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ORIGINAL ARTICLE

Effect of nebivolol on liver regeneration in an experimental 70% partial hepatectomy model

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Summary *Background:* Factors affecting liver regeneration are still relevant. The purpose of this study is to investigate the effect of nebivolol treatment on liver regeneration in rats in which 70% partial hepatectomy was performed.
Methods: Three groups were created: the control group, the low dose group, and the high dose group, with 20 rats in each group and 70% hepatectomy was performed in all rats. Immediately after partial liver resection, 2 mL physiological saline solution was administered to the control group via oral gavage, 0.5 mg/kg nebivolol was administered via oral gavage to the low dose group and 2 mg/kg nebivolol was administered via oral gavage to the high dose group. On the 1st and 5th days after liver resection, 10 subjects were sacrificed from each group, and liver weights and the mitotic count and Ki-67 were measured.
Results: Regenerating liver weight on the 1st and 5th days after partial hepatectomy was statistically different in the low dose and high dose nebivolol groups compared to the control group. Mitotic count on the 1st day after partial hepatectomy was significantly higher in the low dose and high dose nebivolol groups than the control group. There was no statistically significant difference detected between the three groups for the 5th day. On the 1st day, Ki-67 rates were significantly higher in both groups given nebivolol than the control group. However, 5th day results were not statistically significant.
Conclusion: Nebivolol increases regeneration after partial hepatectomy in rats.

Conflicts of interest: The authors declare no conflicts of interest.

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1. Introduction

The liver is an organ that has a known regeneration capability. Developments in surgical techniques have led to rapid advances in liver surgery. Nowadays, the most important limiting factor in liver surgery is liver failure after major liver resections. The remaining liver tissue after liver resection is capable of regeneration. This process is a complex condition in which many different mechanisms play a role.[1,2] Many cytokines have a promoting effect on regeneration, but besides this, some show inhibitory effects.[3,4] There are many studies related to exposing liver regeneration steps and this topic still remains up to date.

Nebivolol is a pharmacologic agent that is clinically used as an antihypertensive. It is a third generation beta-1 adrenoreceptor antagonist. Unlike other drugs in the same type, it blocks beta-1 adrenoreceptors selectively. It is used a single daily dose. Nebivolol is metabolized in the liver and excreted through the kidneys. It is clinically shown that nebivolol is well tolerated and has fewer side effects than the other beta-blockers.[5] It does not increase peripheral vascular resistance like other beta adrenoreceptor antagonists. Conversely, it creates vasodilation by increasing vascular endothelial nitric oxide (NO) levels.[6,7] The increasing vascular endothelial level of NO which is produced in the liver has been shown to enhance the regeneration of the liver.[8] To our knowledge, there is no other study that investigates the effects of nebivolol that causes an increase in NO levels in vascular endothelium, on liver regeneration. In this study, our aim is to investigate the effects of different doses of nebivolol on liver regeneration in rats in which we performed 70% partial hepatectomy.

2. Methods

After review of the literature, the study was approved by the Ankara University Experimental Animal Ethics Committee on June 3, 2013 with 2013-6-46 decision number. The experimental study was performed at the Experimental Animal Research Laboratory of Ankara University Faculty of Medicine in April 2013. In the study, 60 female Wistar Albino rats, 8–10 weeks old, ranging in weight from 200 g to 250 g, were fed with standard laboratory chow. Seventy percent hepatectomy was performed in all rats. Physiological saline solution (2 mL), 0.5 mg/kg nebivolol, and 2 mg/kg nebivolol were administered via oral gavage to the control, low dose, and high dose groups, respectively. Rats were divided into three groups: Group 1 (control group, 2 mL oral gavage of saline), Group 2 (low dose nebivolol group, 0.5 mg/kg oral gavage), and Group 3 (high dose nebivolol group, 2 mg/kg oral gavage).

Ketamine HCl (80 mg/kg) and 12 mg/kg xylazine hydrochloride were administered intramuscularly for anesthesia and muscle relaxation. Laparotomy with a 2.5-cm midline incision was performed in all rats. The pedicles of the left lateral and median lobes of the liver were ligated with 4/0 silk and 70% hepatectomy was performed as described by Higgins and Anderson.[9] The removed livers were weighed and the weight recorded. After controlling hemostasis, the abdomen was closed with single layer sutures. The above-mentioned doses of nebivolol and saline were given up to 24 hours prior to sacrification to the groups that will be sacrificed on the 5th day after liver resection. On the 1st and 5th day after liver resection, 10 subjects from each group were sacrificed by creating hypovolemia with drawing an average of 6 mL blood from the inferior vena cava. Then, the remaining liver tissue was removed, weighed and placed in formol for pathological examination.

2.1. The weight of regenerating liver

Wet weights of removed left and median lobes were weighed after partial resection (RW). Total liver weight before resection (TW) was calculated by assuming 70% of liver weight was resected (TW = RW/0.7). The amount of regeneration was calculated by dividing total liver weight on the day of sacrifice (SW) to the calculated weight before resection (SW/TW $\times$ 100). This formula is known as Kwon Formula, which derives from the name of the originator.[10]

2.2. Histological and immunohistochemical evaluation

Histological and immunohistochemical evaluation was performed in the Pathology Department of Türkiye Yüksek İhtisas Training and Research Hospital. Tissue samples were fixed in 10% buffer formalin and mitosis were counted from hematoxylin–eosin-stained slides in 10 high power fields (Olympus, CX31, Tokyo, Japan). Ratios are given as percent.[11] To determine Ki-67 expression, sections were taken to the slides with poly-L-lysine. Ki-67 (SP6) (Neomarkers, Fremont, CA, USA) immunohistochemically stained with ready-to-use rabbit monoclonal antibody and nuclear staining were counted in 1000 cells. Positively stained nuclei were expressed as percent.

2.3. Statistical analysis

Data analysis was performed using SPSS for Windows 11.5 program (SPSS Inc., Chicago, Illinois, USA). Distribution of continuous variables close to normal was investigated with the Shapiro Wilk test and homogeneity of variances was investigated by the Levene test. Descriptive statistics are shown as median (minimum–maximum). To control the Type I error in all possible multiple comparisons, Bonferroni adjustment was made. According to the Bonferroni adjustment, $p < 0.025$ was considered statistically significant for the results.[12]

3. Results

3.1. Regeneration

Median (minimum–maximum) values of regeneration rates of subjects for groups are shown in Table 1. At the end of the 1st day, there was a statistically significant difference

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