Postischemic effects of prostoglandin E1 in acute intestinal segmental ischemia: An experimental study

Cengiz ÇETİN[1], Ersin ATEŞ[2], Serdar ERKASAP[2], Kenan YÜCE[3], Enver İHTİYAR[2], Ertuğrul KARAHÜSEYİNOĞLU[2], Haluk KİPER[2]

Depts. of [1] Plastic and Reconstructive Surgery and [2] General Surgery, Medical School of Osmangazi University Eskişehir, TURKEY
[3] Dörtyol State Hospital, Hatay, TURKEY

We studied experimentally the post ischemic effects of prostaglandin E1 (PGE1) on acute occlusive mesenteric ischemia in 20 rats. Arteria mesenterica was clemped in all animals for 180 minutes ischemic period. At the end of ischemic period, 0.9% NaCI (25 ml/g/h) olution was started to infuse via jugular catheter for total 60 minutes in control group (n=10). A solution that containing 2 ngr PGE1 in 0.9% NaCI (50 ngr/kgr/h) for 60 minutes in PGE1 group (n=°10). After 24 hours observation perriod, ischemic intestinal segment was examined macroscopically and microscopically in both groups and serum ceratin phosphokinase (CPK) lactic dehydrogenase (LDH) and inorganic phosphorus levels were measured at 0th and 24th hr. Edema and mucosal epithelia fading lesser in severity in PGE1 group than control group, but not statstically significant (p>0.05) Congestron and hemorrage less severe in PGE 1 group than control group and statistically significant. CPK, LDH and inorganic phosphorus levels at 0 and 24th hr were not stastically significant in both groups and were increased significantly at 24th hour (P<0.01). In cocclusion, exogenous PGE1 protects ishemic intestine by dilation of mesenteric vasculature, arrangement of trombocyte formation; and decreament of lysosomal enzymes. [Turk J Med Res 1995; 13(5):169-173]

Key Words: Prostaglandin E1, Ischemia, Intestinal segmental ischemia

The clinical presentation of intestinal ischemia may vary from abdominal angina to complete intestinal infarction with their clinical and pathological findings.

Since Dunply, who described intestinal infarction as result of vascular causes, the subject has been the matter of interest for surgeons (1).

Mortality rates of mesenteric infarction changes between 82-92% in different reports (2,3). High mortality rates are due to delayed diagnosis.

The findings at the initial stage of superior mesenteric artery (SMA) obstruction may mimic ischemic intestinal disease., though it is not spesific. The clinical picture may be misdiagnosed as ileus, acute pancreatitis or perforation of a visceral organ. However, if the patient has a history of cardiopahthy, generilazed atherosclerosis and any intraabdominal septic condition or portal hypertension capable of leading to venous thrombosis, then possible intestinal ischemia should be remembered (2,3).

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Correspondence: Ersin ATEŞ
Medical School of Osmangazi University
Dept. of General Surgery
26480 Eskişehir, TURKEY

Surgical resection was used as the only choise of treatment till 1950, but Klass (1951), Shaw (1957) suggested superior mesenteric artery embolectomy in acute mesenteric occlusion (4,5). It has put on this treatment to other surgical ones (6-10).

The aim of our study is to search the effect of Prostaglandin E1 (PGE1) in acute occlusive segmental mesenteric ischemia that has been used in non occlusive cases in the past.

It has been indicated that this kind of prostaglandin has vasodilatory and cytoprotective effects (11). We aimed PGEI use to reduce the severity of acute segmental occlusive ischemia.

MATERIALS AND METHODS

20 rats weighting in between 250-270 grams have been used. These animals have been fed with standart food for 12 hours before surgery

Preparation Of **The Experimental Animals:** After 12-hour starvation period all animal's weights were checkeed, then ketamin HCL 65 mg/kg was applied intramusculary.

The 0[1h] hour blood samples were taken with intracardiac injection while the animals were in supine position. The operation area was cleaned with 10%

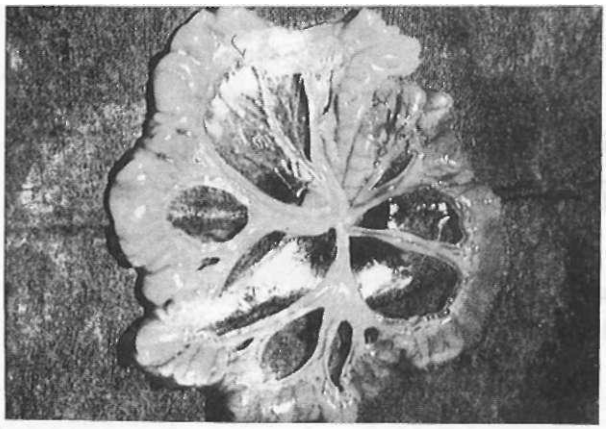

Figure 1. Macroscopic view in control group

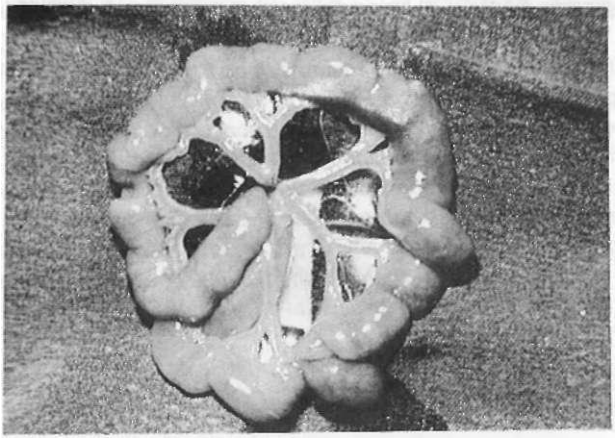

Figure 2. Macroscopic view in PGE1 group

povidone iodine, then this abdomen was insized with median insicion, and buldog vascular clamp was put on mesenteric arterial endorcate in 10 cm while intestinal meso was pulled outside the abdomen. After this procedure the intestina was put in abdomen and 180 minutes ischemia period started. During this period animals were inserted a jugular catheter. Rats were divided into two groups randomly.

Group I (control n=10): Normal saline (25 ml/kg/hr) was started to infuse before the end of the ischemia period via juguler catheter, and infusion was continued for 45 minutes after the end of the ischemia period (totally 60 minutes).

After 180 minutes of ischemia, buldog clamp was released and ischemic segment was examined for edema, congestion and intestinal motility and the abdomen was closed. After stopping infusion, jugular catheter was removed. All animals were put in a cage and observed for 24 hours.

Group II (experiment n=10): A solution that contain 2 ng PGE1 in 0.9% NaCl was started to infuse (50 ng/kg/hr). It was started 15 min. before the end of the ischemia period and continued on 45 min. after this period. After the infusion, juguler catheter was removed and all animals were put in clean cages and observed for 24 hours.

At the end of 24-hr observation period blood samples were taken via intracardiac punction. Then relaparotomy was performed and ischemic and healthy parts of intestines were resected with the meso. Lumen were ligatured at two sides and 10% formaline solution was injected into this lumen. Then these samples were put in 10% formaline solution. All animals were sacrificed by intracardiac sodium pentothal injection. All blood samples were centrifuged and serum was seperated. Then this was kept at -20°C until serum creatine phosphokinase (CPK), serum lactic dehydrogenase (LDH), inorganic phosphorus levels were detected.

Histopathological examinations were done and photographed by a pathologist at Giilhane Military Hospital Pathology Department.

Student's t test, G test have been used for statistical analysis.

RESULTS

1. Histopathologic Analysis

A-Macroscopic Signs

Group I (Control group): After 24 hrs, ischemic segment had many macroscopic differences then other parts (Figure 1). At this segment serosal layer lost its shiny structure and appeared darker than other normal segments. This segment and its meso had got edema and increased thickness when compared to normal healthy segment.

Group II (PGE I group): At exploration applicated at 24 hrs, intestine was dilated generally. Ischemic segment and its meso were edematous (Figure 2). The color of this segment was changed minimally but this was not significant. In this group intestinal motility and strength were decreased, but were more evident.in ischemic part.

B- Microscopic Findings

Group I. It has been observed in samples taken from animals that cylindirical epithelium covering intestinal mucosa has faded.

In the same sample only the mucosa covering epithel at the top point of villus faded, but in the others all villous structures were lost. Presiden this, that area was invaded with inflammatory exudation. At the villous not only the cylindrical epithel but also lamina propria was also lost (Figure 3).

Lamina propria was edematous and there was congestion characterized by vascular structure full of erythrocytes regionally. In all intestinal segmental levels there were congestion and hemorragic focuses in different degrees.

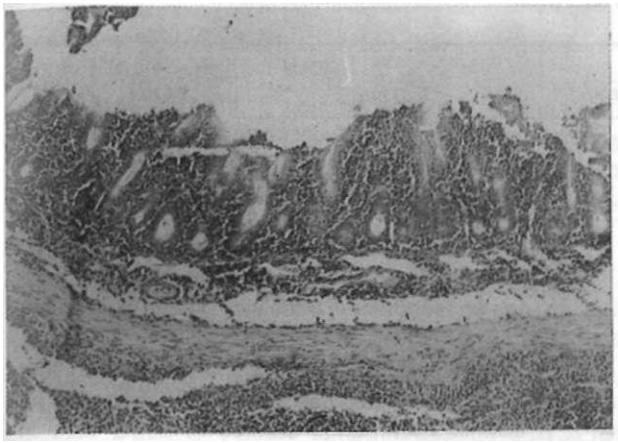

Figure 3. Microscopic view in control group

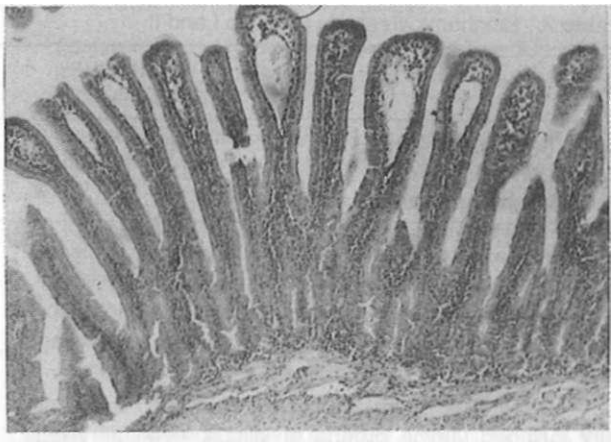

Figure 4. Microscopic view in PGE1 group

Table 1. Histopathologic findings in group I and II

	Edema		Congestion		Hemorrhage		Mucosal Epithelial Spreading	
	GI	GiI	GI	GiI	GI	GiI	GI	GiI
0	–				–	1	1	6
1	3	3	2	5	2	6	4	1
2	4	4	4	4	4	2	3	2
3	3	2	4	–	4	–	2	0
Total	10	9	10	9*	10	9"	10	9

*p<0.05
"p<0.01

Findings of control and experimental groups f are estimated in 4 classes as:

0 Normal

1 Mild

2 Moderate

3 Severe

Histopathologic findings in group I-II are shown in table 1.

Group II: Edema, congestion, hemorrhage was lesser in severity than that of group I. Mucosal ephitelial spreading was superficial and severity was lesser than that of group I (Figure 4).

All two groups have been compared statistically in their own group (Table 1).

2- Biochemical Findings

Serum creatine phosphokinase, lactic dehydrogenase and inorganic phosphorus levels were measured at the time beginning 24th hrs in both groups. Biochemical results are shown in table 2.

DISCUSSION

Nowadays, there is a great interested in acute mesenteric ischemia because of its high mortality rate.

Surgical resection procedure has been the most popular approach for treatment of this disease.

It has been thought that new pharmacological agents may be used to support the surgical treatment since successful applications have been published about these agents (1,3,12).

In the sight of this new opinion, treatment procedure of this disease changed partially.

Chon and his collègues occluded superior mesenteric arteries of dogs with baloon and, then examined changes in intestines at different periods (13). Hemorrhagic necrosis has been seen at 7th hrs in some dogs in all intestinal layers. They also found intestinal perforation occuring at 18th hr.

In our study, we could not find any finding related with necrosis of intestines of animals to which we applicated 180 minutes segmental mesenteric ischemic period. So we classified our findings as edema, congestion, hemorrahge, mucosal fading.

After 24 hrs, pathological analysis of ischemic segments yielded no significant changes between two groups (control and PGEi). (p>0.05). But there were important diferences between control and PGEI group

Table 2. Biochemical results in group I and II

	GROUP I		GROUP II	
	Ohrs	24hrs	0 hrs	24 hrs
Serum CPK (U/L)	1600	2292*	1878	2390*
Serum LDH (U/L)	377	403.1	358.9	364.8
Serum inorganic phosphate (mg/dl)	0.7890	0.399	0.6200	0.3422

*p<0.01

in congestion, hemorhage and mucosal fading. Especially, differences in mucosal structure and hemorrahge were so apparent.

In the first group, mucosal fading and tissue injury included lamina propria of villous, even all villous was lost in the other side (PGEI group). Mucosal injury was only superficial and only mucosal pouring was found. In the same manner, hemorrhagic focuses were not severe then PGEI group which has limited hemorrahgic focuses.

Histopathologically after this result, it has been indicated that exogen PGEI decreased the severity of acute mesenteric ischemia.

In another study about this subject, mucosal fading occured 2 hrs after segmental mesenteric ischemia and it spread thorugh 1/2 of villous neck in 4 hrs (14). This was same in our control group when we compared the results. But when iloprost that has a pharmacologically similar efficiacy with PGI was given the animals beside experimental segmental ischemia, in all intestinal layers and lamina propria, mild edema and venous fullness was found (14).

In this study, one of our biochemistry parameter CPK was not different statistically in two groups at 0 and 24th hrs ($p>0.05$).

This indicates that groups have similar CPK levels. But in two groups, their own 0 and 24th hrs levels were statistically diferent ($p<0.01$).

It is known that CPK is found in brain, heart, skeletal muscle and intestinl in our body. At experimental arterial small intestinal infarction, it has been dedicated that CPK levels might rise before. Some researches suggested that serum CPK levels may be a criteria of intestinal viability and accepted that very high serum CPK levels was a sign of intestinal necrosis (17-19).

Gruber and at all. stressed that serum CPK level has a meaningful rise in acute mesenteric occlusion.

Statistically meaningful rises of CPK level in two groups that have been applied mesenteric segmental ischemia is harmonics with literature. But there is another thing that should be pressed on, exogen PGEI has no effect on serum CPK levels.

Serum LDH levels were not different in two groups at 0-24th hrs respectively. And also their own LDH levels were not different at 0 and 24th hrs statistically, so we got an opinion that serum LDH levels did not change in segmental intestinal ischemia (at 180 min).

There are other studies in the literature also that LDH level is not a valuable parameter as much as CPK is (17). Experimental studies in dogs, also in human beings indicated that analysis of LDH and isoenzymes in intestinal wall has not the same value with CPK in serum for the diagnosis of mesenteric infarction (17).

Our results about LDH levels were same with literature results., But here it is time to underline the relationship between the serum CPK levels clearly that is high CPK levels indicate intestinal necrosis or myocardial infaction in human. So in differential diagnosis there is confusion about these two diseases. But serum LDH levels help the clinicians to differentiate these diseases. In myocardial infarction not only serum CPK levels but also LDH (especially LDH MB isoenzyme) rises. So when myocardial infacrtion and intestinal ischemia are considered, it will be useful to detect serum CPK and LDH levels together for differential diagnosis.

In this study, serum inorganic phosphorus levels were not different statistically in two groups at 0 and 24th hrs respectively.

Also in two groups their own IP levels were not different at 0 and 24 hrs. It has been shown via bioassay analysis that intestinal wall has high phosphate.

Jameson and at all reported that in acute intestinal ischemia organic phosphorus changed into inorganic phosphorous, and rised to detectable level in body fluids (20: Phosphate that cross the systemic circulation from portal vein through hepatic vein, causes to rise its level.

So, exogen PGEI, E kind of prostaglandins, decreases the severity of changes resulted in acute segmental intestinal ischemia via its cytoprotective effect.

Especially, in histopathological analysis, mucosal fading, hemorrahges and congestion were statistically different, so it should be pressed on once more.

This effect of PGEI, may be like that; PGEI has physiologic effect such as different organ functions and its induction of hemodynamics. Intravenous or intraarterial PGEI infusion decreases systolic arterial pressure and increases heart rate and cardiac output (21).

Nakato and at all noticed that PGEI has increased the coronary, brachial, femoral, carotid,

mesenteric and renal arterial blood flow in dog experiments (22).

So as a result, it can be said that exogenous PGEI dilates mesenteric vascuilature, arrengement or thrombocyte formation so inhibits thrombus formation at the reperfusion stage. Beside this, it decreases the lysosmal enzyme, so ischemic organ is protected at the stage after ischemia.

Akut intestinal segmental iskemide prostaglandin Ei'in post iskemik etkisi üzerine deneysel bir çalışma

Prostaglandin E1 'in akut oklusif mesenterik iskemi üzerine olan post iskemik etkisini araştırmak amacıyla 20 deney hayvanında deneysel bir çalışma yaptık. Tüm hayvanlarda arteria mesenterica 180 dakikalık iskemik peryod süresince klampe edildi. İskemik period sonunda hayvanlardan bir grubuna jugular kateter yolu ile 60 dakika boyunca %0.9 NaCI (25 mc/kgr/h) solüsyon infüzyonu yapıldı (Kontrol grubu, n=10). PGE1 grubunda ise (PGE1 grubu, n=10) 2 ng PGI içeren %0.9 NaCI solüsyonu (50 ngr/kgr/h) 60 dakika boyunca infüze edildi. 24 saatlik gözlemleme sonunda iskemik intestinal segment mikroskopik ve makroskopik olarak incelendi. Breatin fosfokinaz (CPK) Laktik Dehidrogenaz (LDH) ve inorganik fosfor serum düzeyleri ölçüldü. PGE1 grubunda ödem ve mucosa epitel dökülmesi kontrol grubuna göre daha az ciddiyette idi, ancak istatistiki olarak anlam yoktu (p>0.05). Ancak konjesyon ve hemoraji PGE1 grubunda anlamlı olarak daha az ciddiyete sahipti (p<0.05). Her iki grupta serum CPK, LDH ve inorganik fosfor düzeyi 0. saat ve 24. saatte anlamlı farklılık göstermiyordu, ancak 24. saatte CPK, LDH ve inorganik fosfor düzeyleri anlamlı olarak yükselmişti (P<0.01). Sonuç olarak dışardan verilen PGE1 iskemik intestinal segmenti, mesenterik damarsal yapılarda diletasyon yaparak, trombosit oluşmasını yeniden düzenleyerek ve lyzozomal enzimleri azaltarak korumaktadır.
[Turk JMed Res 1995; 13(5);169-173]

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