ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 16, Issue, 03, pp. 27635-27637, March, 2024
DOI: https://doi.org/10.24941/ijcr.46899.03.2024

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

ANTIOXIDANTAND ANTIGENOTOXIC EFFECT OF ALPHA LIPOIC ACIDIN OBSTRUCTIVE JAUNDICE IN RATS

[1]*Tülay DİKEN ALLAHVERDİ, [2]Ertuğrul ALLAHVERDİ and [3]Pınar AKSU KILIÇLE

[1]Kafkas University Department of General Surgery, KARS
[2]Kafkas University Department of Orthopedics and Traumatology, KARS
[3]Kafkas University Department of Biology, KARS

ARTICLE INFO

Article History:
Received 14th December, 2023
Received in revised form
20th January, 2024
Accepted 24th February, 2024
Published online 30th March, 2024

Key words:
Alpha Lipoic Acid, Obstructive Jaundice, Bilirubin.

***Corresponding author:**
Tülay DİKEN ALLAHVERDİ

ABSTRACT

Les bassins versants du Burkina Faso, cruciaux pour l'approvisionnement en eau de surface, subissent une dégradation caractérisée par une diminution des superficies des plans d'eau. Cette tendance alarmante a motivé, la présente étude, dont l'objectif est d'analyser l'évolution temporelle et spatiale des plans d'eau du bassin versant du Lac Bam. La méthodologie adoptée repose sur une analyse diachronique des images Landsat des années 1986, 2000 et 2014. Les résultats obtenus révèlent une disparité morphologique de l'espace occupé par les plans d'eau au cours de la période étudiée. En effet, ces plans d'eau sont passés d'une superficie de 2885,67 hectares en 1986 à 1105,75 hectares en 2000, pour atteindre 618,37 hectares en 2014, soit un taux moyen de régression annuel de 2,80% en 28 ans. Quant au réservoir du lac, il a également subi une régression significative de sa superficie et de son périmètre au cours de la même période. Le périmètre du lac a diminué passant de 64,77 kilomètres en 1986 à 48,30 kilomètres en 2000, puis à 42,38 kilomètres en 2014. Parallèlement, sa superficie a également connu une diminution, passant de 853,67 hectares en 1986 à 585,11 hectares en 2000, pour finalement atteindre 349,63 hectares en 2014. Ces résultats mettent en évidence une évolution préoccupante de la dynamique des plans d'eau du bassin versant du Lac Bam, soulignant ainsi l'urgence d'identifier les facteurs sous-jacents à cette régression et de proposer des mesures appropriées pour une gestion durable de ces ressources en eau.

Citation: ***Tülay DİKEN ALLAHVERDİ, Ertuğrul ALLAHVERDİ and Pınar AKSU KILIÇLE.*** **2023.** "Antioxidantand Antigenotoxic Effect of Alpha Lipoic Acidin Obstructive Jaundice in rats*". International Journal of Current Research*, 16, (03), 27635-27637.

INTRODUCTION

Obstructive jaundice is a mechanical obstruction due to a tumor, stone, inflammation and many other extrahepatic or intrahepatic bile duct pathologies and results in accumulation of bile in liver cells and bile ducts(1). Toxic substances that should have been excreted by the bile accumulate in the blood as a result of the ensuing disruption in the enterohepatic cycle. This high toxic substance level causes many complications such as hepatic dysfunction, immunosuppression and hypotension. Obstructive jaundice has a high mortality and morbidity rate due to its complications (1,2,3). Alpha lipoic acid is a molecule with antioxidant characteristic. Lipoic acid is synthesized by lipoic acid synthase found in mitochondria in physiological systems (4). Alpha lipoic acid derivatives react with oxygen radicals and remove them from the environment (5,6). Alpha lipoic acid has also been shown to decrease fibrosis by stopping the PAI-1 inhibitor that plays a role in the fibrosis process (7). We aimed to investigate the effect of alpha lipoic acid on obstructive jaundice by intraperitoneal administration in rats with experimental obstructive jaundice in this study.

MATERIALS AND METHODS

The study was conducted after obtaining permission from the Kafkas University Animal Trials Local Ethics Committee (KAÜ-HADYEK - 2012-31).

Animals: We used 24 Wistar albino female rats with a live weight of 250-300 g divided into 3 groups of 8 animals.

Group I: Sham group (the group where only laparotomy was performed).

Group II: Alpha lipoic acid (a-LA) group (the group administered alpha lipoic acid at a dose of 75 mg/kg intraperitoneally together with an obstructive jaundice model),

Group III: Control group (the group where only the obstructive jaundice model was used),

Surgical procedure: The rats in all study groups were kept in the same laboratory environment for one week before the

experiment and were fed standard rat food *ad libitum*. They were then anesthetized by using a combination of intraperitoneal 10 mg/kg xylazine HCl (Rompun 2%, Bayer - Turkey) and 80 mg/kg ketamin HCl (Ketasol, 50 mg/ml, inj., İnterhas, Turkey). Each animal was placed on the operation table in the supine position and the ventral abdominal region was prepared for aseptic surgery. The anterior abdominal wall was shaved and site cleaning was performed with povidone iodine. The abdomen was entered with median laparotomy. The main bile duct was located and left as is in the Sham group. The main bile duct was again located in Group II and Group III. The bile duct was ligated in both Group II and III. The layers were then anatomically closed with 5/0 silk. The abdominal suture line was cleaned with povidone iodine. We then administered daily 50 mg/kg/day Alpha lipoic acid (a-LA) intraperitoneally (IP) for ten days. Blood was drawn on the postoperative 3rd, 5th and 10th days and the animals were sacrificed by hypovolemia

Cytogenetic Study: The femoral bones of the sacrificed rats were removed. After the bones were cleaned thoroughly from muscles, the femur bone was cut from both ends and the bone marrow was transferred to a centrifuge tube containing 3 ml of calf serum using a syringe. The tubes with bone marrow sample were centrifuged at 2000 rpm for 5 minutes. The supernatant was thrown away. A drop of calf serum was added to the remaining part in the tube and suspended. A drop of this sample was smeared on clean slides. These slides were air dried and fixed in methyl alcohol for 10 minutes. Bone marrow preparations were evaluated with the method first developed by Schmid (8). Fixed preparations were first stained with 0.25% May-Grünwald stain for 5 minutes and washed with pure water. Then they were again stained with 0.125% May-Grünwald stain for 5 minutes and washed in pure water. Finally, they were stained with 20% Giemsa stain for 30 minutes and washed and left to dry. The preparations were examined under an Olympus CX21 light microscope at 1000x magnification and 1000 PCEs (polychromatic erythrocytes) were randomly counted from the preparation. The number of MNPCEs (micronucleated polychromatic erythrocytes, figure 1) was identified and the percentages determined.

Statistical analysis: The SPSS18 software program was used for the statistical analyses of all data obtained from the study. Mean and standard deviations, which are the central distribution criteria, were calculated in the statistical analysis and the intergroup differences of nominal values were determined by using Fisher's definite chi-square test. P values <0.05 were accepted as significant. The Kruskal-Wallis test was used for the analysis of the values obtained by measurement and the significance between the 2 groups for parameters found to be statistically significant was evaluated with the Mann-Whitney U test with Bonferroni correction; P values <0.015 were accepted as significant.

RESULTS

Cytogenetic Results: The number of MNPCEs was found to increase in the group with main bile duct ligation and the group with Ligation + alpha lipoic acid (50 mg/kg/day) compared to the Sham Group with Laparotomy only ($p<0.001$). Besides, administration of alpha lipoic acid together with ligation was found to show a protective effect by decreasing the MNPCE count.

Table 2 presents the MNPCE counts, percentages and group means from a total of 10000 PCE cells counted in each group. (Table1).

DISCUSSION

Obstructive jaundice can develop due to various causes such as benign and malignant tumors of the bile duct, biliary surgery and biliary pancreatitis and results in structural and functional disorder of the hepatobiliary system. It can cause serious complications such as sepsis, renal and hepatic dysfunction, gastrointestinal hemorrhage, coagulopathy, cardiovascular dysfunction, and peripheral vasoconstriction. These complications are among important problems of general surgery due to the mortality and morbidity they cause (1,2). We therefore focused on obstructive jaundice in this study and aimed to investigate the effect of intraperitoneal alpha lipoic acid administration in rats with experimentally-induced obstructive jaundice.

The endotoxemia that develops in obstructive jaundice triggers a pro-inflammatory process and results in the production of free oxygen radicals (1, 2, 3, 4). Glutathione plays a major role in cellular defense against oxygen radicals. MDA is the final product of lipid peroxidation. MDA levels increase in tissue damaged by lipid peroxidation (4,6). The activity of enzymes such as glutathione, peroxidase and superoxide dismutase that remove free oxygen radicals from the environment decreases and thus sensitivity to the tissue damage created by free oxygen radicals increases in rats with induced obstructive jaundice (9). Alpha lipoic acid is a molecule with antioxidant characteristic. Lipoic acid is synthesized by lipoic acid synthase found in the mitochondria in physiological systems (10). Alpha lipoic acid derivatives react with oxygen radicals and remove them from the environment and also protect the cell membrane by reacting with vitamin C and glutathione. It also contributes to the recycling of vitamin E (11,12). Aydın *et al*.(13) studied the protective effect of lycopene, a carotenoid in many fruits and vegetables, against oxidative stress and DNA damage in Wistar albino rats where experimental bile obstruction had been created and reported lycopene to significantly decrease DNA damage and improve the liver and kidney damage seen in rats with obstructive jaundice. Tokaç *et al*.(14) investigated the effects of curcumin, known to have antioxidant characteristics, against DNA damage and oxidative stress created by bile duct ligation in Wistar albino rats and reported curcumin to decrease DNA damage and possibly have a protective effect on cholestasis-caused damage in the rat liver and kidney tissues. Dadhania *et al*. (15) investigated the possible protective effects of alpha lipoic acid against intestinal toxicity created with methotrexate in Sprague-Dawley rats and reported that alpha lipoic acid decreased DNA damage and oxidative stress with a protective effect. Our cytogenetic data showed a significant difference between Group I, II and III for the number of micronuclei ($p<0.001$). Alpha lipoic acid had a protective effect with a decreased number of micronuclei in Group II compared to Group III. We are aware that drugs have side effects in addition to therapeutic effects. We therefore prefer to use drugs at a therapeutic dose in daily practice to decrease the side effect incidence. However, we decided to conduct our study with a moderate alpha lipoic acid dose as determining a drug's effect using various doses can potentially provide a more objective approach.

Table 1. Groups, MNPCE Group Means and MNPCE (%) rates

Groups	Total PCE	MNPCE	MNPCE (%)	Group Mean
Sham Group that Underwent Laparotomy Only (n=10)	10000	32	0.32	3.2
Group that Underwent Bile Duct Ligation (n=10)	10000	165	1.65	16.5
Ligation + Alpha Lipoic Acid (50 Mg/Kg/Day) (n=10)	10000	76	0.76	7.6

PCE: Polychromatic erythrocyte, MNPCE: Micronucleated Polychromatic Erythrocyte

Alpha lipoic acid has been reported to have beneficial effects in various pathologies such as atherosclerosis, diabetes, neuronal degeneration, joint disorders and multiple sclerosis (16). We were similarly able to show that alpha lipoic acid had beneficial effects in obstructive jaundice, a condition we frequently encounter, in a rat model. We believe this drug that is commonly used for many disorders in the clinic can also be used in obstructive jaundice cases in the future. We hope that our study will guide future studies on the subject. In conclusion, we believe that alpha lipoic acid contributes to the prevention of obstructive jaundice when administered intraperitoneally in rats with experimental obstructive jaundice.

REFERENCES

1.Su CH, P'eng FK, Lui WY. Factors affecting morbidity and mortality in biliary tract surgery. World J Surg. 1992; May-Jun; 16(3):536-40.

2.Liu TZ, Lee KT, Chern CL.*et al*. Free radical-triggered hepatic injury of experimental obstructive jaundice of rats involves overproduction of proinflammatory cytokines and enhanced activation of nuclear factor kappaB. Ann Clin Lab Sci. 2001;Oct;31(4):383-90.

3.Papakostas C, Bezirtzoglou E, Pitiakoudis M. *et al*. Endotoxinemia in the portal and the systemic circulation in obstructive jaundice. Clin Exp Med. 2003;Sep;3(2):124-8.

4.Padillo FJ, Muntane J, Montero JL.*et al*. Effect of internal biliary drainage on plasma levels of endotoxin, cytokines, and C-reactive protein in patients with obstructive jaundice. World J Surg. 2002;Nov;26(11):1328-32. Epub 2002 Sep 26.

5.Wang P, Gong G, Wei Z, Li Y. Ethyl pyruvate prevents intestinal inflammatory response and oxidative stress in a rat model of extrahepatic cholestasis. J Surg Res. 2010; May 15;160(2):228-35. doi: 10.1016/j.jss.2009.03. 027. Epub 2009 Apr 21.

6.Akca T, Canbaz H, Tataroglu C. *et al*. The effect of N-acetylcysteine on pulmonary lipid peroxidation and tissue damage. J Surg Res. 2005; Nov;129(1):38-45.

7.Min AK, Kim MK, Seo HY.*et al*. Alpha-lipoic acid inhibits hepatic PAI-1 expression and fibrosis by inhibiting the TGF-beta signaling pathway. Biochem Biophys Res Commun. 2010 Mar 12;393(3):536-41. doi: 10.1016/j.bbrc.2010.02.050. Epub 2010 Feb 12

8.Schmid W. The micronucleus test. Mutat Res. 1975;Feb;31(1):9-15.

9.Ogetman Z, Dirlik M, Caglikulekci M.*et al*. The effect of aminoguanidine on blood and tissue lipid peroxidation in jaundiced rats with endotoxemia induced with LPS. J Invest Surg. 2006;Jan-Feb;19(1):19-30.

10.Çakatay U. Pro-oxidant actions of alpha-lipoic acid and dihydrolipoic acid. Med Hypotheses. 2006;66(1):110-7. Epub 2005 Sep 13.

11.Rimm EB, Stampfer MJ, Ascherio A. *et al*. Vitamin E consumption and the risk of coronary heart disease in men. N Engl J Med. 1993;May 20;328(20):1450-6.

12.Stampfer MJ, Hennekens CH, Manson JE. *et al*. Vitamin E consumption and the risk of coronary disease in women. N Engl J Med. 1993 May 20;328(20):1444-9.

13.Aydın S, Tokaç M, Taner G. *et al*. Antioxidant and antigenotoxic effects of lycopene in obstructive jaundice. J Surg Res. 2013 Jun 15;182(2):285-95. doi: 10.1016/j.jss.2012.10.031. Epub 2012 Nov 7.

14.Tokaç M, Taner G, Aydın S. *et al*. Protective effects of curcumin against oxidative stress parameters and DNA damage in the livers and kidneys of rats with biliary obstruction Food Chem Toxicol. 2013 Nov;61:28-35. doi: 10.1016/j.fct.2013.01.015. Epub 2013 Jan 29.

15.Dadhania VP, Tripathi DN, Vikram A. *et al*. Intervention of alpha-lipoic acid ameliorates methotrexate-induced oxidative stress and genotoxicity: A study in rat intestine. Chem Biol Interact. 2010 Jan 5;183(1):85-97. doi: 10.1016/j.cbi.2009.10.020.

16.Ozbal S, Ergur BU, Erbil G, Tekmen I, Bagriyanik A, Cavdar Z.(The effects of α-lipoic acid against testicular ischemia-reperfusion injury in Rats. Scientific World Journal. 2012; https://doi.org/10.1100/2012/489248.

****