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Hepatocellular Liver Function of Immunosuppressed Rats with Oral Candidiasis after Hyperbaric Oxygen Treatment: Alanine Transaminase and Aspartate Transaminase Levels

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ABSTRACT

Hepatocellular utility is observed by measuring the hepatocellular enzymes. Changes in its serum levels are related to liver dysfunction. Liver is one of the immunoprotective organs. Continuous use of immunosuppressive drugs can cause oral candidiasis and give effects to liver function. Hyperbaric oxygen treatment (HBOT), while reducing fungal infections, can also repair the liver function. The aim of this study was to investigate the alanine transaminase (ALT) and aspartate transaminase (AST) levels of immunosuppressed rats with oral candidiasis treated with hyperbaric oxygen. Twelve Wistar rats were divided into three groups: K− (normal/ healthy), K+ (oral candidiasis immunosuppressed rats), and P (oral candidiasis immunosuppressed rats treated hyperbaric oxygen). K+ and P groups were immunosuppressed by giving dexamethasone 0.5 mg/day/rat orally for 14 days, added with tetracycline 1 mg/day/rat. HBOT was given in five days successively. Blood serum of rats in all groups were taken to calculate the ALT and AST levels. ALT and AST levels in K+ showed higher value than K− and P groups. The data were analysed with one-way ANOVA test and showed significant difference in ALT levels ($p < 0.05$), while in AST levels there was no significant difference among the groups ($p > 0.05$). This study showed that HBOT affected the ALT and AST levels of immunosuppressed rats with oral candidiasis.

Keywords: *ALT; AST; hepatocellular; hyperbaric oxygen; immunosuppressed; oral candidiasis*

INTRODUCTION

Immunosuppression can be defined as the decrease of the body's immune system. Immune system is the defence mechanism against pathogenic microorganism, autoimmune, and cancer. Some immunosuppressant agents can cause the decrease of local and systemic defence mechanism, such as reduced cellular immunity and salivary secretion, which can induce the occurrence of oral candidiasis (Meurman *et al.*, 2007). Corticosteroid is known to have immunosuppressive and anti-inflammation effect. Several mechanisms of steroid are by inhibiting the recognition of antigen by dendritic cell, stabilising the lysosomal membrane, decreasing the

amount of CD4+ in circulation, reducing IL-1 transcription, and inhibiting the IL-1 dependent lymphocyte activation (Choudhary *et al.*, 2013).

Kupfer cells on liver tissue have crucial role in eliminating organisms such as bacteria and virus (Hall, 2011). Oral administration of immunosuppressant drugs will cause drugs to enter the liver through vena porta hepatica and metabolise in the liver. The continuous use of immunosuppressant drugs and exceeding the maximum amount can cause oral candidiasis and make the liver to work harder, which in turn can damage the hepatocyte cells, decreasing the work and function of the liver (Meurman *et al.*, 2007; Prasetiawan *et al.*, 2012).

Alanine transaminase (ALT) and aspartate transaminase (AST) are both enzymes synthesised in liver, kidney, cardiac and skeletal muscles, brain, and pancreas. AST is mainly cytoplasmic, while ALT is exclusively cytoplasmic with its values being indicators of hepatocellular integrity. ALT serum level is associated with acute hepatocellular involvement, and its changes are related to organic dysfunction (da Silva Caldeira *et al.*, 2014).

Hyperbaric oxygen treatment (HBOT) is the therapeutic choice in liver transplantation, acute liver injury, non-alcoholic steatohepatitis, fibrosis and liver cancer (Oter *et al.*, 2005; Segal *et al.*, 2007; Sun *et al.*, 2018). HBOT acts as a protective agent by increasing the mitochondrial function and decreasing the ischemia-reperfusion in liver parenchymal tissues (da Silveira *et al.*, 2014). HBOT can enhance the amount of dissolved oxygen form, so that it will be easily accepted by the tissues. The use of HBOT will raise vascularisation and tissue perfusion, so that it will be able to supply oxygen to infected tissue (Huda, 2010). Therefore, it is the interest of this study to investigate the impact of HBOT to hepatocellular liver function in immunosuppressed rats with oral candidiasis by measuring the ALT and AST levels.

MATERIALS AND METHODS

This study was a post-test only control group design. The use of Wistar rats in the study has been approved by the Ethics Commission, Faculty of Dentistry, Universitas Hang Tuah, Surabaya, Indonesia (Ref. no: EC/010/KEPK-FKGUHT/VII/2019). Twelve 6-month-old male Wistar rats with body weight around 200 g to 250 g were divided randomly into three groups: K− (normal/healthy rats), K+ (oral candidiasis immunosuppressed rats) and P (oral candidiasis immunosuppressed rats treated hyperbaric oxygen). Immunosuppressed rats were made by giving dexamethasone 0.5 mg/day and tetracycline 1%/day orally. Then, the dose at the 4th day were reduced at 10% for dexamethasone and tetracycline, and the rats were induced with 0.1 cc of *Candida albicans* (ATCC-10231) 6×10^8, applied on the dorsum tongue of rats using sterile cotton bud three times a week for two weeks (Pargaputri & Andriani, 2018; Andriani & Pargaputri, 2019).

HBOT was given to P group for five consecutive days. During HBOT, the rats were still given tetracycline 0.1 mg/day to prevent bacterial infection (Andriani *et al.*, 2017). The rats were placed in a monoplace chamber. The pressure was increased up to 2.4 Atmospheres Absolute (ATA) and pure oxygen (100%) were flowed for 30 minutes at 3 intervals of 5-minute breathing normal air. After that, the pressure was reduced to primary condition (1 ATA) (Majdina *et al.*, 2016). The blood of all rats, about 3 cc, in each group was taken from their heart using syringe, then centrifuged to obtain the blood serum to count the ALT and AST levels.

Statistical analyses were done with Lavene statistical test to perform homogeneity of the data. The statistical one-way ANOVA test were used to show the different levels of ALT and AST between groups. The post-hoc least significant different (LSD) test was used to show the significant difference among each group.

RESULTS AND DISCUSSION

The result of the present study showed that the highest average value of ALT and AST levels was in the K+ group, while the lowest average value was in the K− group (Table 1).

Table 1 Average value (mean) and standard deviation (SD) of ALT and AST levels on each group

	ALT (Mean ± SD)	AST (Mean ± SD)
K−	110.25 ± 23.9	136.75 ± 33.9
K+	154.25 ± 9.5	165.50 ± 16.7
P	123.50 ± 18.2	151.75 ± 15.2

Table 2 LSD test on ALT levels

Groups	K−	K+	P
K−	–	0.006*	0.325
K+	0.006*	–	0.030*
P	0.325	0.030*	–

Note: * $p < 0.05$

Table 3 LSD test on AST levels

Groups	K−	K+	P
K−	–	0.162	0.448
K+	0.162	–	0.485
P	0.448	0.485	–

There was significant difference of ALT levels in K− groups compared with K+ group, and K+ group compared with P group (Table 2). However, there was no significant difference of AST levels between each group (Table 3).

The elevation of ALT and AST levels was associated with damage to hepatocellular integrity through persistent necroinflammation and also with the amount of injured cells (Oter *et al.*, 2005; Hall & Cash, 2012; Aleya & Berawi, 2015; Rosida, 2016). In the present study, ALT and AST levels in P group decreased nearly to the values of healthy rats group (K−), compared with immunosuppressed rats with oral candidiasis group (K+) (Figure 1). HBOT, besides being able to reduce the fungal infections also has a good impact on the injured liver function (Oter *et al.*, 2005; Segal *et al.*, 2007). Therefore, HBOT has become the therapeutic choice for liver transplantation, acute liver damage, non-alcoholic steatohepatitis, fibrosis and liver cancer (Sun *et al.*, 2018). HBOT can also be an adjuvant therapy which can increase the liver function on septic rats (Oter *et al.*, 2005). HBOT has a role as protective agent by reforming mitochondrial function and degrading ischemic on liver parenchymal tissue (da Silveira *et al.*, 2014). HBOT will produce reactive oxygen species (ROS)

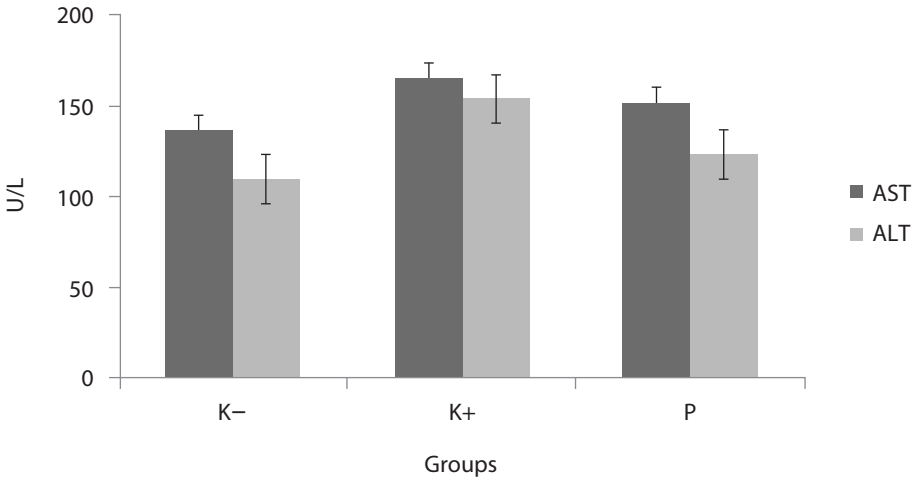

Fig. 1 ALT and AST levels of the research groups.

which play imperative role in pathogenesis of the disease. ROS has been reported as one of the crucial agents causing the liver dysfunction. However, ROS from HBOT has therapeutic effects such as antibacterial effect and can promote improvement of cellular function. The rise of ROS is accompanied by the rise of lipid peroxidation level. However, oxygen pressure that is exerted at 2.4 ATA can reduce the rise of lipid peroxidation, necrosis, and prevent the decease of hepatocytes (Oter *et al.*, 2005; Sun *et al.*, 2018).

Previous in vitro study showed that HBOT can stimulate hepatocytes proliferation through normalisation of localisation Mrp-2 to apical membrane (Sun *et al.*, 2018). Furthermore, HBOT can stabilise energy metabolism by increasing the oxygen transport to the injured liver tissues (Mizugichi *et al.*, 2005). HBOT can decrease malondialdehyde (MDA) and enhance the antioxidant activity such as glutathione and superoxide dismutase, which promotes the regeneration of liver cells (Nagamine *et al.*, 2004).

The levels of AST showed no significant differences between each group (Table 3). It could be interpreted that the administering of immunosuppression drugs in the present study had not caused serious liver damage and it did not significantly inhibit liver function. However, the increase of AST levels in K+ compared with K− and P group, might indicate hepatocytes damage. Further study is needed to investigate the hepatocytes of immunosuppressed rats that could have direct link with hepatocellular activity treated with hyperbaric oxygen.

CONCLUSION

Based on the present study, it can be concluded that HBOT 2.4 ATA given for five days, affected the ALT and AST levels of immunosuppressed rats with oral candidiasis. ALT and AST levels experienced a change in approaching the value of the healthy rats.

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