

Effect of pre- and probiotics on liver regeneration after resection - a randomised, double-blind pilot study

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Abstract

Background: Liver regeneration is a prerequisite for extended liver surgery. Several studies have shown that the bacterial gut flora is able to modulate liver function.

Previously we observed that synbiotics could partly reverse impaired mitosis rate of hepatocytes in a rat model of synchronous liver resection and colon anastomosis.

The effect of synbiotics on liver function after hepatic resection has not been analysed yet.

Research methods: A prospective randomized double-blind pilot trial was undertaken in 19 patients scheduled for right hepatectomy. All patients received enteral nutrition immediately postoperatively. Comparison was made between the verum group receiving a combination of four probiotics and four fibers (Synbiotic 2000) and the placebo group receiving the fibers only starting the day before surgery and continuing for 10 days. Primary study end point was the liver function capacity measured by ¹³C-Methacetin-breath-test (LiMax) and indocyanine green plasma disappearance rate (ICG-PDR). Portal vein flow, liver volumetry, laboratory parameters for liver function, length of hospital stay, postoperative complications and side effects of synbiotic therapy were recorded.

Results: Liver function capacity was comparable in both groups. Complications had a negative impact on liver function. Because complications were more severe in the verum group, a sub-analysis was performed. In case of an uncomplicated course, liver function capacity was better in the patients with synbiotics. No severe side effects occurred.

Conclusion: Synbiotics were able to increase liver function capacity in patients after standard hepatectomy.

Key words: probiotics; synbiotics; liver regeneration; hepatectomy; ¹³C-Methacetin-breath-test; indocyanine-green-plasma-disappearance-rate

Introduction

Liver regeneration is regulated by a complex interaction of hepatocytes and non-parenchymal cells (figure 1). This interaction is directed by a network of cytokines, growth hormones and metabolic factors which lead to a balanced hypertrophy and hyperplasia of the liver within six months following liver resection [1]. Liver regeneration following hepatic resection is a prerequisite for major liver surgery. In healthy livers, up to 75% of liver tissue can be resected without danger of liver failure. Complications like biliary leakage with consecutive bacterial peritonitis have a severe negative impact on the postoperative course. In case of bacteremia, the risk of liver failure increases to more than 50% and mortality to more than 40% [2].

Certain probiotics are known to modulate the gut flora, reduce the inflammation cascade and enhance the immune system. Thus, selected strains have been shown to prevent bacterial infections following abdominal surgery. We and others have shown in several clinical trials, that synbiotics are able to reduce bacterial infections after pancreatic surgery, liver resection and liver transplantation [3456].

The gut also plays an important role in liver regeneration. In two animal studies, proliferating cell-nuclear antigen or hepatic DNA and protein synthesis as parameters for hepatic regeneration were reduced if hepatic resection was combined with small bowel or colon resection [78]. The model of simultaneous liver resection and colon anastomosis is clinically relevant especially in patients with colon carcinoma and

synchronous liver metastasis. Some authors report a significantly increased morbidity and mortality in the case of simultaneous resection presumably caused by bacterial infections [9].

In order to assess the effect of synbiotics in this setting, we performed an experimental study in rats. We observed that simultaneous liver and colon resection led to increased bacterial translocation and impaired liver regeneration compared to liver resection alone. Oral application of the same synbiotic combination used in the present clinical study (Synbiotic 2000) was able to reduce bacterial overgrowth and translocation and, surprisingly, also to increase the mitosis rate. [10].

Other experimental and clinical studies could show that some synbiotics may influence liver function in chronic hepatitis via different pathways like prevention of inflammation or lipid peroxidation [11,12]. Therefore, the effect of synbiotics on liver regeneration is probably direct and not only via prevention of infections.

Liver regeneration is difficult to measure. We recently evaluated a new bedside test for liver function capacity which was able to predict residual liver function in 329 patients scheduled for hepatectomy [13]. The decrease of the absolute count (in $\mu\text{g}/\text{h}/\text{kg}$ BW) of this LiMAx test correlates well with the loss of liver volume following resection. Therefore, it enables us to measure postoperative hepatic regeneration.

Up to now, the interaction of synbiotics and liver regeneration after resection in healthy livers has not been studied. We conducted a prospective pilot study to assess the effect of synbiotics on liver regeneration following standard hepatectomy.

Patients and Methods

The study was performed at the Department of General, Visceral and Transplantation Surgery of the University Hospital Charité, Berlin, Germany. The study protocol was

approved by the local ethics committee and all patients gave their written informed consent. Between April 2007 and December 2008, 33 patients scheduled for liver resection in our department were prospectively enrolled into the study.

Inclusion criteria

Adult patients scheduled for right or extended right hemihepatectomy without bilioenteric anastomosis were eligible for this study.

Exclusion criteria

Exclusion criteria were a previous liver transplantation or porto-systemic shunt, chemotherapy within six months prior liver resection, concomitant acute infectious diseases, renal insufficiency and liver fibrosis or cirrhosis.

Study Design

The study was a prospective, randomised, double-blind placebo controlled single-center pilot trial. Randomisation was performed by sealed envelopes.

Group A: A specific synbiotic composition of pre- and probiotics (Synbiotic 2000® Medipharm, Kågeröd, Sweden and Des Moines, Iowa, USA) was administered twice daily orally or via feeding tube. All the strains used are deposited at the Belgian Coordinated Collection of Microorganisms – BCCM – deposition number provided below within parenthesis. Each dose of the combination contains four different lactic acid bacteria: 10^{10} *Pediococcus pentosaceus* 5-33:3 (dep.nr LMG P-20608), *Leuconostoc mesenteroides* 77:1 (dep.nr LMG P-20607), *Lactobacillus paracasei* subspecies *paracasei* F19 (dep.nr LMG P-17806) and *Lactobacillus plantarum* 2362 (dep.nr LMG P-20606) plus four bioactive fibers: 2,5 g of each betaglucan, inulin,

pectin and resistant starch, totally 10 g per dose, or 20 g per day. The treatment started on the day before operation and continued during the first 10 days after the operation.

Group B: Identical treatment as group A, with the only difference being that the patients received only the four fibers and no probiotics (placebo group).

The sachets and its content looked identical in both groups. All persons involved in the clinical treatment of the patients were blinded for the study group.

Enteral nutrition after surgery: Oral intake started on the operation day 6 h after surgery. If the patient did not have sufficient oral intake, enteral nutrition with a low-fiber formula (Fresubin®, Fresenius, Bad Homburg, Germany) was started via nasojejunal tube. The initial infusion rate was 25 ml an hour. If well tolerated, the enteral infusion rate was increased to 1ml/kg body weight/hour.

Study end point

Primary study end point was the extent of postoperative restoration of liver function measured by LiMAx- test.

In order to rule out differences in intra- and postoperative risk factors for impaired liver regeneration, the following parameters were analysed: age, preoperative body mass index (BMI) and state of health measured by American Society of Anaesthetists (ASA) -classification, operating time, number of intraoperatively transfused units of blood and plasma and incidence of surgical complications and bacterial infections. In addition, total hospital stay and side effects of the study investigational product were evaluated. Total length of hospital stay was defined as the period between day of operation and discharge.

Surveillance and definition of infection

Body temperature was measured twice daily. The diagnosis of bacterial infection was based on fever (>38 °C), elevation of C-reactive protein, specific clinical symptoms of infection as shown below and a positive bacterial culture.

Pneumonia: fever, cough, dyspnea, reduced arterial oxygen, typical pulmonary infiltrate on chest x-ray, positive culture from sputum or bronchoalveolar lavage.

Cholangitis: fever, elevation of cholestatic enzymes, positive culture from T-tube.

All patients received single-shot intravenous prophylaxis with cefuroxime (1,5g) and metronidazole (500mg) 30 minutes before operation. After that, antibiotics were only given in case of bacterial infection.

Parameters of liver regeneration

To evaluate the extent of liver regeneration and its influence factors, the following parameters were measured on the day of operation and on postoperative days 1,4, 5,10 and 14:

- liver function capacity by ¹³C-Methacetin-breath-test or LiMAx-test® and indocyanine green plasma disappearance rate (ICG-PDR)
- laboratory tests (haematology, clinical chemistry including ASAT, ALAT, GLDH, bilirubin, γGT, AP, PCHE, albumin and CRP, INR, factor II and VII)
- portal vein flow (duplex-sonography)
- clinical data (ascites).

13C-Methacetin-breath-test / LiMAx-test®

Methacetin is a substance exclusively metabolized by the CYP1A2 enzyme system of

the liver. This enzyme system is only expressed in hepatocytes and it is proportional to the parenchymal volume of the liver. Furthermore, it is not influenced by drugs or genetic variations. The ^{13}C -methacetin-breath test / LiMAX-test® is a method to determine patient liver function capacity by measuring the $^{13}\text{CO}_2/^{12}\text{CO}_2$ -ratio in the expired air with an isotope- selective nondispersive infrared spectrometer (FANci2-db16, Fischer Analyseinstrumente, Leipzig, Germany). ^{13}C -methacetin is methylated by cytochrome P4501A2 to paracetamol and ^{13}C . During this reaction, the stable isotope ^{13}C binds to oxygen and is eliminated with the expired air as $^{13}\text{CO}_2$.

After a minimum of 6 hours fasting, the baseline $^{13}\text{CO}_2/^{12}\text{CO}_2$ -ratio was recorded and the mean was used for the delta-over-baseline calculation. Ten minutes later, 2 mg/kg BW ^{13}C -methacetin were intravenously applied and consecutively, 46 breath samples were taken for each LiMAX test with a specially designed face mask for real-time analysis. Results are shown in [$\mu\text{g}/\text{kg}/\text{h}$]. Details of the technique have been previously published [¹⁴].

In addition, the indocyanine green plasma disappearance rate (ICG-PDR) was measured in each patient as a parameter for liver function. This test is well established but the results are influenced by various factors such as intrahepatic cholestasis [¹⁵].

Liver Volumetry

Preoperative liver volumes were measured by CT volumetry (LightSpeed 64; GE Medical Systems, Milwaukee, IL) using a 4-phase contrast enhanced examination technique. Image-guided volumetric measurement was performed using AMIRA software (Mercury Computer Systems, Chelmsford, MA). The volume of the resected liver was measured intraoperatively by water displacement volumetry and was multiplied by a factor of 1.15 to compensate for the unperfused state [¹⁶]. The

residual liver volume was then calculated and given in [%].

Statistical analysis

The statistical analysis was performed using SPSS 15.0 (Chicago, Illinois, USA). Non-parametric variables were compared by Mann-Whitney-U-test. A p-value < 0,05 was considered statistically significant.

The study was designed as a pilot study. Therefore, no sample size was calculated.

Results

Demographic and operative data

14 of the 33 enrolled patients were excluded from the study due to inoperability of the patients because of advanced tumor (n=8) and necessity of a bilio-enteric anastomosis (n=6). In total, 19 patients completed the study (group A= 9 patients, group B= 10 patients). Indications for resection were colorectal metastasis (n=10), cholangiocellular carcinoma (n=8) and hepatocellular carcinoma (n=1). Age, gender, ASA-classification, BMI and preoperative indocyanine green plasma disappearance rate were equally distributed between the two groups. However, patients in the placebo-group had a significantly higher preoperative LiMAx- test than patients in the verum group (table 1).

Operating time was longer in the verum group. Resection type was right hemihepatectomy in 14 cases and extended right hemihepatectomy in five cases (three verum group, two placebo group). There were no significant differences regarding length of hospital stay, number of intraoperatively transfused red packed cells or fresh frozen plasma and number of postoperative complications but a trend towards a more complicated perioperative course in the verum group reflected by nearly all of these parameters (table 2).

No perioperative mortality was observed in both groups. Complications in the verum group were papillary stenosis requiring endoscopic papillotomy, bilioma, cholangitis, hepatic abscess and pneumonia (n=1 each). In the placebo group, one patient each had a hepatic abscess and cholangitis. In addition, three patients in this group had persistent high volumes of postoperative ascites requiring paracentesis.

The residual liver function measured by LiMAx- and ICG-PDR-test and the residual liver volume were comparable between the groups (table 3).

Portal vein flow and laboratory parameters

There were no significant differences regarding the portal vein flow between the two groups.

The mean values of ASAT and GLDH on postoperative day 1 were significantly higher in the verum group reflecting a greater liver damage. The ALAT peak was also more pronounced but not significant (figure 2). In parallel, gGT and bilirubin levels were higher in the verum group, but only the difference for bilirubin on postoperative day 5 was significant. The markers of liver synthesis, INR, factor II and VII, albumin and PCHE were comparable.

Regarding infection markers, the CrP on postoperative days 10 and 14 was significantly increased in the verum group whereas leucocytes were comparable.

LiMax and ICG-PDR

Liver regeneration was compared using the relative differences of LiMAx and ICG-PDR. They were calculated defining the LiMAx and ICG-PDR on postoperative day 1 as 100 percent and analysing the other values in comparison to it. The results in both groups were comparable. The mean values of the LiMax are depicted in figure 4.

Effect of complications on liver regeneration

Patients with postoperative complications had an impaired liver regeneration reflected by a significantly lower increase of the LiMAx values on postoperative day 10 (figure 4).

Effect of synbiotics on liver regeneration

In order to rule out the negative effect of complications on liver regeneration and to purely analyse the effects of synbiotics, the LiMAx of patients without complications was compared in the two groups. In this subgroup the relative increase of liver functional capacity measured by LiMAx on postoperative days 3 and 5 was significantly higher in the verum group (figure 5).

Side effects of enteral nutrition

The synbiotic combination was well tolerated in all patients. Mild side effects (abdominal distension and cramps) occurred in three patients of each group but disappeared under symptomatic therapy.

Discussion

Results from the present prospective, randomised, double-blind pilot study, indicate that a mixture of four pre- and probiotics might increase liver function in the early postoperative course following right or extended right hepatectomy. Unfortunately, severe surgical complications more often occurred in the synbiotic group. Probably due to this bias, overall there was no significant improvement in liver function with synbiotics versus placebo. Only the small subgroup of patients with an uncomplicated course had significant higher liver function capacities in the early postoperative

period.

So far, the experience with synbiotics in patients after hepatic resection is limited. Two clinical studies have shown that a synbiotic combination of *Lactobacillus casei* strain Shirota, *Bifidobacterium breve* strain Yakult and galactooligosaccharides is able to decrease the incidence of bacterial infections following hepatectomy for biliary cancer [4]. The authors postulated that synbiotics acted via correcting intestinal microbial imbalance, enhancing natural immunity and deactivating the cytokine cascade. No data on liver function were published in this study.

In a mouse model of non-alcoholic steatohepatitis, the probiotic combination VSL#3 including *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium longum*, *Lactobacillus plantarum*, *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus bulgaricus* and *Streptococcus thermophilus* as well as TNF-antibodies led to a reduced steatosis, inflammation and lower ALT-levels compared to control animals [17]. The same probiotic combination achieved an improvement of liver function in patients with alcoholic cirrhosis [12]. In addition, the authors observed a normalisation of TNF-alpha, IL-6 and IL-10 and of markers of lipid peroxidation (Malondialdehyd, 4-Hydroxynenal and S-Nitrosothiol) which were increased at the beginning of probiotic therapy. Therefore, probiotics might act via down-regulation of endotoxin and pro-inflammatory cytokines. These cytokines are able to induce liver fibrosis and lipid peroxidation which is a trigger for the development of steatohepatitis. TNF-alpha and IL-6 are also involved in the process of liver regeneration (figure 1). One might speculate that probiotics also have an influence in this setting. However, the authors did not assess liver regeneration directly. This might be based on the fact, that measurement of liver function and liver regeneration after hepatic surgery is difficult. This problem has been overcome in the present study, using the newly developed LiMAx test. This test is a reliable tool for the

determination of liver functional capacity [14] and thereby a surrogate parameter for liver regeneration.

Liu et al showed that cirrhotic patients who received oral synbiotics (Synbiotic 2000) had a significant improvement of minimal hepatic encephalopathy and the Child Pugh score compared to the control group [18].

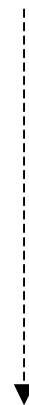
In the present study, only patients with healthy livers lacking severe parenchymal damage scheduled for a right hepatectomy with low risk for hepatic failure were included in order to focus on liver function and to increase the homogeneity of the study groups. The LiMax test was chosen because this test has been shown to be very accurate and easy to perform in previous studies and in clinical practice [13]. In addition, an ICG-PDR was performed in each patient as a control test. Both tests showed similar results.

As expected, patients with postoperative complications had significant impairment of liver function. Comparison of mean LiMAX and ICG-PDR values between the whole verum and placebo group did not show any differences. This fact might be explained by a higher incidence of severe surgical complications in the verum group. In addition, patients in the verum group had higher levels of ASAT, GLDH, bilirubin and CrP immediately following operation thus reflecting a greater liver damage.

The study was planned as a pilot study. Therefore, patient numbers are too small and the type of complications too diverse to analyse all subgroups separately. Further studies with more patients are needed to confirm these results. In this case, synbiotics could be very useful especially in patients with extended hepatectomies.

table 1: Preoperative data of both study groups

	<i>Verum</i>	<i>Placebo</i>	<i>p</i> [§]
number of patients [n]	9	10	
age [years]	59 ± 11	61 ± 16	0,327
gender (m/f)	8/1	6/4	0,165
BMI (mean and SD)	26,9 ± 4,7	23,7 ± 2	0,06
ASA score (mean)	2,2	2	0,125
LiMAx [µg/kg/h] preop (mean and SD)	360 ± 68	476 ± 164	0,034
ICG-PDR [%/min] preop (mean and SD)	16,6 ± 2,6	21,4 ± 10,5	± 0,438



(BMI=Body mass index; ASA=classification of the American Society of Anaesthesiologists, ICG-PDR=indocyanine green plasma disappearance rate, § statistical comparison of verum vs. placebo group)

table 2: Perioperative data of both study groups

	<i>Verum</i>	<i>Placebo</i>	<i>P</i>
operating time [min] (mean and SD)	263 ± 81	191 ± 60	0,031
red packed cells [n] (mean and SD)	0,25 ± 0,7	0,4 ± 1,3	0,927
fresh frozen plasma [n] (mean and SD)	3 ± 4	0,4 ± 1,3	0,126
<i>complications [n]</i>			
none	4	5	
infectious	3	2	
others	2	3	
severe	4	1	

(RPC=red packed cells, FFP=Fresh-Frozen-Plasma)

table 3: Residual LiMAx-, ICG-PDR, liver volume and resected liver volume in both study groups (mean and SD)

	<i>Verum</i>	<i>Placebo</i>	<i>p</i>
residual liver function (LiMAx) [%]	42 ± 17	46 ± 12	0,253
residual liver function (ICG-PDR) [%]	53 ± 22	59 ± 19	0,462
residual volume [%]	52 ± 14	56 ± 10	0,643
resected liver volume (ml)	990 ± 326	845 ± 312	0,331

Residual LiMAx [%] = $100 \times \text{LiMAx 1. POD [MW]} / \text{LiMAx preop [mean]}$. Residual ICG-PDR [%]= $100 \times \text{ICG 1. POD [mean]} / \text{ICG-PDR preop [mean]}$. Residual liver volume [%] = $100 - (100 \times \text{resected volume [mean]} / \text{CT-volume preop [mean]})$

Figure legends

figure 1: liver regeneration after hepatic resection

figure 2: mean levels of ASAT, ALAT and GLDH in the two groups (*= difference statistically significant)

figure 3: mean percental LiMAx postoperatively in the two groups (POD 1 = 100 %), error bars represent standard deviation)

figure 4: mean percental LiMAx in the patients with (n=10) and without (n=9) complications (error bars represent standard deviation, * = difference statistically significant)

figure 5: mean percental LiMAx of patients without complications in the two groups (verum n=4 , placebo n=5, error bars represent standard deviation, * = difference statistically significant))

figure 1:

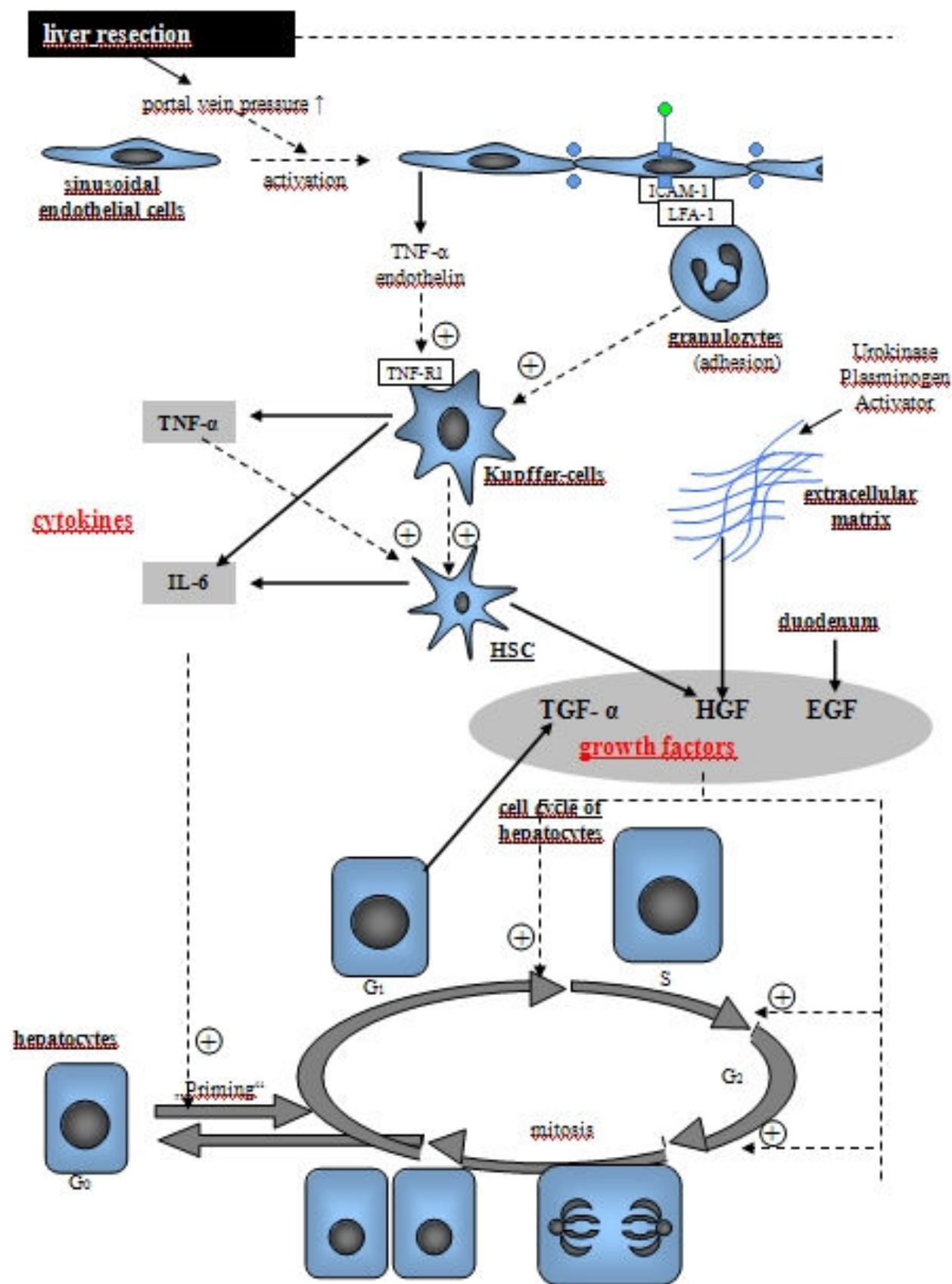


figure 2:

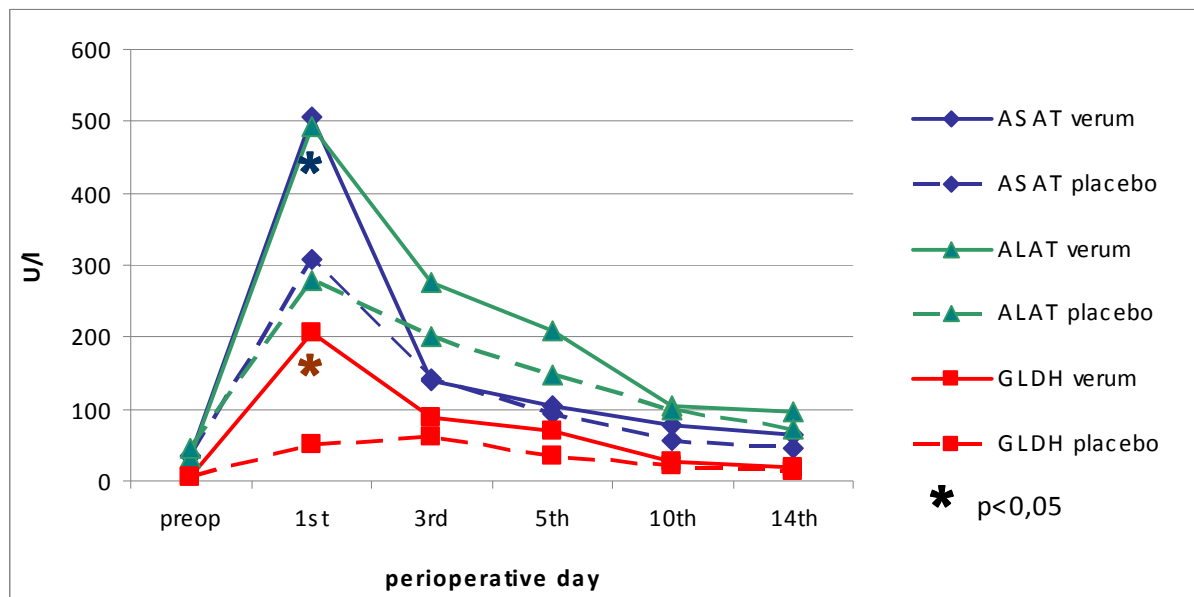


figure 3:

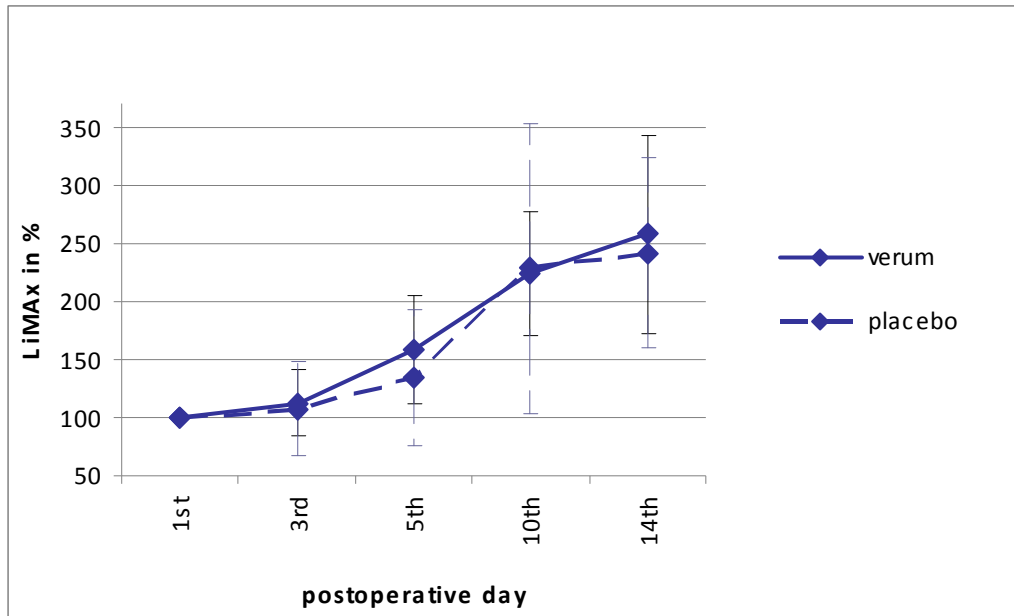


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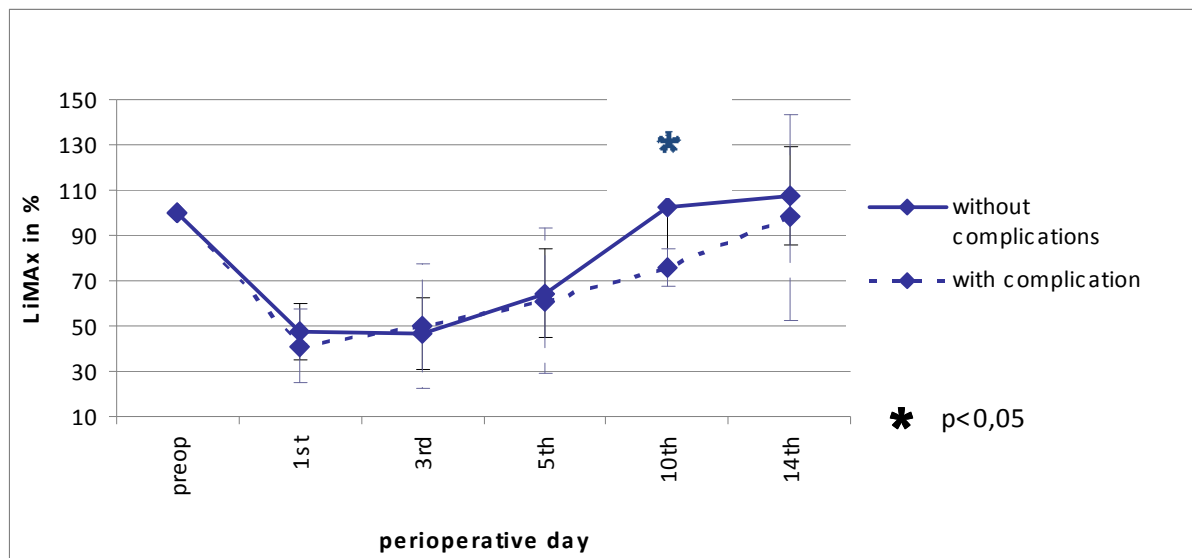
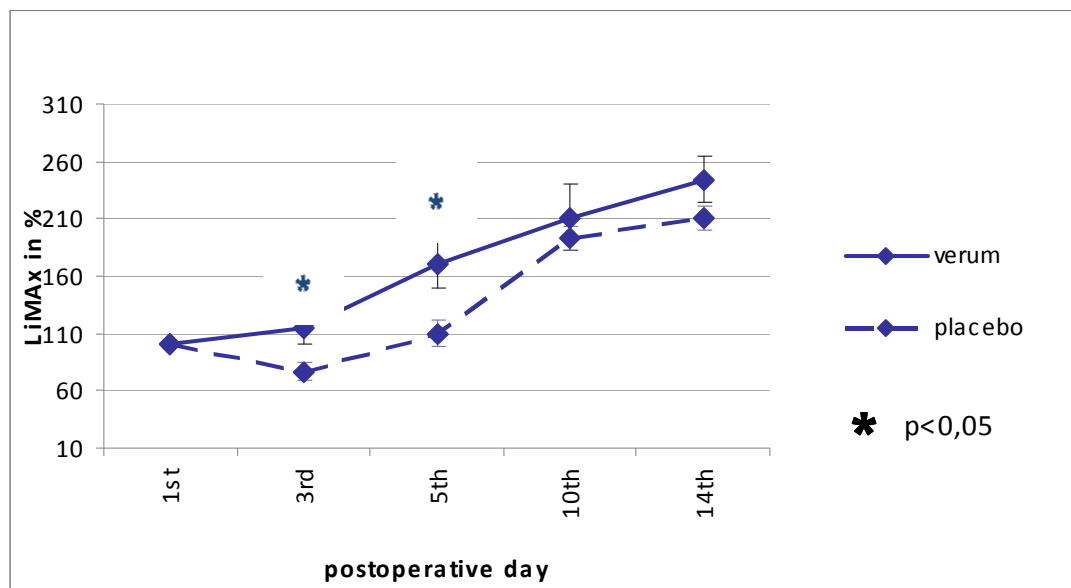


figure 5:



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figure 1: liver regeneration after hepatic resection

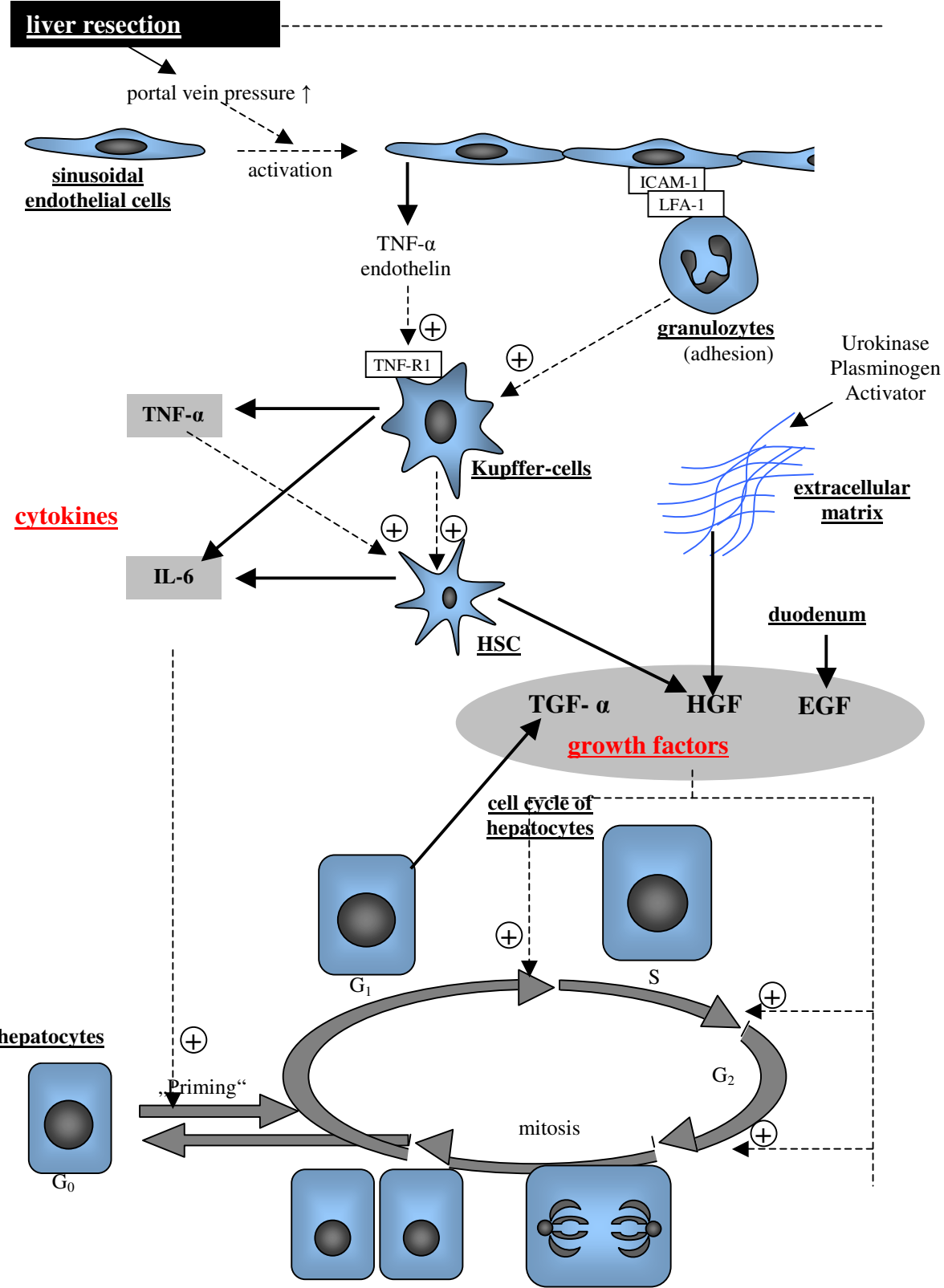


Figure 1

figure 2: mean levels of ASAT, ALAT and GLDH in the two groups (*= difference statistically significant)

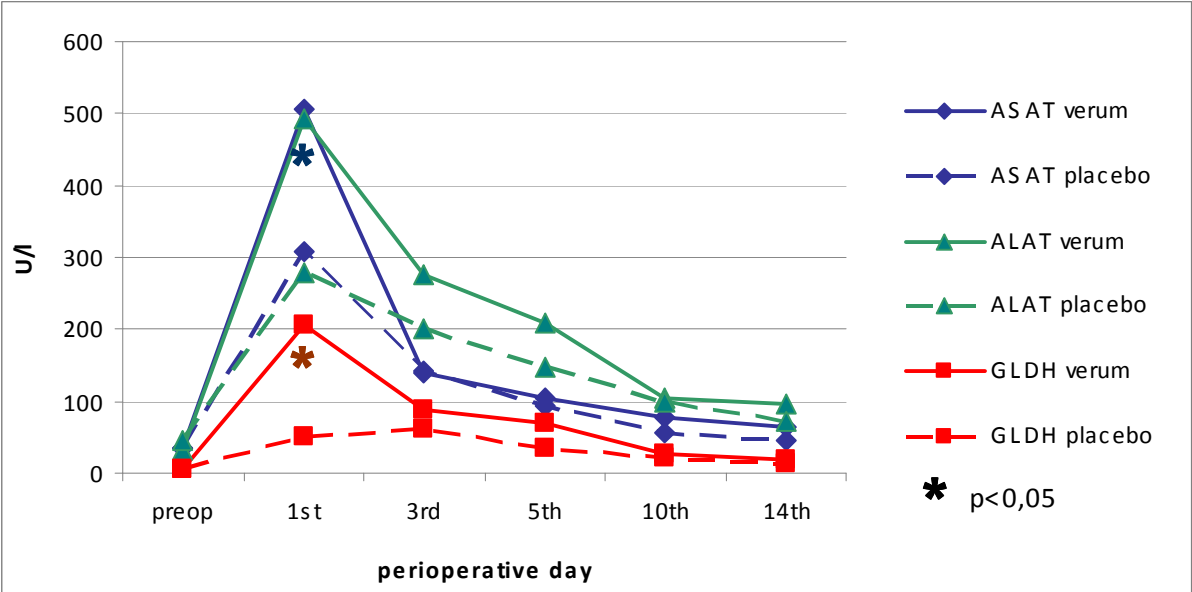


Figure 2

figure 3: mean percental LiMAx postoperatively in the two groups (POD 1 = 100 %), error bars represent standard deviation)

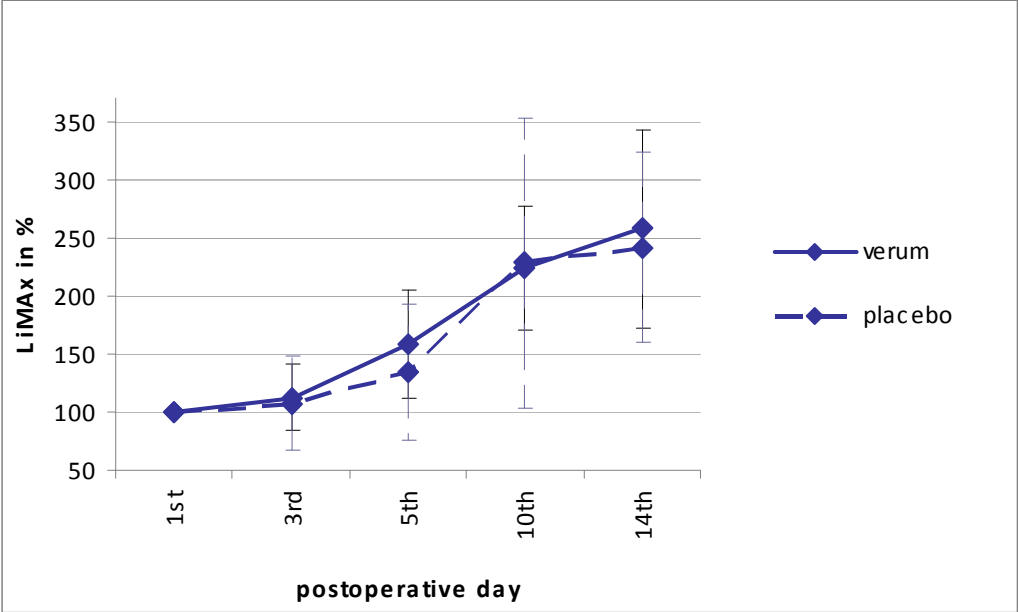


figure 4: mean percental LiMAx in the patients with (n=10) and without (n=9) complications (error bars represent standard deviation, * = difference statistically significant)

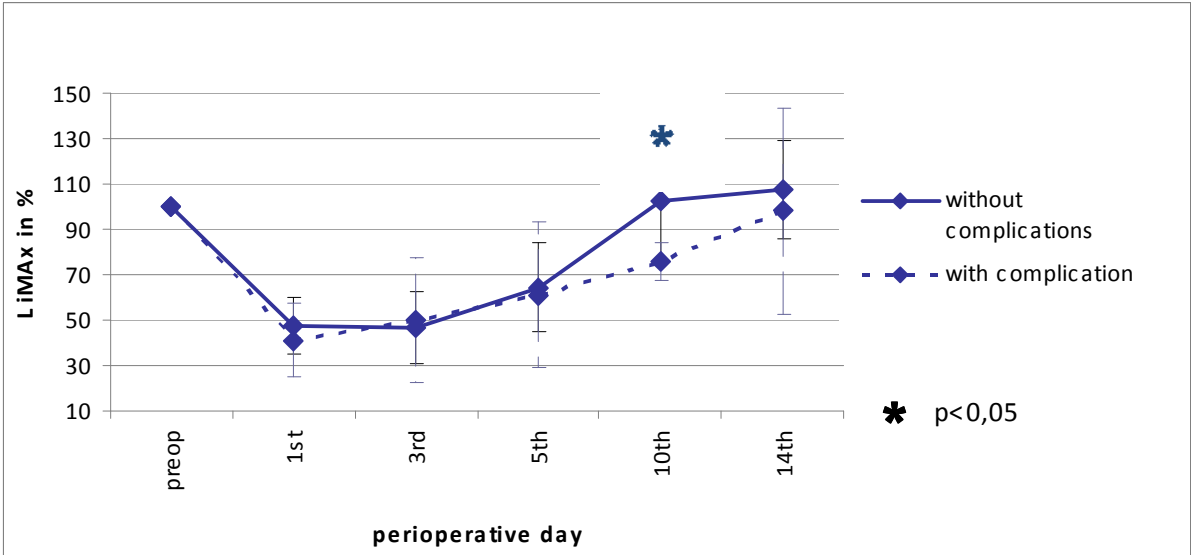


Figure 4

figure 5: mean percental LiMAx of patients without complications in the two groups (verum n=4 , placebo n=5, error bars represent standard deviation, * = difference statistically significant)

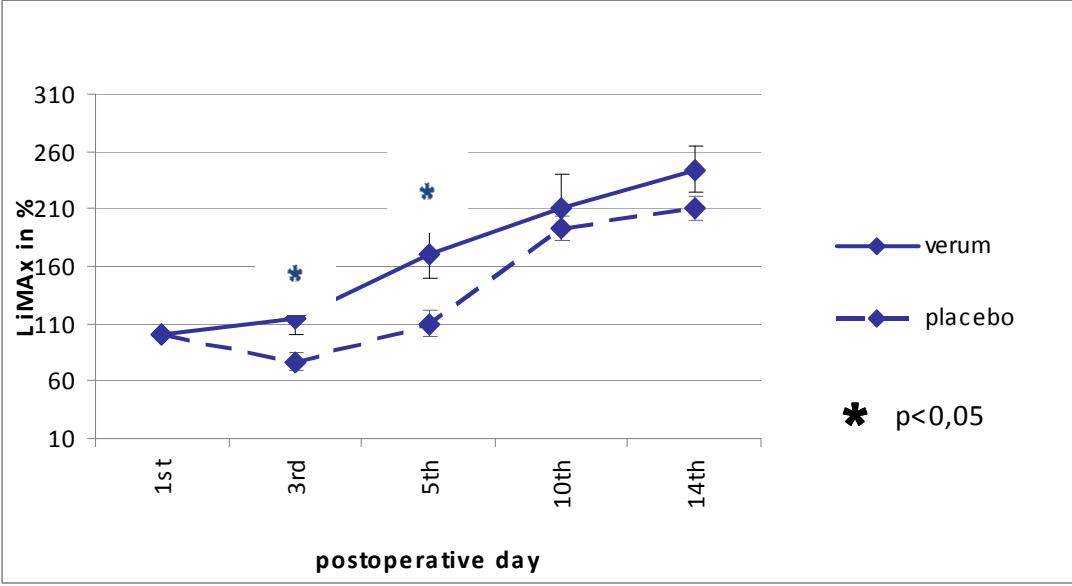


Figure 5