Effects of nimodipine administration on small bowel mucosa under conditions of laparotomy and consequent 48-hour starvation in a rat model

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BACKGROUND/AIMS: *The combination of starvation and surgical trauma induces disturbances to the intestinal mucosal structure and function, as well as changes in mucosal barrier function in the rat small bowel. The aim of the present study was to evaluate the effects of nimodipine administration, on intestinal mucosal structural changes and enterocyte apoptosis, following laparotomy and subsequent postsurgical starvation (PSS) in the rat.*
METHODS: *Thirty Wistar rats were divided into two experimental groups: A: Control group (n=15), where the animal models underwent laparotomy and consequent 48-hours PSS and B: Nimodipine group (n=15), where the rats underwent laparotomy, followed by intraperitoneal nimodipine administration and consequent 48-hour (h) PSS. Small bowel mucosal structural changes and enterocyte epithelial apoptosis were determined 48 h following laparotomy.*
RESULTS: *Nimodipine rats (group B) demonstrated a significant decrease in small bowel villous height in jejunum ($p=0.016$) and ileum ($p=0.002$). Similarly, crypt depth decreased in jejunum ($p<0.001$) and ileum ($p<0.001$). Nimodipine group exhibited significantly higher apoptotic index in ileum compared to control rats ($p=0.006$).*
CONCLUSION: *Nimodipine did not protect the intestinal mucosa from damage caused by surgery and consequent PSS and had obvious damaging effects on intestinal mucosa with derangements to its structure and subsequent mucosal atrophy.*

KEY WORDS: Apoptosis, Intestine, Ischemia-reperfusion, Nimodipine, Surgery.

Introduction

Operative procedures anywhere in the body could lead to surgical stress response and furthermore changes in human homeostasis. The intestine's role in the development of postoperative complications, such as sepsis, the systemic immune response syndrome (SIRS) and multiple organ failure syndrome (MOFS), has been well studied [1].
The gut is thought to be highly susceptible to surgical stress and trauma. Laparotomy, mild intestinal handling [2,3] and starvation [4,5] could lead to derangements to the intestinal mucosal structure and function. The possible underlying mechanism for these drastic changes, following surgery and trauma, might be related to several factors, such as ischemia-reperfusion (I/R) and inflammatory mediators that could induce intestinal mucosal damages [1,3,6].
Splanchnic hypoperfusion is known to be a common finding in trauma. In systemic pathological stresses [1,3,7], some adaptive response exists, mediated by neuroendocrine [8,9], which results in selective splanchnic vascular spasm in order to maintain the normal supply of blood to vital organs. Consequent reduction in oxygenation, which affects the small bowel and particularly its mucosa, is greatly influenced by those alterations. After a period of intestinal ischemia, restoration of blood flow is necessary, in order to sustain cell function and

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viability. However, reperfusion might initiate a series of events that could potentially exacerbate tissue injury, via the formation of reactive oxygen species (ROS) and other toxic and inflammatory mediators [10,11].
Necrosis had been thought to be equivalent to epithelial cell death after an ischemic insult in various tissues. Nevertheless, more recent reports have underlined the significance of apoptosis in cell death after I/R. Ischemia and/or I/R could provoke a cascade of apoptotic events in several tissues, including the brain [12], liver [13], kidney [14], myocardium [15], pancreas [16] and stomach [17]. More recently, the effects of I/R on enterocytic apoptosis in the intestine have been demonstrated [14-21].
Although a pleiad of studies and investigators have noted that the disturbances of the intestinal blood flow play an important role in the development of intestinal mucosal damage during and following surgery and trauma, the potential role of nimodipine treatment in this process has not yet been studied and still remains unclear. Nimodipine is a Ca^{2+} antagonist that affects the L-type calcium channels in the cell membrane, mainly in the smooth muscle, causing some vasodilation effects.
The aim of the present study was to evaluate the effect of intraperitoneal nimodipine administration on structural mucosal changes in the small bowel induced by surgical trauma and subsequent PSS in a rat model and to elucidate the possible pathophysiological pathways, by which restoration of local circulation and surgical stress/trauma/laparotomy-induced intestinal ischemia influences intestinal structure.

Methods

Surgical preparation

After approval by the Directorate of Veterinary Services of the Prefecture of Athens, Attica, Greece, 30 male Wistar rats, weighting 250–450 g, were acclimatized at 21°C on 12-h day and night cycles for a minimum of 1 week before experimentation. The rats had free access to water and were fed with standard chow. Rats were fasted for 48 h after the experiment, but were allowed free access to water.
Animals were randomly assigned to one of the two experimental groups, consisted of 15 rats each, with the use of a sealed envelope. Laparotomy plus starvation rats (Control group) and laparotomy plus starvation, with intraperitoneal nimodipine administration rats (Nimodipine group).

Surgical procedure

The rats were anesthetized with ketamine (90mg/kg) & xylazine (4mg/kg) intramuscularly. Under aseptic conditions, the abdomen was opened through a midline incision and laparotomy was performed. Before closure of the abdomen, the rats were treated with intraperitoneal administration either with the solvent (Control group) - Dimethylsulfoxide (DMSO) (1ml/kg) (Sigma-Aldrich, USA) or nimodipine (Nimodipine group), 10 mg/kg, (Batch No.10920320001, Union Quimico Farmaceutika S.A, Spain), dissolved in DMSO. This dose of nimodipine has been shown to induce vasodilation 1h (after treatment) in the ileum & jejunum [22]. The abdominal cavity was then closed in two layers with a running suture of Dexon S polyglycolic acid 3/0 & Silk 3.0 respectively. The rats were then fasted for 48h, but access to water was ad libidum. The rats were euthanatized and samples from the proximal jejunum and distal ileum were harvested.
The small bowel was excised quickly, washed with cold isotonic saline and divided into three segments: duodenum, jejunum and terminal ileum.
Histological sections were prepared from the proximal jejunum and distal ileum. The samples of intestinal tissues were fixed in a 10% formaldehyde solution (2-3% methanol), clearly labelled, coded, embedded in paraffin wax, using standard techniques and finally sectioned.

Intestinal mucosal parameters

Sections (4 Ìm each) were cut and stained with hematoxylin and eosin. As a measure of mucosal atrophy, villous height and crypt depth were determined by randomly selecting at least 30 complete well-oriented crypt-villous units from each section. Crypt depth was determined by measuring the distance from the base of the crypt to the crypt-villous junction. Villous height was determined by measuring the distance from the crypt-villous junction to the villous tip. Slides were photographed using a Nikon Eclipse 80i microscope (Nikon Corp. Tokyo, Japan) attached to a 1600x1200 pixel resolution digital camera under a 20x magnification. The villous height and crypt depth for each specimen were digitally measured using Image ProPlus software (Image ProPlus v. 5.1.2.59 for WinXP, Media Cybernetics Inc, USA). Villous height and crypt depth data were derived from all rats in each group and each measurement consisted of the mean of 30 villi and crypts.

Immunohistochemistry & villous cell apoptosis

The apoptosis of ileal cells was detected by immunohistochemical (IHC) staining with anti ssDNA monoclonal antibody F-7-26 (CHEMICON International, Inc, USA). The procedure, according to manufacturer's instructions, included the following steps: 4 Ìm sections were obtained from the blocks and attached to SuperfrostPlus slides (Menzel-Glaser GmbH, Germany). After standard deparaffinization and rehydration, slides were immersed into phosphate buffered saline solution (PBS), incubated in saponine (0.1 mg/mL in PBS) for 20 min and in proteinase K (another 20 min in room temp), rinsed in distilled water, treated with in water bath with formamide in 56°C and transferred into ice cold PBS for 5 min. Non specific antibody binding was blocked by treating the slides in 3% non fat dry milk

for 30 min. The F-7-26 mAb was applied in a dilution 1:10 and rinsed again in PBS. Chromagen solution (DAB) as substrate and light counterstain with haematoxylin were applied at the end. Known positive controls as well as negative were also stained in each run.
The apoptotic index (AI) was determined in ileum and defined as the number of apoptotic cells/100 villous epithelial cells per villi, selecting, at least, 20 complete well-oriented villi from each section.
All measurements were performed by a qualified pathologist blinded to the source of intestinal tissue.

Statistical analysis

Data are expressed as mean ±1 standard deviation (S.D.). The Kolmogorov–Smirnov test was used to assess normality of the distributions. Comparisons of continuous variables were analyzed using the unpaired t-test and Mann-Whitney non-parametric test, as appropriate. Linear relationships between quantitative normally distributed parameters were assessed with Pearson's two way test, otherwise Spearmans' rho was used. All performed tests were two-sided. Differences were considered as statistically significant at the level of 5% ($p<0.05$).

Results

Microscopic bowel appearance

The homogenic intestinal response to nimodipine was suggested by the following strong statistically significant correlations ($p<0.001$):

(i) Mean crypt depth in the ileum positively correlated with mean crypt depth in the jejunum.
(ii) Mean villous height in the ileum positively correlated with mean villous height in the jejunum.
(iii) Strong positive correlations were detected between mean crypt depth and mean villous height in the ileum as well as in the jejunum.

These statistical observations are summarized in table 1.

Table I - *Statistically significant correlations between the measured parameters.*

Correlations	**c.c p**
Crypt depth (Ileum) - Crypt depth (Jejunum)	0.835 p<0.001
Villous height (Ileum) - Villous height (Jejunum)	0.702 p<0.001
Villous height (Jejunum) - Crypt depth (Jejunum)	0.698 p<0.001
Villous height (Ileum) - Crypt depth (Ileum)	0.648 p<0.001

Villous height significantly decreased in jejunum ($p=0.016$) and ileum ($p=0.002$) in the nimodipine rats compared to control animals. Crypt depth showed a pattern similar to that of the villous height. The nimodipine group demonstrated a lower crypt depth in jejunum ($p<0.001$) and ileum ($p<0.001$) compared to control animals (Table II).
Ileum and jejunum sections from the control rats showed better architecture of the intestinal epithelium. Both ileum and jejunum from nimodipine rats demonstrated subepithelial space at villous tip, inflammatory cell infiltration extending through the wall, shortening and loss of villi, as well as reduction of crypt depth. Whereas, the effect of Nimodipine on microscopic bowel appearance, following laparotomy plus consequent PSS in rat, is shown in Figures 1-4.

Cellular apoptosis

The AI increased following nimodipine administration in ileum ($p=0.006$) compared to control animals, as summarized in Table III.

Table II - *Effect of Nimodipine on microscopic bowel appearance following laparotomy plus consequent PSS in rat.*

Parameters	**Control (n=15)**	**Nimodipine (n=15)**	**p**
VILLOUS HEIGHT (μm)			
Jejunum	130.77±26.41	104.93±24.44	p=0.016
Ileum	129.99±34.03	91.11±20.11	p=0.002
CRYPT DEPTH (μm)			
Jejunum	55.66±17.67	27.72±6.49	p<0.001
Ileum	54.77±10.84	26.83±9.12	p<0.001

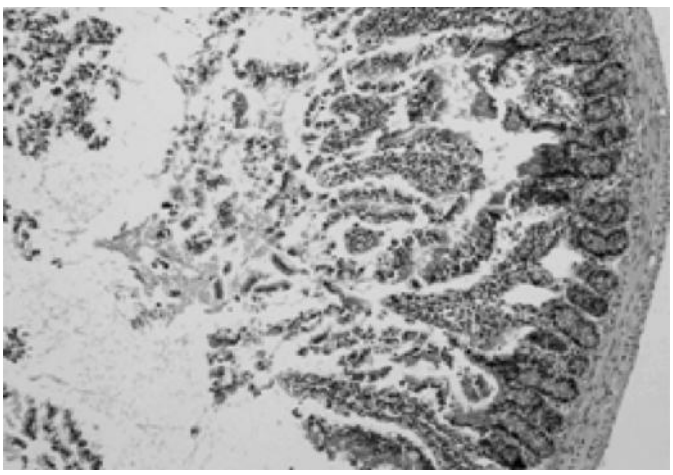

Fig. 1

TABLE III - *Effect of nimodipine administration on (ileum) enterocyte apoptosis in a rat model of laparotomy and (consequent postsurgical) starvation.*

Parameters	Control (n=15)	Nimodipine (n=15)	p
APOPTOTIC INDEX			
Ileum	1.59±0.22	3.05±1.95	p=0.006

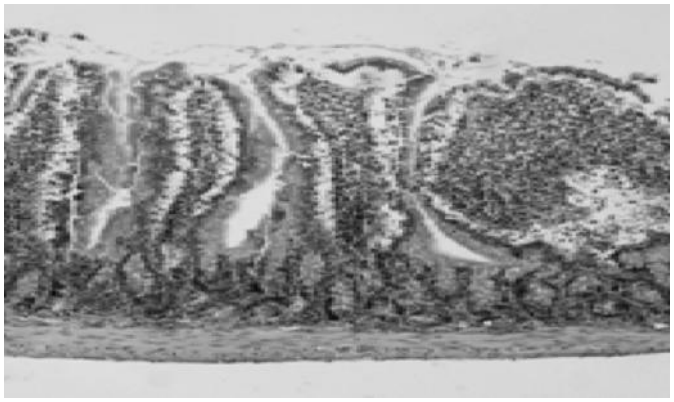

Fig. 2

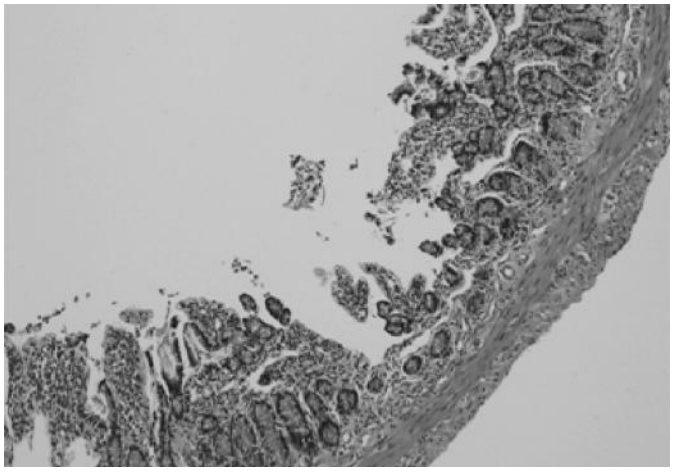

Fig. 3

The immunostaining with anti-ssDNA antibody showed that nimodipine has damaging effects on intestinal mucosa, as it increased the frequency of apoptotic ileal epithelial cells. The ileal mucosal apoptotis in each group is shown in Figures 5 and 6.

Discussion

Surgical stress response causes biochemical and physiologic changes resulting in perturbations of essentially every homeostatic axis [8]. These responses include: sympathetic nervous system activation, hypothalamic-pituitary-adrenal (HPA) axis activation and immunological/haematological changes [9].

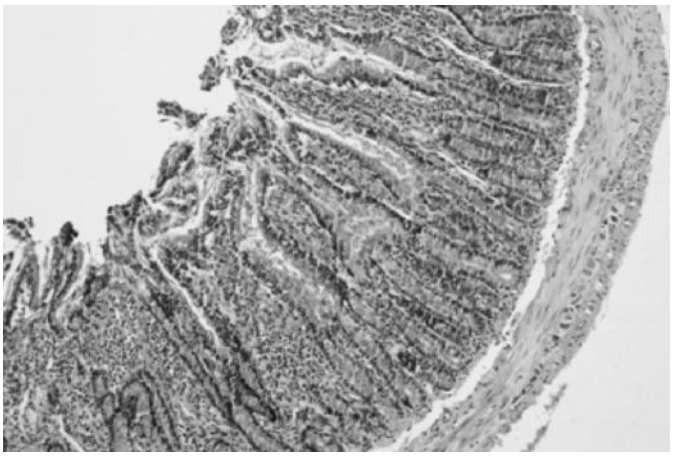

Fig. 4

Figures 1-4: Low-power photomicrographs of the full-thickness hematoxylin-eosin stained sections of distal ileum (Fig.1, Fig.2) and proximal jejunum (Fig.3, Fig.4) in control and nimodipine group, respectively (100x magnification). Photos are showing the damage in the intestinal mucosa and the structural changes in the nimodipine group compared to control group. Mean villous height is significantly decreased and similarly decreased is also the crypt depth consisting mucosal atrophy.

Mesenteric hypoperfusion is a common finding in trauma and the small bowel mucosa is vulnerable to the ischaemic insults, which result in increased gut permeability, alteration of enteral immune function, mucosal edema and atrophy, epithelial necrosis and apoptosis, and even focal mucosa ulcer, which might contribute to bacterial and endotoxin translocation [3,6].

These responses could partly be attributed to the microvascular anatomy; meaning that the presence of a villous counter-current exchanger mechanism [23] results in shunting of oxygen at the base of villi during low-flow states, causing hypoxia to villous tips. The high intestinal content of xanthine dehydrogenase is thought to be another important predisposing factor during ischaemia and produces oxygen-derived free radicals upon reperfusion [24].

Microscopically, ischemia appears to lead to some degree of detachment of the villous epithelium, possibly leaving denuded villi. In addition, significant vascular dilatation, congestion and hemorrhage is apparent in the lamina propria. In parallel, submucosal vessels show dilatation and congestion. Whereas, in I/R, villi could appear collapsed, shortened and broadened and there could be further detachment of villous epithelium [24].

Reperfusion after a period of intestinal ischemia seems to play an important role in the maintenance of cellular function and integrity. However, the reintroduction of oxygen in the reperfusion phase could give birth to unwanted events, which could cause injury [10,19] and apoptosis in small intestinal mucosa [17,20,21]. Various mechanisms have been implicated in the initiation and progression of intestinal I/R injury, such as overproduction of ROS and reactive nitrogen species (RNS), increased lipid

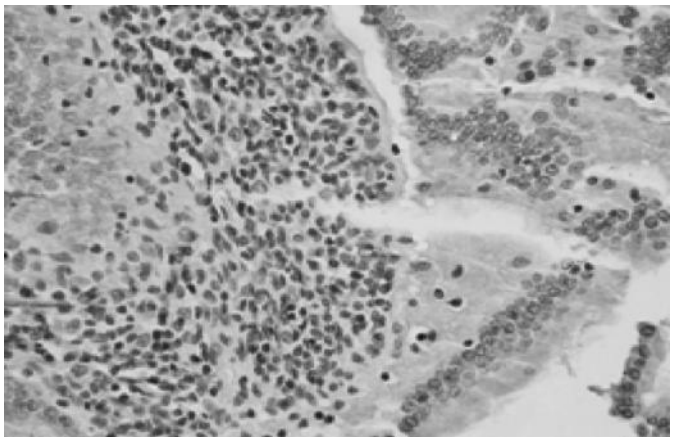

Fig. 5

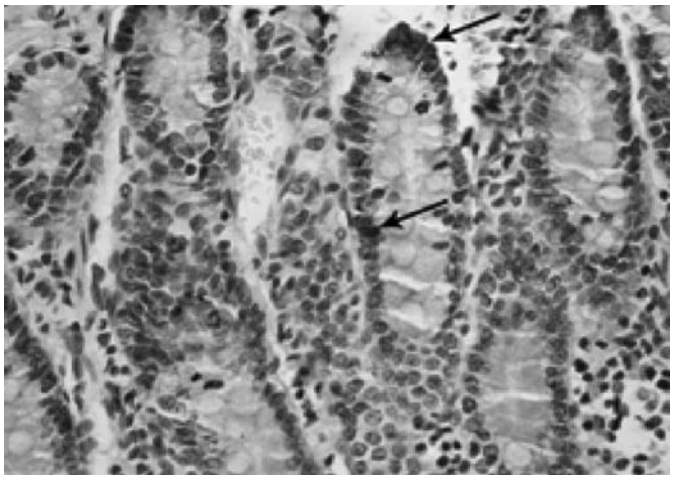

Fig. 6

Figures 5-6: Ileal mucosal apoptosis in control (Fig. 5) and nimodipine (Fig. 6) rats. Nimodipine treated animals had significantly more apoptotic cells/100 epithelial cells/villi than control animals (p=0.006) subjected to laparotomy and consequent postsurgical starvation. (The tiles were photographed under 400x magnification.). In the present study, the immunohistochemical method based on the detection of apoptotic cells with a monoclonal antibody (MAb) to single-stranded (ss) DNA was applied for the analysis of apoptosis

peroxidation, increased expression of adhesion molecules and infiltration of leukocytes and production of inflammatory mediators [21]. At the microcirculatory level, I/R injury is thought to be initiated by chemotactic accumulation of circulating leukocytes and their activation and interaction with the endothelium of postcapillary venules [25,26,27]. In addition, oxygen free radicals are thought to play an important role in the pathogenesis of I/R injury [28-32]. Following reperfusion, an increase in mucosal inflammatory cell infiltration and epithelial apoptosis occurs in crypts and villi [23].

The present study was designed to elucidate the effects of an intestinal vasodilator on the structural mucosal changes in the small bowel induced by surgery trauma and consequent PSS in a rat model and its effect on enterocytic apoptotic death.

Nimodipine, a dihydropyridine calcium channel blocker, exhibits its effects on cerebral and peripheral vessels and seems to favor the capillary blood flow, which nourishes tissues, at the expense of the non-nutrient blood flow, especially in the skeletal muscles [22]. Nimodipine has been reported to attenuate brain damage either from ischemia [33] or high doses of pilocarpine [34]. In a rat model with partially reversible cerebral ischemia nimodipine infusion reduced the infarct volume [35]. In addition, nimodipine is clinically used to prevent and treat cerebrovasospasm in subarachnoid haemorrhage. Nimodipine, per se, induces vasodilation in the small bowel, myocardium, diaphragm and other muscles [22].

The absence of intestinal feeding the first postoperative 24-h periods is a common situation in abdominal surgery. Handling of the intestine is a usual procedure in any surgery involving the abdomen and postsurgical ileus is a well-studied complication [36]. In addition, starvation alone has been shown to induce small bowel mucosal atrophy and also plays a pivotal role in enterocytic apoptosis [4,5].

Our histomorphometric mucosal studies showed that the nimodipine group demonstrated a significant lower crypt depth in jejunum ($p<0.001$) and ileum ($p<0.001$) compared to control animals. In addition, villous height significantly decreased in jejunum ($p=0.016$) and ileum ($p=0.002$) in the nimodipine group compared to control group. In parallel, the immunohistochemical staining with anti single-stranded DNA antibody of the ileum showed that the frequency of apoptotic ileal epithelial cells was increased following nimodipine administration ($p=0.006$) compared to control animals.

These data indicate that nimodipine infusion did not protect the intestinal mucosa from damage caused by surgery and consequent PSS in the rat laparotomy model. Our results demonstrate that nimodipine has obvious damaging effects on intestinal mucosa, as suggested by villous height and crypt depth, which are specific indices for the evaluation of mucosal damages [4]. The observed significantly decreased villous height and crypt depth in jejunum as well as ileum in this model support this conclusion. This impaired effect was accompanied by a significantly increased enterocyte loss via apoptosis.

Possibly the aggressive reversal of the gut vasospasm/ischemia-induced by surgical stresss/trauma and the subsequent acute restoration of the intestinal blood flow and reoxygenation/reperfusion enhanced the mucosal atrophy, which was induced by laparotomy and consequent PSS. This aggravation might be associated with derangements of the autoregulation of intestinal blood flow on one hand, which occurs normally after an intestinal ischemic insult and results in redistribution of blood flow within the layers of the gut, preserving initially some mucosal blood flow [37] and on the other hand, with an increase of the degree of the intestinal reperfusion injury, which occur physiologically during and following surgery.

In conclusion, nimodipine caused a marked intestinal

mucosal injury in the rat laparotomy and consequent PSS model. The aforementioned disturbance resulted in increased epithelial cell apoptosis, which may be responsible for this negative effect. Exposure to nimodipine did not prevent surgery-induced ischemic damage, possibly via derangement of the autoregulation of intestinal blood flow.

Riassunto

La combinazione di trauma chirurgico e di non somministrazione di cibo nel postoperatorio, provoca delle alterazioni alla struttura ed alla funzionalita' della mucosa intestinale, come pure alla funzionalita' della barriera intestinale, all'intestino tenue di rati da sperimentazione. Lo scopo del presente paper originale e sperimentale, fu quello di valutare, come la somministrazione di nimodipina, su modeli sperimentali di intestino tenue di rati, potesse provocare delle modifiche strutturalli della mucosa da una parte ed una pronunciata apoptosi cellulare epiteliale dall'altra, se somministrata per via intraperitoneale, in seguito ad un intervento di laparotomia e prima che iniziasse il periodo postoperatorio di non somministrazione di cibo, della complessiva durata di 48 ore. A detto scopo, 30 rati da sperimentazione di razza Wistar, sono stati divisi in 2 gruppi, di cui uno di controllo (Gruppo A), composto da 15 di essi, i qualli furono sottoposti ad un intervneto di laparotomia ed alla non somministrazione di cibo per le prime 48 ore nel immediato postoperatorio ed un altro (Gruppo B) sempre composto da 15 ratti, i qualli sono stati sottoposti, alla pari dei rati del gruppo di controllo ad un interveto di laparotomia ed alla non somministrazione di cibo per le prime 48 ore nel postoperatorio, ma tra la fine dell'intervento di laparotomia ed il periodo postoperatorio di astinenza dal cibo, gli si e' somministrata, per via intraperitoneale, la Nimodipina.
In entrambi i gruppi, 48 ore dopo l'intervento della laparotomia, sono state valutate sia le modifiche strutturali della mucosa intestinale che il grado, da essa giunto, di apoptosi cellulare.
In conclusione di detta sperimentazione, si e' messo in evidenza che la nimodipina, non solo non protegeva la mucosa intestinale, dal danno provocatele dall'intervento chirurgico laparotomico e dal succesivo, all'intervento, periodo di non somministrazione di cibo per 48 ore, ma provocava anche dei ben evidenti danni alla mucosa intestinale, in quanto, in seguito alla sua somministrazione per via intraperitoneale, si verificarono intense alterazioni dell'arcitettura della mucosa intestinale ed una sua consistente atrofia.

References

1) Thomas S, Balasubramanian KA: *Role of intestine in postsurgical complications: involvement of free radicals*. Free Radic Biology Med, 2004; 36:745-756.

2) Anup R, Aparna V, Pulimood A, Balasubramanian KA: *Surgical stress and the small intestine: Role of oxygen free radicals*. Surgery, 1999; 125:560-69.

3) Thomas S, Kang G, Balasubramanian KA: *Surgical Manipulation of the Intestine Results in Quantitative and Qualitative Alterations in Luminal Escerichia coli*. Ann Surg, 2004; 240:248-54.

4) Chappell VL, Thompson MD, Jeschke MG, Chung DH, Thompson JC, Wolf SE: *Effects of incremental starvation on gut mucoca*. Dig Dis Sci, 2003; 48:765-69.

5) Wiren M, Soderholm JD, Lindgren J, Olaison G, Permert J,Yang H, Larsson J: *Effects of starvation and bowel resection on paracellular permeability in rat small-bowel mucoca in vitro*. Scand J Gastr, 1999; 34:156-62.

6) Hang CH, Shi JX, Li JS, Wu W, Yin HX: *Alterations of intestinal mucosa structure and barrier function following traumatic brain injury in rats*. World J Gastr, 2003; 12:2776-781.

7) Ramzy PI, Wolf SE, Irtun O, Hart DW, Thompson JC, Herndon DN: *Gut epithelial apoptosis after severe burn: effects of gut hypoperfusion*. J Am Coll Surg, 2000; 190:281-87.

8) Udelsman R, Holbrook NJ: *Endocrine and molecular responces to surgical stress*. Curr Probl Surg, 1994; 31:653-720.

9) Desborough JP: *The stress response to trauma and surgery*. Br J Anaesth, 2000; 85:109-117.

10) Madesh M, Ramachandran A, Pulimood A, Vadranam M, Balasubramanian KA: *Attenuation of intestinal ischemia/reperfusion injury with sodium nitroprusside: studies on mitochondrial function and lipid changes*. Biochim Biophys Acta, 2000; 1500:204-16.

11) Zimmerman BJ, Granger DN: *Mechanisms of reperfusion injury*. Am J Med Sci, 1994; 307:284-92.

12) Tagami M, Ikeda K, Nara Y, Fujino H, Kubota A, Numano F, Yamori Y: *Insulin-like growth factor-1 attenuates apoptosis in hippocampal neurons caused by cerebral ischemia and reperfusion in stroke-prone spontaneously hypertensive rats*. Lab Invest, 1997; 76:613-17.

13) Yadav S, Sindram D, Perry DK, Clavien PA: *Ischemic preconditioning protects the mouse liver by inhibition of apoptosis through a caspase-dependant pathway*. Hepatology, 1999; 30: 1223-231.

14) Yin T, Sandhu G, Wolfgang CD, Burrier A, Webb RL, Rigel DF, Hai T, Whelan J: *Tissue-specific pattern of stress kinase activation in ischemia/reperfused heart and kidney*. J Biol Chem, 1997; 272:1943-950.

15) Maclellan WR, Schneider MD: *Death by design. Programmed cell death in cardiovascular biology and disease*. Circ Res, 1997; 81:137-44.

16) Fujimoto K, Hosotani R, Wada M, Lee JU, Koshiba T, Miyamoto Y, Doi R, Imamura M: *Ischemia-reperfusion injury on the pancreas in rats: identification of acinar cell apoptosis*. J Surg Res, 1997; 71:127-36.

17) Fukuyama K, Iwakiri R, Noda T, Kojima M, Utsumi H, Tsunada S, Sakata H, Ootani A, Fujimoto K: *Apoptosis induced by ischemia-reperfusion and fasting in gastric mucosa compared to small intestinal mucosa in rats*. Dig Dis Sci, 2001; 46:545-49.

18) Luo CC, Shih HH, Chiu CH, Ma WC, Chung HY: *Reduced apoptosis in newborn compared to adult rat intestine after ischemia-reperfusion*. Biol Neonate, 2004; 85:90-93.

19) Sukhotnik I, Helou H, Mogilner J, Lurie M, Bernsteyn A, Coran AG, Shiloni E: *Oral arginine improves intestinal recovery following ischemia-reperfusion injury in rat*. Pediatr Surg Int, 2005; 21:191-96.

20) Noda T, Iwakiri R, Fujimoto K, Matsuo S, Aw TY: *Programmed cell death induced by ischemia-reperfusion in the rat intestinal mucosa*. Am J Physiol, 1998; 274:270-76.

21) Ikeda H, Suzuki Y, Suzuki M, Koike M, Tamura J, Tong J, Nomura M, Itoh G: *Apoptosis is a major mode of cell death caused by ischemia and ischemia/reperfusion injury to the rat intestinal epithelium*. GUT, 1998; 42:530-37.

22) Karlsson BM, Koch M, Koskinen LO: *Nimodipine affects the microcirculation and modulates the vascular effects of acetylcholinesterase inhibition*. Upsala J Med Sci, 2003; 108:141-49.

23) Shah KA, Shurey SS, Green CJ: *Characterization of apoptosis in intestinal ischaemia-reperfusion injury - a light and electron microscopic study*. Int J Exp Path, 1997; 78:355-63.

24) Parks DA, Granger DN: *Ischemia-induced vascular changes: role of xanthine oxidase and hydroxyl radicals*. Am J Physiol, 1983; 245:285-89.

25) Hernandez L, Grisham B, Twohig B, Arfors KE, Harlan JM, Granger DN: *Role of neutrophils in ischemia-reperfusion-induced microvascular injury*. Am J Physiol, 1987; 253:699-703.

26) Walden DL, McCutchan HJ, Enquist EG, Schwappach JR, Shanley PF, Reiss OK, Terada LS, Leff JA, Repine JE: *Neutrophils accumulate and contribute to skeletal muscle dysfunction after ischemia-reperfusion*. Am J Physiol, 1990; 259:1809-812.

27) Granger DN, Benoit JN, Suzuki M, Grisham MB: *Leukocytes adherence to venular endothelium during ischemia-reperfusion*. Am J Physiol, 1989; 257:683-88.

28) Klausner JM, Paterson IS, Kobzik L, Valeri CR, Shepro D, Hechtman HB: *Oxygen free radicals mediate ischemia-induced lung injury*. Surgery, 1989; 105:192-99.

29) Menger MD, Barker JH, Messmer K: *Capillary blood perfusion during postischemic reperfusion in striated muscle*. Plast Reconstr Surg, 1992; 89:1104-114.

30) McCord JM: *Oxygen-derived radicals: a link between reperfusion injury and inflammation*. Federation Proc, 1987; 46:2402-406.

31) Suzuki M, Inauen W, Kvietys PR, Grisham MB, Meininger C, Schelling ME, Granger HJ, Granger DN: *Superoxide mediates reperfusion-induced leukocyte-endothelial cell interactions*. Am J Physiol, 1989; 257:1740-745.

32) Zweier JL, Kuppusamy P, Lutty GA: *Measurement of endothelial cell free radical generation: Evidence for a central mechanism of free radical injury in post-ischemic tissues*. Proc Natl Acad Sci USA, 1988; 85:4046-050.

33) Uematsu D, Araki N, Greenberg JH, Sladky J, Reivich M: *Combined therapy with MK-801 and nimodipine for protection of ischemic brain damage*. Neurology, 1991; 41:88-94.

34) Marinho MM, de Bruin VM, de Sousa FC, Aguiar LMV, de Pinho RSN, Viana GSB: *Inhibitory action of a calcium channel blocker (nimodipine) on seizures and brain damage induced by pilocarpine and lithium-pilocarpine in rats*. Neurosci Lett, 1997; 235:13-16.

35) Roda JM, Carceller F, Diez-Tejedor E, Avendano C: *Reduction of infarct size by intra-arterial nimodipine administered at reperfusion in a rat model of partially reversible brain focal ischemia*. Stroke, 1995; 26:1888-892.

36) Quigley EM, Thompson JS: *The effects of surgery on gastrointestinal motor activity*. Braz J Med Biol Res, 1998; 31:889-900.

37) Reilly PM, Bulkley GB: *Vasoactive mediators and splanchnic perfusion*. Crit Care Med, 1993; 21:55-68.

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RECENSIONI DI VIDEO-TAPE DI ANNALI ITALIANI DI CHIRURGIA E DELLA VIDEO REVITA DE CIRURGIA

(a cura del Direttore)

Il valore didattico del film in chirurgia

di Giuseppe Romagnolo, Biagio Trojanello

DVD- 21' 41"- Italiano
Pubblicato da : Salvatore Cafiero Audiovisi- 2001

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Recensione:
Rassegna storica, riccamente corredata di iconografia classica, che ripercorre la storia della tecnica chirurgica moderna non semplicemente nelle tappe dei suoi progressi tecnici quanto nell'ottica della dimostrazione dei mezzi strumentali storici, della didattica finalizzata all'apprendimento.
Nella prima parte vengono esibiti disegni e figure statiche da affreschi e miniature classiche, per passare quindi ad una breve rassegna fotografica esemplificativa di patologie e situazioni cliniche. Vengono rievocati ritratti celebri di altrettanti celebri chirurghi nell'atto docente della dimostrazione anatomo-patologica e chirurgica.
L'arrivo dell'invenzione dei fratelli Lumière ha modificato radicalmente l'aspetto didattico della chirurgia non direttamente vissuta ed osservata, poiché essa venne adottata già due anni dopo della sua prima dimostrazione per dimostrare atti chirurgici su pellicola bianco e nero, con intervento del Prof. Roberto Alessandri.
Dopo un primo periodo euforico, in cui singoli chirurghi si avvalevano della tecnica chirurgica su pellicola – costosa - per dimostrare le personali capacità tecniche, la cinematografia chirurgica ha dimostrato sempre di più il suo valore didattico intrinseco. Ma la vera esplosione si è avuta con l'introduzione della tecnica di ripresa e postproduzione digitale, che ha consentito di confezionare prodotti didattici di grande valore. Prevedendo addirittura non solo la multimedialità ma anche l'interattività tra dimostrazione e spettatore discente.

L'interesse del DVD è di tipo storico , ma il suo valore intrinseco risiede anche nell'entusiasmo delle finalità dimostrate con convinzione e capacità dagli Autori