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Beneficial Effect of Total Splenectomy on Liver Function after Partial Hepatectomy in a Rabbit Model

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Abstract: Small for size syndrome is a widely recognized clinical complication after living donor liver transplantation or extended hepatectomy due to inadequate liver mass. The purpose of this study was to investigate the role of splenectomy in rabbits after massive hepatectomy, a surrogate model of small for size graft. Animals were divided into 3 groups, 6 rabbits each: control (C), hepatectomy (Hp) group and hepatectomy and splenectomy (Hp and Sp) group. Three days after surgery, liver function tests (AST, ALT and Total bilirubin) were evaluated. Compared with the C and Hp group, the Hp and Sp group had better liver function ($P<0.05$).

Key words: Total Splenectomy · Partial Hepatectomy · Small For Size · Liver Function · Rabbits

INTODUCTION

Surgical resection offers the best survival to patients with hepatocellular carcinoma and colorectal metastasis, which are ones of the most prevalent malignancies. The multifocal nature of these lesions frequently requires extensive hepatectomy, which results in an inadequate remnant liver mass [1].

Small for size syndrome is a widely recognized clinical complication after living donor liver transplantation or extended hepatectomy due to inadequate liver mass. The clinical manifestations of small for size syndrome consist of poor bile production, delayed synthetic function, prolonged cholestasis and intractable ascites, leading to septic complications and higher mortality [2, 3].

Therefore, we hypothesized that total splenectomy is beneficial for massive hepatectomy and its beneficial effect may be mediated through reduced cytolysis and cholestasis severity after partial hepatectomy. To test our hypothesis, alanine aminotransferase (ALT), aspartate transaminase (AST) and total bilirubin (TBIL) in partial hepatectomy (Hp) group and partial hepatectomy with splenectomy (Hp and Sp) group were measured.

MATERIALS AND METHODS

Experimental Design: The study was carried out by using eighteen male local rabbits with a mean weight of 1.5 - 2 kg which were randomly assigned into three groups as follow: Control (C) shame operation, Hepatic resection (Hp) (n = 6) and hepatic resection with splenectomy (Hp and Sp) (n = 6). Prior to any procedure, animals were acclimatized for 3 days under standardized laboratory conditions in a temperature-controlled room. Rabbits were individually housed, had free access to standard laboratory food and water and were subjected to a 12 h light/dark cycle per day.

Three days after skin closure, serum alanine aminotransferase (ALT), aspartate transaminase (AST) and total bilirubin (TBIL) were measured.

Surgical Procedures: Rabbits were weighed after shaving and cleaning skin with povidone-iodine. All surgical procedures were performed, after an overnight fasting, under general anesthesia induced by intramuscular injection of: 0.8 mg/kg of Acepromazine, 0.05 mg/kg of Buprenorphine and 40 mg/kg of Ketamine.

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In the control group, animals underwent an upper midline incision with left subcostal extension. The abdominal wall was then sutured with a running 2-0 Polyglactin 910 suture and the skin with a simple interrupted 2-0 Polyamide.

Hepatic resection was performed as described previously by Higgins and Anderson [4]. After opening the upper abdomen and exposure of the liver, the lobe to be resected was gently lifted while a 3-0 silk suture tie was placed underneath it and positioned as proximal to the origin of the lobe as possible. The two ends of the suture were tied over the top of the lobe at its base near the inferior vena cava. Three knots were tied and dissecting scissors were used to cut the tied lobe just distal to the suture. Then the abdominal wall was reapproximated with a running 3-0 Polyglactin 910 suture and the skin was closed with a simple interrupted 2-0 polyamide suture.

After exactly the same surgery, rabbits in the Hp and Sp groups received a splenectomy, in which the splenic artery and vein were ligated with 3-0 silk and the spleen was removed from the abdomen.

Biochemical Measurements: All rabbits in the three groups were sacrificed at day 3 after surgery and blood samples were taken. In all blood samples, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were assessed to examine the degree of liver damage. Serum total bilirubin (TBIL) was determined as indirect measure of hepatic function (hepatic uptake and excretory function).

Dosage of hepatic transaminases was performed by enzyme kinetics at 37 °C and serum total bilirubin was determined by the method Jendrassik.

Statistical Analysis: Results of assessed parameters were expressed as mean values ± SD. A One-way ANOVA test was performed by STATISTICA ver. 8 for windows and used to analyze the response of assessed variable to the surgical procedure in each group. Values of P less than 0.05 were regarded as significant.

RESULTS

Results of liver function tests expressed as Mean±SD are summarized in Table 1.

Partial hepatectomy resulted in marked increases in ALT, AST and Total Bilirubin at day 3 after operation. However, serum levels of ALT and AST were lower in the Hp and Sp group than the Hp group ($P<0.005$). Compared with the Hp group, splenectomy in the Hp and Sp has reduced significantly the serum levels of total bilirubin ($P<0.02$).

Table 1: Serum biochemical parameters in the C, Hp and Hp and Sp groups (Mean±SD)

	C	Hp	Hp and Sp
AST (IU)	49,33±12,70	133,83±36,20	80,66±33,36 **
ALT (IU)	68,50±11,29	226,67±82,95	159,33±45,09 **
TBIL (mg/dL)	0,46±0,08	0,91±0,33	0,71±0,16 *

TBIL: Total bilirubin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; C: Control; Hp: Hepatectomy; Sp: Splenectomy. *: $P<0.02$ vs C and Hp groups, **: $P<0.005$ vs C and Hp groups.

DISCUSSION

Small for size syndrome refers to an organ size mismatch insufficient to meet metabolic demands after liver transplantation and/or massive hepatectomy. A smaller liver volume frequently leads to intrahepatic cholestasis and increased portal pressure [5]. The mechanism by which this process occurs is not fully understood and therapeutic strategies are very limited [6].

The role of splenectomy in small for size livers is under debate [6]. On one hand, some surgeons believe that splenectomy should not be recommended with liver transplantation or major hepatectomy. Samimi *et al.* [7] found that splenectomy with orthotropic liver transplantation has a significantly higher patient mortality mainly due to septic complications. Also, Neumann *et al.* [8] showed that splenectomy is a major risk factor for the development of opportunistic pneumonia caused by *Legionella pneumophila*, *Pneumocystis carinii*, *Aspergillus* species and *Cytomegalovirus* after liver transplantation.

Otherwise, some studies indicated that splenectomy is effective in improving disorders of small for size livers via down-regulating transforming growth factor-β [9], increasing HO-1 and inhibiting tumor necrosis factor-α [10], infiltration and apoptosis [11]. However, the exact mechanism is still unclear. Recent studies focused on the hemodynamic changes of the liver after splenectomy and indicated that the beneficial effect of splenectomy in small for size livers can be attributed to a reduced portal venous hyperperfusion to the remnant liver [3, 12].

Serum ALT, AST and TBIL reflect the extent of liver tissue injury. Our results showed low serum ALT, AST and TBIL levels in Hp and Sp group compared to C and Hp groups, suggesting direct beneficial effect of splenectomy on liver function after partial hepatectomy. This is in accordance with results obtained by Ren *et al.* [6] showing that splenectomized rats had better liver function after massive hepatectomy and Magdy Elsebae and Nadia Abu-Zekri [13] findings, reporting that

splenectomy is effective in improving remnant liver function after partial hepatectomy when performed under total vascular exclusion for 30 minutes in hamsters.

In summary, splenectomy leads to resolution of liver function in a rabbit model. The mechanism of this beneficial effect needs further researches to be clarified.

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