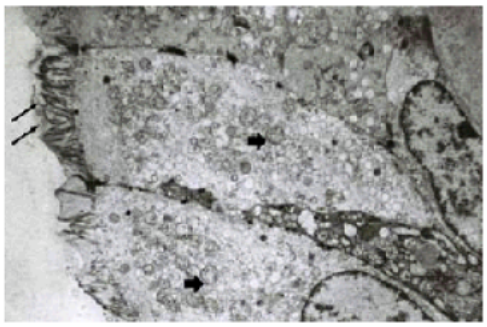

Fig. 5: Transmission electron micrograph of jejunum after ischemia in the control group. Microvilli of epithelial cells were irregular and less in number (thin arrows). Cristalysis was observed in mitocondria (thick arrows). Uranyl acetat-lead citrateX9000

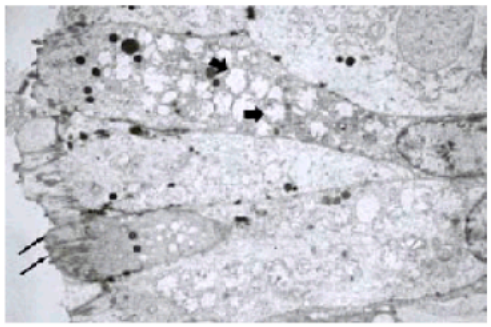

Fig. 6: Transmission electron micrograph of jejunum after reperfusion in control group. Lost of microvilli and their irregular shapes are observed in the apical cell membranes (thin arrows). According to the ischemia group, there was more cristae in the mitocondria. Lots of vesicular structure were observed in the cytoplasm. In mitocondria, a lot of cristalysis was observed (thick arrows). Uranyl acetate-lead citrateX9000

intracytoplasmic vacuolisation were observed (Fig. 6). Prostacyclin group samples revealed irregular and short microvilli when compared with the control group, crystalysis and no cytoplasmic large vacuols were observed at the end of ischemia (Fig. 7). After reperfusion, short but regular microvilli and mitochondria with a lot of cristae was observed in prostacyclin group that this appearance was more similar to normal samples taken before the occlusion (Fig. 8).

TNF α and IL-6 results: Before occlusion, serum TNF α concentrations were 143.93±142.68 pg mL^{-1} in the control group and 110.50±54.03 pg mL^{-1} in the prostacyclin group. The serum TNF α levels in the horses at the control group were increased during the experimental period. In contrast, the serum TNF α levels in prostacyclin group were decreased at the experimental period. Because of the large range of values for serum TNF α

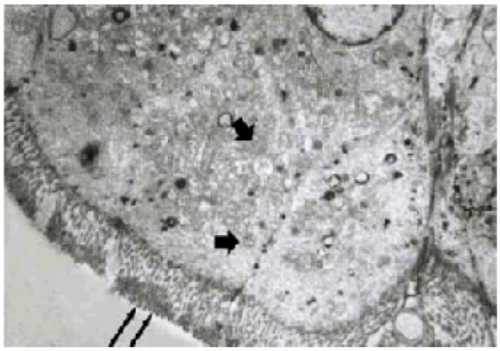

Fig. 7: Transmission electron micrograph of jejenum after ischemia in prostacyclin group. Microvilli were irregular and short according to the control group (thin arrows). Mitocondrions were lost their electron dense. Mitocondrions were pale and they had cristalysis (thick arrows). Uranyl acetate-lead citrateX9000

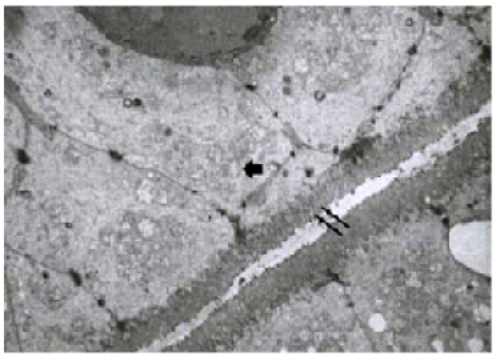

Fig. 8: Transmission electron micrograph of jejunum after perfusion in prostacyclin group. Microvilli were regular but short (thin arrows). Mitocondrions had lots of cristae (thick arrows). Uranyl acetate-lead citrate X9000

concentration in the control and the prostacyclin group horses, no significant difference was observed ($p>0.05$). Two horses from the control group had detectable serum IL-6 prior to the occlusion with a mean serum IL-6 concentration of 1.86 pg mL^{-1}. The prostacyclin group had no detectable serum IL-6 before the occlusion and after the reperfusion. After the occlusion, only one horse in the prostacyclin group had detectable serum IL-6. Serum IL-6 concentration of control group horses were 1.86±0.61 and 1.93±1.13 pg mL^{-1}, after occlusion and reperfusion, respectively. There was no significant difference between the control and the prostacyclin group for IL-6 concentration ($p>0.05$). Serum TNF α and IL-6 levels are shown in Table 1A and B, Fig. 9A and B.

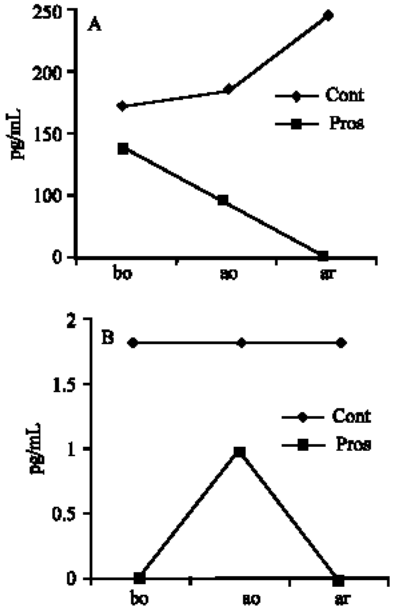

Fig. 9A, B: Changes in serum TNF α (A) and IL-6 (B) levels in the control (n:5) group horses and the prostacyclin treated (n:7) horses (cont: Control group, pros: prostacyclin group, bo: before occlusion, ao: After occlusion, ar: after reperfusion)

Table 1A: Serum TNF α (A) and IL-6 (B) levels in horses (pg mL^{-1})

	Control group		Prostacycline group	
	n	x±Sx	n	x±Sx
Before occlusion	7	143.93±142.68	5	110.50±54.03
After occlusion	7	162.57±140.17	5	60.50±40.76
After reperfusion	7	229.29±132.32	5	6.70±6.09

Table 1B: Serum TNF α (A) and IL-6 (B) levels in horses (pg mL^{-1})

	Control group		Prostacycline Group	
	n	x±Sx	n	x±Sx
Before occlusion	7	1.86±1.42	5	0.00±0.00
After occlusion	7	1.86±0.61	5	1.00±1.00
After reperfusion	7	1.93±1.13	5	0.00±0.00

DISCUSSION

Survival rate is known to be low in intestinal strangulation obstruction in horses despite surgery whereas rapid development of irreversible intestinal necrosis resulted by IR at the intestinal wall and terminally endotoxic shock is reported to play a major role for this process. Thus, preserving of the intestinal tissues viability are also thought to be as important as surgical techniques (Blikslager *et al*., 1997; Moore *et al*., 1995; Sullins *et al*., 1985; White *et al*., 1980; Freeman *et al*., 2000). Mucosal injury was observed in horses (Dabareiner *et al*., 1995; Moore *et al*., 1995) and dogs (Chiu *et al*., 1970) experimentally induced low flow

ischemia. Furthermore White *et al.* (1980), recorded that progress of mucosal injury during the reperfusion in no flow ischemia in equine jejunum by SEM and histopathologic parameters. Hydroxyl (OH) radicals, PAF (Platelet Activating Factor) and eicosanoids (e.g., leucotriens and prostaglandins) activated by phospolipase A2 are known to be responsible for intestinal ischemia reperfusion injury (Moore, 1997; Moore *et al.*, 1995), however in horses DMSO (OH. radical scavenger) (Arden *et al.*, 1989; 1990), XO inhibitor and DMSO (Moore *et al.*, 1995), in dogs glucocorticoids as phospolipase A2 inhibitors (Moore *et al.*, 1995), are failed to prevent intestinal damage. Moore *et al.* (1982) considered that the increase in mucosal permeability by cyclooxygenase inhibition, is due to the release of leucotriens caused by shunting of arachidonic acid to lipoxygenase pathway. Campbell and Blikslager (2000) reported that inhibition of the cyclooxygenase pathway in IR caused greater increase in mucosal permeability which may be caused by inhibition of some mucosal protective prostaglandines ($_{PGI2}$, PGE_2). Furthermore they stated out that spesific COX2 inhibitor etodolac increases PGI_2 and PGE2 levels and transepithelial resistance and it is more superior to nonspesific cycloxygenase inhibitor flunixine meglumine. A previous study of Blikslager *et al.* (1977) revealed decreased mucosal permeability in ischemia injured tissues treated by PGI_2 and PGE2 in porcines. In dogs, iloprost which is a synthetic analogue of PGI_2, is recorded to reduce myocardial ischemia reperfusion injury according to the TNF α levels (Katırcıoğlu *et al.*, 1998) and spinal injury grading by Tarlow method (Katırcıoğlu *et al.*, 1996), whereas it is reported to reduce intestinal ischemia in rabbits (Katırcıoğlu *et al.*, 1997) and horses (Öztamur, 2002) according to the electron and the LM results, respectively.

Sullins *et al.* (1985) and Öztamur (2002) observed that the dark muddy brown colour of jejunal segment after two h of total arteriovenous occlusion and the histopathologically grade 4 injury at the end of IR. Öztamur (2002), recorded grade 1, 2 and 3 injury after 2 h of ischemia followed by 1 h of reperfusion in equine jejunum in the prostacyclin treated group. Current study revealed that the dark muddy brown appearance remained the same after 2 h of arteriovenous occlusion followed by 1 h of reperfusion in the control group whereas in prostacyclin treated group, moderately anemic intestinal segment has recovered after the reperfusion.

Arden *et al.* (1990) reported that inracelluler organels were within normal levels after 1 h of no flow ischemia, whereas intercellular fluid accumulation, microvilli brush border damage, deprivation of cell adhesion of erythrocytes, but not mitocondrial cristalysis were detected after 1 h of reperfusion. Dabareiner *et al.* (1995) detected increased microvascular permeability and mitochondrial cellular damage after 1 h of reperfusion in equine jejunum followed by 1 h of low flow ischemia. Meschter *et al.* (1991) observed demarcation of columnary epithelial cells from basement membrane, intracellular injury in epithelial cells, mucosal necrosis and excessive neutrophyl infiltration after 2 h of reperfusion in equine colon followed by 1 h of ischemia. Katırcıoğlu *et al.* (1997), observed that severe mitochondrial damage and vacuolisation after 1 h of intestinal no flow ischemia and 1 h of reperfusion in control group, but were less marked changes in prostacyclin treated group in rabbits.

Current study revealed irregular microvilli and excessive mitochondrial cristalysis after 1 h of reperfusion following 2 h of no flow ischemia in the control group (Fig. 6), whereas short but regular microvilli and mitochondria with many cristae were detected in the prostacyclin group (Fig. 8). At the end of reperfusion, irreversible injury was observed in the control group whereas prostacyclin group revealed similar appearance to the samples taken before the occlusion. Findings were verifying beneficial effects of prostacyclin in reducing the intestinal IR injury in horses and they are in correspondence with TEM and LM findings of Katırcıoğlu *et al.* (1997) and Öztamur (20052), respectively.

In an experimental study (Katırcıoğlu *et al.* 1997) performed in rabbits on intestinal IR, TNF α and IL-6 levels were found to be significantly low in prostacyclin treated group when compared with the control group, following removal of the mesenteric artery occlusion ($p<0.05$). Another study (Katırcıoğlu *et al.*, 1998) on dogs revealed considerably low TNF α levels when compared with the control group, in correspondance to that iloprost increases myocardial performance and decreases IR injury. TNF concentrations were detected in intestinal strangulating obstruction in horses (Morris *et al.*, 1991), however Moore *et al.* (1995) were failed to detect colonic venous plasma TNF α and IL-6 levels in low flow ischemia and reperfusion in equine large colon.

Current study revealed higher mean levels of TNF α in the control group (229.29±132.32 pg mL^{-1}) than the prostacyclin group (6.70±6.0 pg mL^{-1}) after the reperfusion even though the difference between the groups were not statistically significant ($p>0.05$). However, the increase of TNF α levels in the control group and the decrease in prostacyclin group after reperfusion (as seen in the table) showed that prostacyclin has beneficial effect on distant organ injury. No consideration could be made for IL- 6 levels which were mostly failed to be detected. As a conclusion, prostacyclin was observed to have beneficial effects on reducing the intestinal IR injury in horses within the

experimental doses used for other species according to the macroscopic and the TEM findings. Prostacyclin also caused a decrease in the TNF α levels which are responsible for distant organ injury.

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