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EFFECTS OF HEPATECTOMY AND ARGININ ENRICHED DIET ON COLONIC MUCOSA ORIGINATED INFLAMMATORY CYTOKINES

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ABSTRACT

Aim: *To assess the effects of arginine-enriched diet and partial hepatectomy in rats on gut-originated inflammatory cytokines.*

Methods: *Of 24 rats, Group 1 and 2 animals were fasted 24 hours before surgery, Group 3 and 4 animals received regular plus arginine-enriched diet(AED). Group 2 and 4 animals had undergone 30% hepatic resection. Leukotriene B4 (LT B4) levels were detected in colonic mucosa and mucosal perfusates immediately after resection. Mean leukocyte counts (MLC) were detected also in mucosa.*

Results: *In the basis of fasting situation regardless hepatectomy, all MLC were lower in Group 3 and 4 but LTB4 levels both in mucosa and perfusate were higher . On hepatectomy based comparison there was not any statistically significant difference between groups but mucosal perfusate LTB4 levels. But when hepatectomy added on fasted animals MLC levels were lower than fed by AED + sham operation. LTB4 levels were insignificant in both perfusate and mucosa. When hepatectomy added on AED animals (Group 4), MLC decrased and mucosal LTB4 increased when they compared with fast without hepatectomy Group 1.*

Conclusions: *AED prior to extra-intestinal operations may trigger inflammatory cascade and complications via leucocyte degradation and LTB4.*

Key words: *Hepatectomy, colon, arginine*

INTRODUCTION

Infections constitute a major cause of morbidity and mortality following partial hepatectomy and mechanisms of this complication have been poorly understood. There is increasing evidence that septic complications may be caused by gram negative bacteria, translocating from gut.[1-3] Hepatectomy was shown to increase translocation, aerobic caecal bacterial population, and decrease in colonic villus height and capillary permeability.[1,3] On the other hand, since the introduction of general anesthesia, patients have been required to be fasted for overnight prior to surgery. Similarly, enteral feeding is also avoided in the first few days after surgery. It was believed that the gastrointestinal tract (GIT) was paralysed in all patients during the first few days after surgery. Lack of enteral food ingredients, particularly food for the large intestine, fibres, has several rather immediate pathophysiologic consequences like inhibition of motility and splanchnic circulation, increased virulance of the subflora of potentially pathogenic microorganisms, reduction and inhibition of the protective mucosa, and atrophy of the mucosa of the small intestine and colon.[4-6]

It is well known that leucocyte-originated leukotriene B4 (LTB4) is a lipoxygenase pathway product, which plays a critical role in the acute phase response and inflammatory response to various types of cell damage.[7-11] It is also demonstrated that arginine may reduce bacterial translocation and improve mucosal regeneration and villus height in large bowel and small intestine.[12,13] Besides, arginine enhances tymic activation[14] and improves immunologic mechanisms.[15]

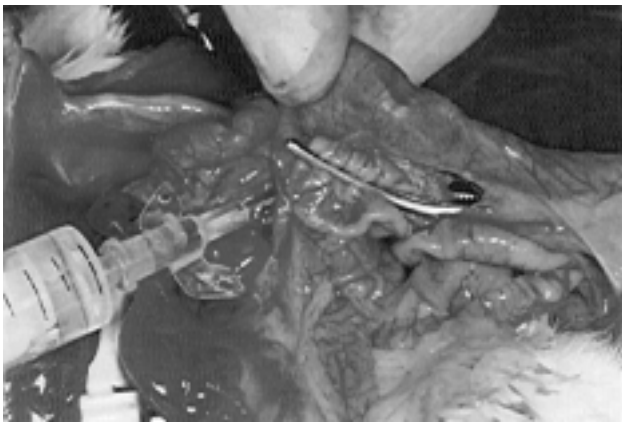
This study was designed to assess how partial hepatectomy affects the colonic mucosa, LTB4 production and MLC, and its possible role in septic complications following an operation in rats.

METHODS

Twenty-four Swiss albino rats weighed between 160 to 220 grams were used. Approval of ethical committee has been held before study. All animals received humane care in compliance with the Guide for the Care and Use of Laboratory Animals prepared by The National Academy of Sciences and published by the National Institute for Health (NIH publication No. 85 – 23 revised 1985). The animals were randomly assigned to one of the four groups and every group was consisted of 6 rats. The

animals were kept in individual cages in rooms with controlled temperature and free access to water and food (purina chow) prior to experiment. While Group 1 and 2 were fasted for 24 hours prior to surgery, Group 3 and 4 were allowed to free access to water and food (purina chow) in the same period. Group 1 and 3 were served as a sham operation groups for fasted + hepatectomised and fed + hepatectomised animals respectively. Sham operation has been performed by just a blunt dissection around medial liver lobe and mesocolon. Rats in Group 3 and 4 were also gavaged through gastric tubes with a commercially available arginine enriched diet (Perative®, – Abbott) in amount of 60 ml which has been calculated according to Clarke formula described elsewhere.[16] The rats in Group 2 and 4 underwent a 30 % hepatic resection consisting in resection of the medial lobe. As a resume, groups were classified as follows: Group 1: Sham operation (FastSG), Group 2: Fasted 24 hours prior to surgery and 30% hepatectomised (FastH), Group 3: Fed before surgery with arginine and purina chow and sham operated (FedSG), Group 4: Fed before surgery with arginine and purina chow and 30% hepatectomised (FedH). Colonic mucosa biopsies were performed for LBT4 analysis and histopathological examination immediately after partial hepatectomy and sham operation in Group 1. Colonic mucosal perfusates were also collected by using a method described below. This model designed by authors for this experiments originally.

Mucosal perfusate: The superior mesenteric vein and the middle colic artery were dissected and cannulated. A colonic segment of approximately 5 cm of length was isolated in-situ by ligating all collateral vessels (Picture 1). This procedure has been done before partial hepatectomy. A prepared segment was perfused for 3 minutes with saline through the arterial catheter in low pressure, until clear wash-out was observed immediately after hepatectomy or sham operation. The wash-out from the middle colic vein in the last minute was collected and regarded to represent colonic mucosal perfusate.



Picture 1. Mucosal perfusate method described originally in this study.

Mucosal biopsy specimens: Following biopsy, two pieces of mucosa harvested for LTB4 analysis, of which one was immediately put in Phosphate Buffer Saline (PBS) and deep frozen to -70 degree centigrade. The other piece was put into the 10% formaldehyde solution for later histologic examination.

Histopathologic examination: The specimens were embedded in paraffin blocks and cut in 5 m thick slices. The slices were dyed in hematoxyline – eosine dye and examined in light microscopy examination by an experienced pathologist. In order to prevent any bias arising from observational and researchers fault, pathologist has evaluated specimen blindly and in addition, laboratory values has not been reported to pathologist. In each specimen, 10 randomised areas were selected and leucocytes counted using a magnification of 40X .

LTB4 analysis: All tissue samples were extracted and purified with the use of High Pressure Liquid Chromatography - HPLC (Waters 625 LC system®, MA,USA). Dry extracts from each sample were dissolved in 20 µl acetonitril / metanol / phosphoric acid (130: 5: 1.5) mixture and injected to Silasorb Si 60 5u analytic colons (250x2.0 mm ID Alltech, USA). A flow rate was 0.2 ml / min was used, the lambda used was 210 nm at UV detector. Elution and retention times were detected by using synthetic 1 – 0 – hexadecyl – 2 – 0 – acetyl – sn – glycero – 3 – phosphocholine. HPLC eluates were collected from the UV detector outlet from the 16th to the 18th minute and evaporated with liquid nitrogen until completely dryness. LT separation was performed on a Separon SGXC18 super analytical column®, (250x2.0 mm I.D) and precolumn (100x2.0 mm I.D) with a methanol:water:acetic acid gradient measuring at 280 nm UV wavelength and a 0.22 ml/min flow rate. Retention times were 11' for LTB4. LT quantitation was calculated from an LT calibration curve that was determined using synthetic LT and PGB2 as internal standard. Results were expressed as pg / mg tissue.

Statistical analysis: Statistical analyses were performed in personal computer by using SPSS Software package (ver. 10.0 – SPSS Corp.) by analyses of variance in 95% confidence interval. Tukey and Bonferroni post-Hoc tests were used to

determine differences between groups. P values under 0.05 regarded as statistically significant.

RESULTS

Mean leucocyte counts (MLC), mucosal LTB4 and perfusate LTB4 values are shown in Table 1,2, and 3 respectively. Although all data were parametric, statistical analyses have been performed by Mann Whitney U test because of limited rat number in each group and p value lower than 0.005 has been accepted for statistical significance.

MLC (cell counts/x40) were; 66.95±1.50, 75.00±2.08, 41.18±0.96, and 41.90±0.71 respectively.

Table 1. Mean leucocyte counts were dropped significantlly in AED fed groups.

	GRUP 1 FastSG	GRUP 2 FastH	GRUP3 FedSG	GRUP4 FedH
	MLC(X40)			
	62,5	69,2	40,8	43,1
	69,2	72,9	39,9	41,2
	68,6	78	39,9	39
	64,9	74,8	39,4	41,3
	72,3	71,6	45,8	43,6
	64,2	83,5	41,3	43,2
AVERAGE	66,95	75	41,18333	41,9
SD	3,68713981	5,116639522	2,36424759	1,748141871
Minimum	62,5	69,2	39,4	41,2
Maximum	72,3	83,5	45,8	43,6

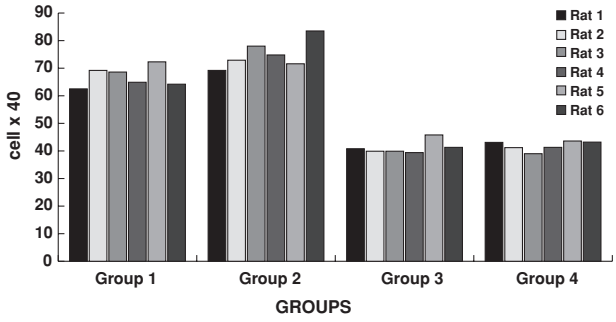


Figure 1. Mean leucocyte counts were dropped significantlly in AED fed groups.
Statistically significant comparisons were between Groups 1-3, 2-4, 1-4, and 2-3.

MLC values were revealed statistically significant decrease in Group 3(fedSG) and 4(fedH) than Group 1(fastSG) and 2(fastH) ($p<0.05$). All animals which were received arginine enriched diet, had lower MLCs than those fasted during surgery. There was no difference between fedH and fedSG animals (Table 1). Fasted groups were revealed significant inflammatory cellular infiltration (mostly leucocytes) in colonic submucosa and lamina propria layers in a light microscopic examination. Besides, some regenerative epithelial changes were observed. On the other hand, inflammatory infiltration was minimal in fed groups and all glandular structures were normal. These findings were parallel to mucosal MLCs.

Table 2. Mucosa LTB4 levels in colon mucosa in rats. Levels were increased with AED significantly.

	GRUP 1 FastSG	GRUP 2 FastH	GRUP3 FedSG	GRUP4 FedH
	MLC LTB4	pg/mg tissue		
	8	28	76	400
	10	7	140	210
	19	6	210	220
	36	27	70	500
	32	41	22	500
	48	47	160	260
AVERAGE	25,5	26	113	348,3333
SD	15,795569	16,92335664	69,05939473	135,7080199
SEM	6,448514041	6,90893142	28,19338	55,40257
Minimum	8	6	22	210
Maximum	48	47	210	500

Mean mucosal LTB4 levels were (pg/mg tissue±SEM) 25.50±6.44, 26.00±6.90, 113.00±28.19, 348.33±55.40 and values were higher statistically in groups 3(fedSG) and 4(fedH) than others ($p<0.05$). While hepatectomy did not cause any increase in mucosal LTB4 levels in fasted animals, significant increase detected in fed animals. Hepatectomy caused almost fourteen-fold increase in mucosal LTB4 levels in animals fed with arginine enriched diet regarding to the fasted animals (Table 2).

Mean Perfusate LTB4 levels(pg/ml±SEM) were 49.50±9.60, 42.00±3.19, 186.16±51.27 and 118.5±22.92 in groups respectively. Values were higher in groups 3 and 4 than others ($p<0.05$) (Table 3).

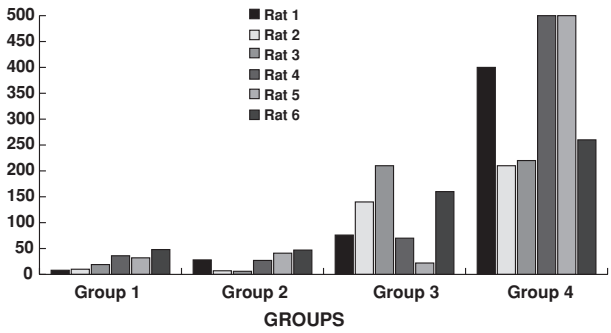


Figure 2. LTB4 levels in mucosal perfusate fluid. Statistically significant comparisons were between Groups 1-3, 2-4, 1-4, and 3-4.

Table 3. LTB4 levels in mucosal perfusate fluid.

	GRUP 1 FastSG	GRUP 2 FastH	GRUP3 FedSG	GRUP4 FedH
	Perfusate LTB4	pg/mg tissue		
	36	51	84	87
	84	45	39	54
	30	36	180	186
	72	30	168	66
	48	48	256	162
	27	42	390	156
AVERAGE	49,5	42	186,1667	118,5
SEM	9,604686356	3,193744	51,2799	22,9227
SD	23,5265807	7,8230429	125,60958	56,14891
Minimum	27	30	39	54
Maximum	84	51	390	186

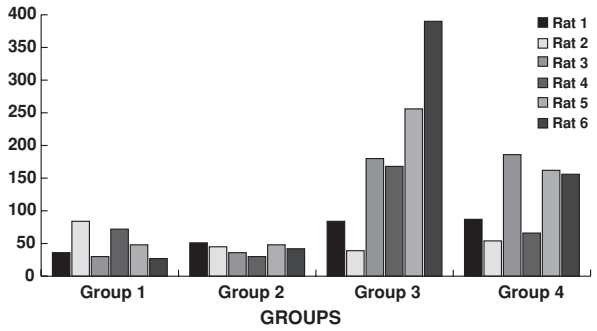


Figure 3. Mucosa LTB4 levels in colon mucosa in rats. Levels were increased with AED significantly. Statistically significant comparisons were between Groups 1-3 and 2-4.

When it has been compared in basis of fasting situation regardless hepatectomy, i.e. Group 1 vs. 3 and Group 2 vs. 4 all MLC were lower in Group 3 and 4 but LTB4 levels both in mucosa and perfusate were higher . Similarly, on hepatectomy based comparison i.e. Group 3 vs. 4 and Group 1 vs. 2 there was not any statistically significant difference between groups in terms of all parameters except mucosal perfusate LTB4 levels were higher in Group 4 than Group 3(when animals were fed with AED). But when hepatectomy added on fasted animals MLC levels were lower than fed by AED + sham operation. LTB4 levels were insignificant in both perfusate and mucosa. But when hepatectomy added on AED animals (Group 4), MLC decrased and mucosal LTB4 increased when they compared with fast without hepatectomy Group 1.

DISCUSSION

It has been shown in humans that the mucosa in the lower GIT, especially the colon, is for its growth and function almost entirely dependent on luminal nutrition.[4,5] It has also been demonstrated in transplantation donors with relatively short hospital stays that translocation is an early phenomenon at least in one third of them, and bacterial growth most often found in mesenteric lymph nodes, lungs, liver and spleen.[17] It has been

also shown, that the glycogen stores of the liver cells can seen after only a few hours of starvation cannot be filled during or immediately after surgery because of adrenergic activity following the operative trauma.[18,19,21-23] On the other hand a single intravenous injection of lead nitrate to rats induces proliferation of liver cells without the accompanying liver cell loss. The mechanism of this so-called direct hyperplasia is not fully understood and the growth response is not associated with any significant changes in the hepatic levels of known growth factors such as HGF and TGF alpha. Instead there is a rapid increase in TNF alpha levels in the liver. Controversially hepatectomy alone lead hepatocyte proliferation primarily due to growth factors. So it can be claimed that hepatectomy respectless of resected volume, might yield to non inflammatory proliferation in rat liver cells. It means that our model does not cause any inflammatory cytokine arising from liver during or right-after surgery. Besides, it lets us time saving to concentrate better to perfusate model.[24]

Maintenance of colonic feeding is regarded as essential to prevent mucosal damage, inflammation and bacterial translocation. It has also been formerly shown that increased portal pressure is not the only and sole cause of bacterial translocation and inflammatory cell infiltration in colon during hepatectomy.[25] The incidence of bacterial translocation and inflammatory changes originating from colon increased with the extent of hepatectomy and could lead to secondary infections after liver resection in rats.[26] This finding was also observed in hepatectomised patients and increased infectious complications were reported following hepatectomies.[27] In our study partial hepatectomy did not yield any change in colonic mucosal MLCs in fasted and fed groups, but arginine enriched diet caused significant decrease in MLCs in both groups of rats with or without hepatectomy . Hence we can say that hepatectomy alone either as a general manner (trauma) or as a spesific operation did not reveal any effect on leucocyte infiltration of colon mucosa. But arginine enriched diet caused significant decrease in MLCs. It can also be said that leucocyte infiltration may be dependent to fasted situation rather than hepatectomy. In the literature colon itself always was shown as a primary source of inflammatory changes following hepatectomy and tried to be related to the extent of hepatectomy.[26,28] Pearson et al. also showed that perioperative nutritional support can reduce complications after hepatectomy.[24] Our study may add an information about interrelation between hepatectomy and fasting as a source of inflammation.

Wachtler et al. stated that elective surgery does not yield any change in LTB4 / LTB5 ratio in both well nourished and malnourished patients.[18] LTB4 is a potent chemotactic factor for polymorphonuclear leukocytes and induces superoxide generation and degranulation of neutrophils. This finding may clarify in our study, why MLC are less in groups which have high mucosal and perfusate LTB4 levels than those low LTB4 levels. Leukocytes degranulates and produces leukotrienes. In addition to this finding another explanation can also be made. Leucocyte migration may be dependent to any other factors rather than LTB4 chemotaxis during or right after hepatectomy. Leduc and Zipser[29] have been nicely indicated that colon mucosa itself source of LTB4 and leucocyte migration is independent from LTB4 release. This theory seems more applicable to our data regarding to relation between LTB4 levels and MLC in colon mucosa. Same authors also showed that stimulated eucosanoid release lasts 2 or 3 minutes. That's why we have collected specimens immediately after hepatectomy.

In our study hepatectomy solely did not cause any change in mucosal or perfusate LTB4 levels in both fast and fed animals. But feeding caused significant increase in both mucosal and perfusate LTB4 levels. Perfusate solution was held to define pure LTB4 levels extracted from mucosa and excreted to systemic circulation via mesenteric circulation. By perfusion, colonic mucosa were cleared from systemic effects brought by mesenteric blood supply. Perfusate LTB4 levels in our study were parallel to those in mucosa. On the other hand Hafström et al. reported that fasting causes reduced release of LTB4 from neutrophils despite an increased aminoacide content.[19] It also supports our results and explains why LTB4 levels are less in fasted groups (Group 1 and 2) than fed groups (Groups 3 and 4). Physopathologic mechanism of this result was also explained by Hafström et al. in same study. In healthy subjects fasting causes an increase in aminoacid levels in plasma but decrease prostaglandine formation from aminoacids. It means that decreased metabolism of fatty acids appears in fasting. The source of fatty acids is body fat stores and released in fasting along with linoleic acid. This is also another mechanism which clarifies why leukotriene levels are less in fast groups in our study. Li & Kudsk reported that antigen uptake into the GALT results in stimulation of B cells and T cells that leave the lymphoid tissues.[20] In this authors' study,

the consistent relationship between decreased T-cell and B-cell yield and decreased IgA recovery suggests an interdependency and potentially immunosuppressive effect of intravenous or elemental enteral feeding. It also helps to define why leucocytes and LTB4 levels are lower than others in enterally fed animals.

The most important data from our study is hepatectomy does not have any effect on colonic mucosal changes. Nutritional status and local mucosal conditions are more important than hepatectomy. When it has been compared in basis of fasting situation regardless hepatectomy, i.e. Group 1 vs. 3 and Group 2 vs. 4 all MLC were lower in Group 3 and 4 but LTB4 levels both in mucosa and perfusate were higher. Similarly, on hepatectomy based comparison i.e. Group 3 vs. 4 and Group 1 vs. 2 there was not any statistically significant difference between groups in terms of all parameters except mucosal perfusate LTB4 levels were higher in Group 4 than Group 3 (when animals were fed with AED). But when hepatectomy added on fasted animals MLC levels were lower than fed by AED + sham operation. LTB4 levels were insignificant in both perfusate and mucosa. But when hepatectomy added on AED animals (Group 4), MLC decrased and mucosal LTB4 increased when they compared with fast without hepatectomy Group 1.

We conclude that;

1. AED increases mucosal LTB4 and lowers MLC in all groups independently from hepatectomy, but hepatectomy does not make the same changes independently.
2. It might be said that AED in hepatectomised rats causes leucocyte degradation and LTB4 release in mucosa.
3. In this situation, LTB4 possibly comes from outside of colonic mucosa, because perfusate LTB4 was not high when MLC was still lower than those in both AED alone and hepatectomy alone.
4. A practical conclusion it may be adapted to clinical situations is, AED prior to extra-intestinal operations like partial hepatectomy may trigger inflammatory cascade and complications via leucocyte degradation and LTB4. It should be judged with other factors for preoperative nutrition regarding to inflammatory reactions.

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