



Using Local Estrogen with Implication of Modified Guillotine Technique to Improve Regenerative Process of pPartially Resected Liver in Rabbits

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ABSTRACT

This research planned to determine the effect of local estrogen on the regeneration of partially hepatectomized rabbits. Twelve male rabbits were included in the present study, hereby allocated randomly into two equal groups. In the control group, partial hepatectomy was performed with the modified guillotine technique. In the treatment group, the steps are similar to the control (included partial hepatectomy) with the application of estrogen (0.2 mg). Macroscopic, laparoscopic, histopathological and immunohistochemical changes were recorded at 1, 2, and 4 weeks. Clinically, all rabbits survived a long period of experiment. Grossly, in the second group, 7 days post-surgery, there were no signs of inflammation and no intraoperative fluid. The results of laparoscopy 30 days in the control group indicated a change in liver color with severe adhesion between the liver and viscera; in the treatment group, the results indicated the presence of mild adhesion between the liver and viscera and normal liver structure and color. Histopathological results at 7 days in the control group showed cell swelling, congestion, and inflammatory cells, whereas the results at 30 days exhibited mild congestion of sinusoid, binucleate hepatocyte and fibrosis. In the treatment group, the results at 7 days indicated the presence of normal hepatocytes, fibrosis, and mild congestion in the sinusoid. At 30 days, results indicated the presence of normal hepatocytes, sinusoid and central veins. Immunoreactivity of tumor necrosis factor alpha (TNF- α) in the control group at 14 days indicated high expression, indicated as brown granules in hepatocytes, whereas in the treatment group at 14 days the expression was very mild as brown granules in hepatocytes. Based on laparoscopic, histopathological and immunohistochemistry changes, the application of estrogen on the hepatectomized site is beneficial and feasible to improve the regenerative process of the liver in rabbits.

Keywords: Estrogen, Modified guillotine, Partial hepatectomy, Rabbit, TNF- α .

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INTRODUCTION

The liver plays an important function in immune support and metabolism of food and other important functions related to the activities of body physiological processes. These include blood volume regulation, cholesterol and fat homeostasis and lastly, endocrine regulation of growth pathways (Yovcheva *et al.*, 2012; Trefts *et al.*, 2017; Kilimci, 2020).

Liver affections represent global health challenges, and liver dysfunction may result from overnutrition, tumor, trauma or infection or fibrosis (Bhavsar *et al.*, 2021; Bürgisser *et al.*, 2021). In case of cholestasis resulting in ductal distension. And the biliary system is infected with the bacteria, resulting in ascending hepatitis (Negasee, 2021). Partial hepatectomy (lobectomy) is a surgical procedure that is

performed in veterinary medicine for many purposes, such as tumor excision, repair of trauma and liver transplantation (Tüzün *et al.*, 2015; Tao *et al.*, 2021; Wu *et al.*, 2023), and liver regeneration after trauma (Olthof *et al.*, 2017). Also, this operation was performed to estimate the different degrees of liver warm ischemia-reperfusion trauma and its regeneration and partial resection of the caudal lobe of the liver in rabbits. Anatomically the rabbit represented a perfect model for experimental surgical techniques because it had a larger volume of gallbladder than other animals and functions closer to the human liver (Páramo *et al.*, 2017).

Healing and regeneration of the liver, including different cytokines and signaling events to restore lost hepatic mass. This event delayed, after partial

hepatectomy, potential therapeutic targets to promote successful liver regeneration (Jeong *et al.*, 2023). Sex hormones affect the healing process of wounds; estrogen is one of these hormones. A wide range of cutaneous cell types (e.g., fibroblast, endothelial, epithelial, and inflammatory) expressed estrogen receptors, indicating potential estrogen responsiveness (Al-Kadhimi and Ghani 2015; Voboda *et al.*, 2018). Many workers demonstrate that the local application of estrogen on skin diminished the delays in wound healing (Ashcroft *et al.*, 1999; Ashcroft *et al.*, 2003). Estrogen directly affects the function of neutrophil cells also related to cytokines in growth factor production (Khan and Ansar, 2015).

Laparoscopy has many advantages over the traditional method: short stay, animal return to full activity, painless method, noninvasive less stress, and many surgical interventions can be performed, such as cystectomy in dogs (Alhamdany and Alkattan, 2019) and nephrectomy in cats (Alkattan *et al.*, 2014). Laparoscopic hepatectomy is rarely performed in veterinary surgery and represents a real challenge due to the expense and complexity of the procedure with the risk of great bleeding (Yoshida *et al.*, 2019).

Tumor necrosis factor alpha (TNF- α) plays an important role as a pathological component of the same disease as autoimmune diseases and binds with different receptors to take its effects and contribute to some cellular responses, such as cell differentiation, regeneration, cell survival and proliferation (Jang *et al.*, 2021). It also plays an important role in the pathology of some diseases, such as liver fibrosis, cancer and the treatment of fatty liver changes (Vachliotis *et al.*, 2023). This study aimed to determine the effect of local estrogen on the regeneration of partially hepatectomized rabbits.

MATERIALS AND METHODS

Ethical approval

This research was approved by Animal Care and Committee procedures at the University of Mosul, College of Veterinary Medicine No: UM.Vet.VET.2024.075.

Study preparation

This research conducted on twelve male rabbit their weight and age were (2 ± 0.4 kg), (6 ± 0.3 months), respectively rabbits accommodated in the animal house in collage of veterinary medicine university of Mosul.

A protocol of anesthesia including a mixture of 10% ketamine hydrochloride (30 mg/kg BW) and 2% xylazine (5 mg/kg BW). The operative rabbits were prepared aseptically, according to routine principle line of surgery incision done at the left. Para costal approach: the liver was determined, then the left lobe

was exteriorized, and by using Doyen forceps, a portion of the liver about 3 by 1cm was identified and ligated by using a modified guillotine suture technique with polyglactin 910 Vicryl 2/0 suture to demarcate the portion of the liver (two striated needles were introduced in the same thread and inserted simultaneously at the liver parenchyma to obtain six pieces of the same thread to ligate the liver parenchyma; every two thread pieces were connected together as shown in Fig. 1). In group C (control), the resected site of liver lifted without any treatment (Fig. 2, A), whereas in the second group treated with local application of 0.2 ml of estrogen (Fig. 2, B). The subcutaneous tissue and skin closed routinely.



Fig.1: Represented modified guillotine suture technique (MG) for ligation hepatic tissue (yellow L).

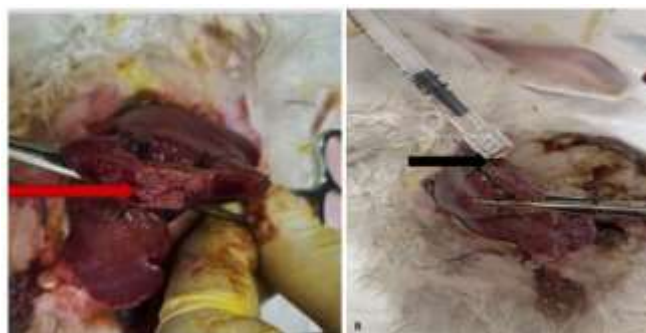


Fig. 2: A, represented partial hepatectomy without treatment (control) (red arrow). B, represented local application of estrogen on hepatectomized liver (black arrow).

Macroscopic, laparoscopic, histopathological and immunohistochemical investigations were estimated to determine the effect of estrogen use on the regeneration of the liver at the periods of 1, 2 and 4 weeks post-surgery. In both groups, two ports to introduce laparoscopic instruments (KARL STORZ Endoscopy America, Inc., Germany). CO₂ gas was delivered smoothly into the abdominal cavity of the rabbit to produce pneumoperitoneum at 6 mmHg at a flow rate of about 2.4 L/min (Albadrany, 2009); the

manipulation and visualization were satisfactory in all rabbits during the period of investigation to diagnose the status of the liver after partial hepatectomy. Then gross pathological investigation was performed and tissue samples collected without euthanizing the rabbits. The collected tissue was sectioned and processed to obtain stained slides for histopathological estimation according to Luna (1968), and immunohistochemistry estimation was achieved by using the avidin-biotin technique for expression of TNF α and primary antibodies anti-TNF monoclonal antibodies according to Jang *et al.*, (2021).

RESULTS

In this research, clinical examination indicated that all experimental rabbits in the two experimental groups survived the period of the experiment with normal activity and health, with no major complications in any operative animals and no signs of loss of appetite, and the wounded site seemed clean and healthy without pain signs. There was no presence of stitch abscess, infection or signs of jaundice.

Grossly, in the control group, 7 days after the results showed the site of hepatectomy with the presence of surgical thread and no intraoperative fluid (Fig. 3). At 30 days there was severe adhesion between the hepatectomy site and abdominal viscera (Fig. 4). In the treatment group with estrogen, 7 days post-surgery the investigations showed no signs of inflammation, presence of intraoperative fluid or blood, or bleeding at and around the hepatectomized site, and also the surgical thread was seen (Fig. 5). Whereas at 30 days there was mild adhesion at the operative site (Fig. 6).

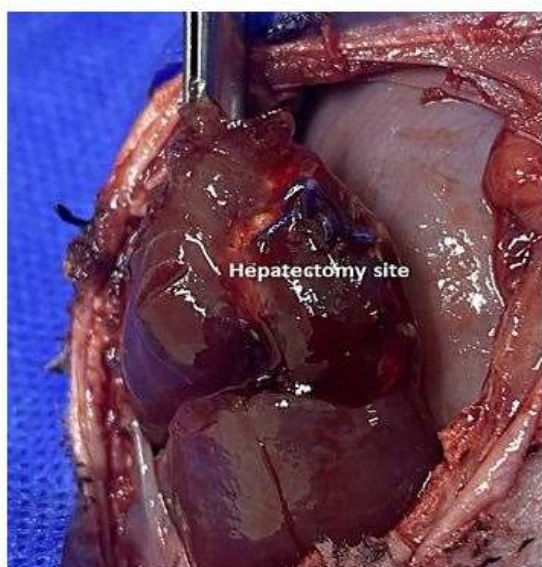


Fig.3: Gross section of the site of operation 7 days post-surgery in control group demonstrated site of hepatectomy with the presence of surgical thread

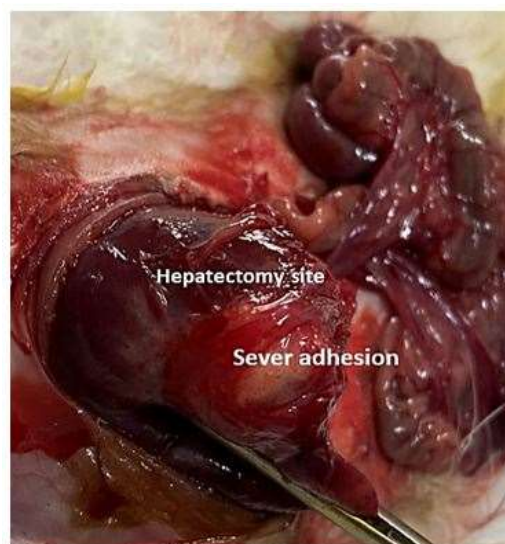


Fig.4: Gross section of the site of operation 30 days post-surgery in control group demonstrated site of hepatectomy with sever adhesion.

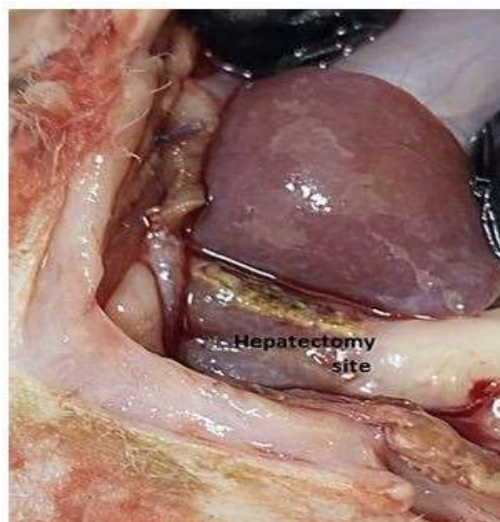


Fig.5: Gross section of the site of operation 7 days post-surgery in treatment group demonstrated site of hepatectomy.

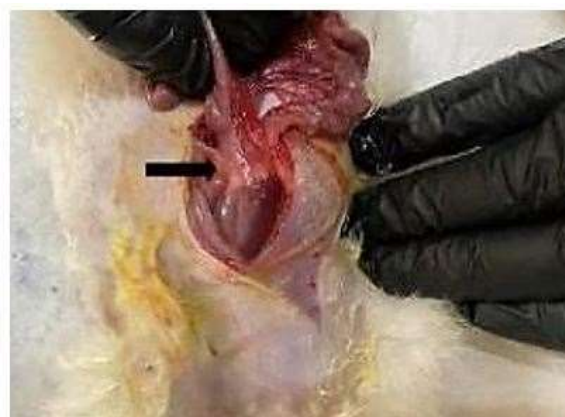


Fig.6: Image represented gross section of the site of operation 30days post-surgery in treatment group. group demonstrated site of hepatectomy with mild adhesion .

Laparoscopic changes in the first group exhibited no fluid intraoperatively; at 30 days, the hepatectomized site was pale in color with severe adhesion between liver tissue and viscera (**Fig. 7**). In the second group, at the month post-surgery, laparoscopic investigation indicated the presence of mild adhesion between the liver, viscera and abdominal wall and no abnormality in the structure configuration of the liver (**Fig. 8**).

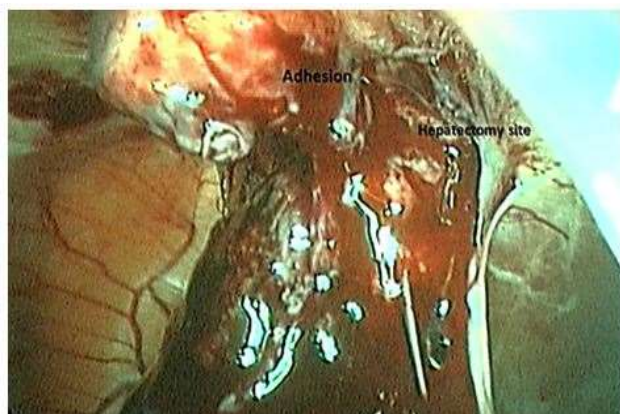


Fig.7:. Laparoscopic Image the site of operation exhibited hepatectomized area at 30 days post-surgery in control group.



Fig.8: Laparoscopic Image the site of operation exhibited hepatectomized area at 30 days post-surgery in treatment group.

Histopathological changes 7 days post-treatment in the control group was represented by the presence of cell swelling, congestion, infiltration of inflammatory cells, and fibrosis (**Figs. 9.1 and 2**). On day 14, the changes exhibited the presence of mild vacuolar degeneration, congested blood vessels, and fibrosis; H&E (**Fig. 10, 1**): 100x, mild vacuolar degeneration, and congested sinusoid (pyknosis of hepatocyte); H&E (**Fig. 10, 2**): 400x.

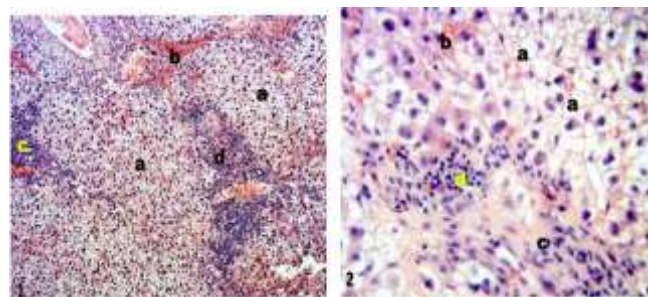


Fig.9: Histological surgical section of liver in control (7days), show a- acute cell swelling b- congestion c- infiltration of inflammatory cells H&E, 1:100x,2:400x.

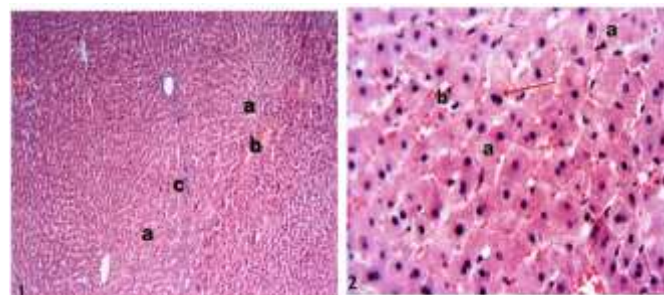


Fig.10: a- congested blood vessels c- fibrosis, H&E (Fig.10,1): 100x, mild vacuolar degeneration b- congested sinusoid, arrow (Pyknosis of hepatocyte) H&E (Fig.10,2): 400x.

At 30 days post-surgery, the changes indicated the presence of moderate congestion of blood vessels and fibrosis and pyknosis of some hepatocytes (**Fig. 11, 1**): mild congestion of sinusoid and fibrosis (presence of binucleate hepatocyte) (**Fig. 11, 2**).

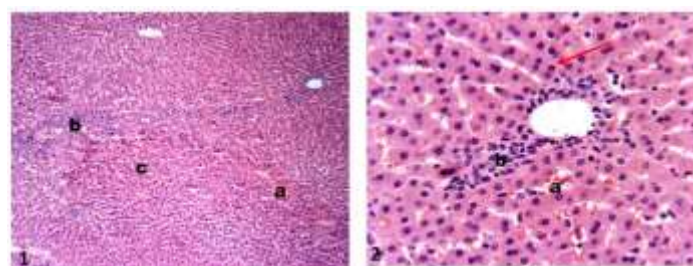


Fig.11: Histological surgical section of liver in control (30days) a. moderate congestion of blood vessels, b- intralobular fibrosis pyknosis of some hepatocyte, (Fig.11,1):H&E 100x., a. mild congestion of sinusoid b- intralobular fibrosis, arrow (presence of binucleate hepatocyte), (Fig.11,2):H&E 400x.

The histopathological changes on day 7 post-operation in the treatment group with estrogen, represented by the presence of normal hepatocytes, fibrosis, and infiltration of inflammatory cells (**Fig. 12, 1**), H&E 100x, normal hepatocyte, fibrosis, mild congestion in sinusoid, mild infiltration of inflammatory cells (**Fig. 12, 2**): H&E 400x. At 14 days, the changes represented by normal hepatocytes and pyknotic nuclei (increase in the number of Kupffer

cells) (**Fig. 13, 1**): H&E 100x, normal articular liver tissue, and mild congestion of sinusoid (increase in the number of Kupffer cells) (**Fig. 13, 2**): H&E 400x. At 30 days shown Normal hepatocyte, normal sinusoid, normal central vein (**Fig. 14, 1**): H&E 100x, (**Fig. 14, 2**): H&E 400x.

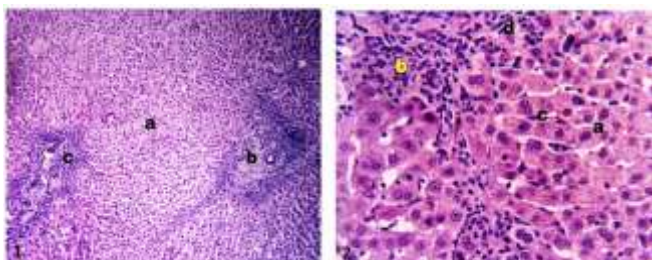


Fig.12: Histological surgical section of liver in treated group (7 days) a-normal hepatocyte b- fibrosis c- infiltration of inflammatory cells, (Fig.12,1): H&E 100x, a. normal hepatocyte, b- fibrosis, c- mild congestion in sinusoid, d- mild infiltration of inflammatory cells (Fig.12,2): H&E 400x.

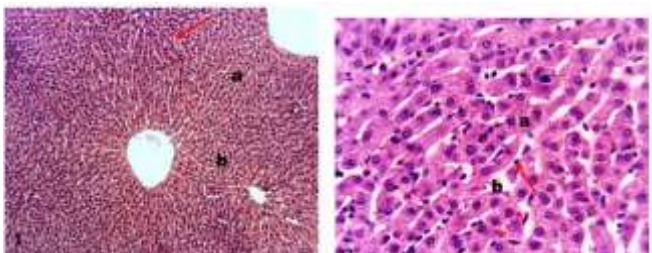


Fig.13: Histological surgical section of liver in treated group (14 days), shown a. normal hepatocyte architecture. b- pyknotic nuclei, arrow (increase number of Kupffer cells) (Fig.13,1): H&E 100x, a. normal architecture of liver tissue b- mild congestion of sinusoid, arrow (increase number of kupffer cells) (Fig.13,2): H&E 400x.

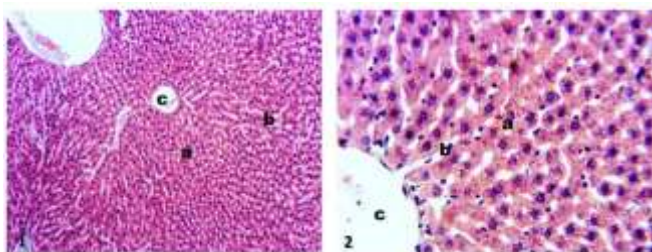


Fig.14: Histological surgical section of liver in treated group (30days), shown a. normal hepatocyte architecture, b- normal articular sinusoid c- normal central vein (Fig.14,1): H&E 100x, (Fig.14,2): H&E 400x.

The results of immunoreactivity expression of TNF- α in the control group at 7 days exhibited moderate expression as brown color granules in hepatocytes (cytoplasm and nucleus) (**Fig. 15**), whereas results at 14 days indicated high expression as brown color granules (**Fig. 16**) and mild expression as in hepatocytes

(cytoplasm and nucleus) at 30 days post-treatment (**Fig. 17**). In the treated group for 7 days, the results exhibited mild-moderate expression as brown color granules in hepatocytes (cytoplasm and nucleus) (**Fig. 18**) and very mild expression at 14 days (**Fig. 19**) and low expression at 30 days (**Fig. 20**).

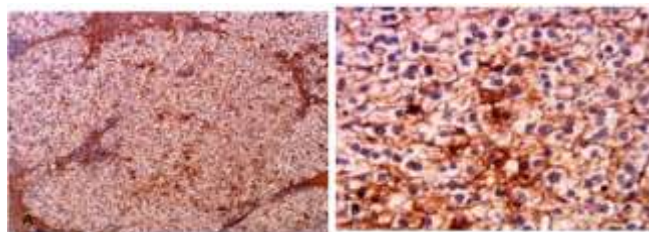


Fig.15: Immunoreactivity expression tumor necrosis factor in control group (TNF- α)7 days exhibited moderate expression as brown color granules in hepatocyte (cytoplasm and nucleus), A:100 x B:400 x.

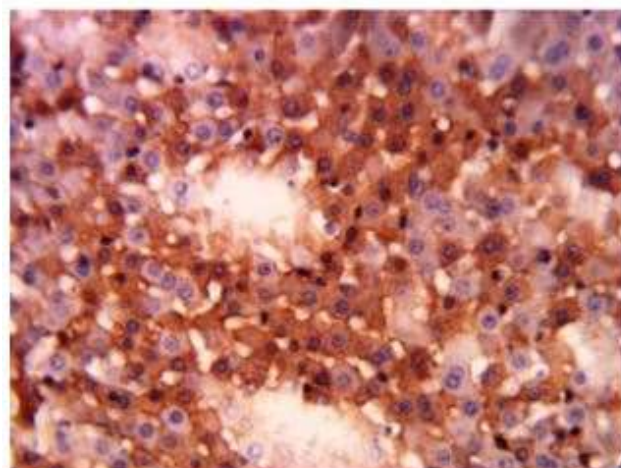


Fig.16: Immunoreactivity expression tumor necrosis growth factor in control group (TNF- α)14 days exhibited high expression as brown color granules in hepatocyte (cytoplasm and nucleus) 400x.

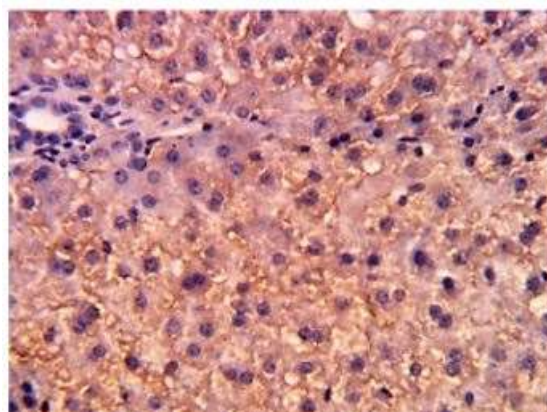


Fig.17: Immunoreactivity expression tumor necrosis growth factor in control group (TNGF)30 days exhibited mild expression as brown color granules in hepatocyte (cytoplasm and nucleus) 400x.

DISCUSSION

In the current trial, experimental rabbits underwent partial hepatectomy, the parenchyma ligated by a modified guillotine ligation technique. So, in this technique, the ligation was the perfect method for controlling bleeding during partial hepatectomy. Many workers demonstrated that the use of the 'clamp-crush' technique can safely transect the hepatic tissue and arrest the bleeding and prevent blood flow through the resected parenchyma after partial hepatectomy in dogs (Li *et al.*, 2018; Khalil *et al.*, 2022). Different methods were used to ligate the liver parenchyma during partial hepatectomy as the intracorporeal knotting technique during laparoscopic hepatectomy in dogs, which used a needle with silk suture material to ligate the lobe of liver (Zhang *et al.*, 2020).

On the other side, a simple method was used to arrest liver tissue bleeding by using a heat gun. This method does not depend on surgeon experience and skill as other techniques for ligation and dissection do (Alheani and Al-kennany, 2013). In the presence study, the outcome demonstrated that the modified guillotine technique fast and secure method for controlling bleeding without tearing parenchymal tissue by using Vicryl suture material. This agrees with other workers that use Vicryl without any complications (Alheani and Al-Kennany, 2013). All experimental rabbits remained alive throughout the experiment without effects on health condition, liver function, spontaneous activity or animals' behavior. This outcome is consistent with Drude *et al.*, (2016).

The topical application of estrogen enhances the healing process. In this group, there were neither inflammatory reactions nor intraoperative fluid. This result agrees with previous work that showed that the topical application of estrogen improves and promotes cutaneous wound healing; the estrogen reduces the inflammatory reaction reduces wound area and promotes regeneration of tissue (Mukai *et al.*, 2019). The use of estrogen topically in this study improves the healing process and may be due to reducing the size of the wounded area and stimulation to deposit new hepatic tissue. As this result is mentioned and aligned by other researchers (Al-Kadhimy and Ghani, 2015), enhancing the proliferation of hepatic cells is done through estrogen receptor α (Batmunkh *et al.*, 2017).

The topical estrogen interacts with some signaling pathways, including interplays between proteases and some growth factors; it plays an important role in new vessel formation (Rajabi and Rajabi, 2007). On the other hand, the use of topical estrogen reduces the occurrence of inflammatory reaction or abscessation. This outcome agrees with another study

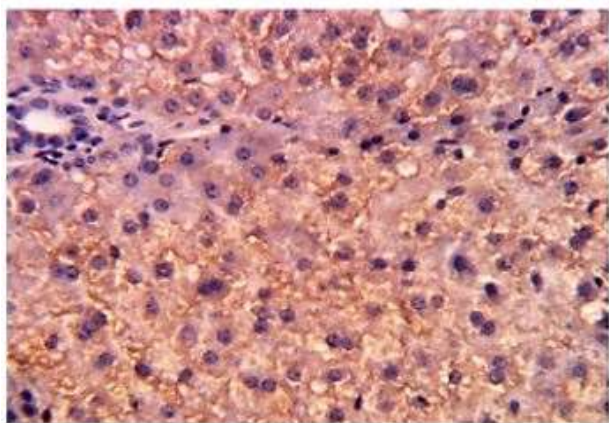


Fig.18: Immunoreactivity expression tumor necrosis growth factor in treatment group (TNF- α)7 days exhibited mild -moderate expression as brown color granules in hepatocyte (cytoplasm and nucleus) 400x.

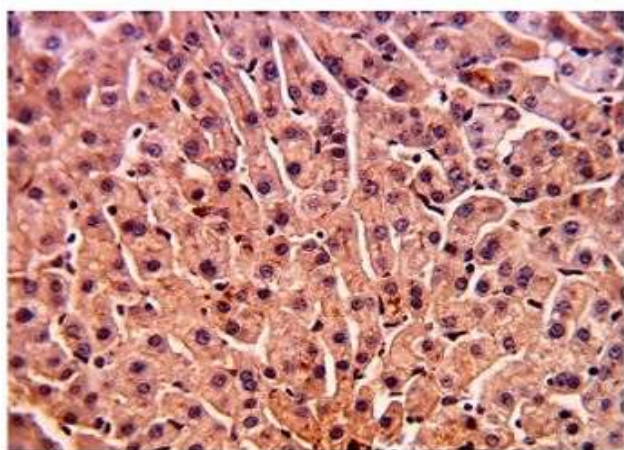


Fig.19: Immunoreactivity expression tumor necrosis growth factor in treatment group (TNF- α)14 days exhibited very mild expression as brown color granules in hepatocyte (cytoplasm and nucleus) 400x.

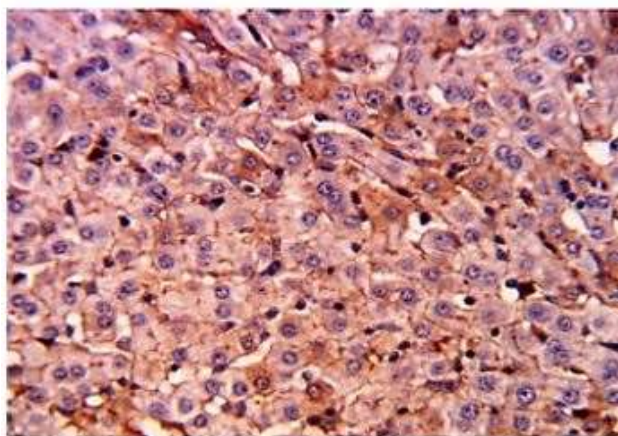


Fig.20: Immunoreactivity expression tumor necrosis growth factor in treatment group (TNF- α)30 days exhibited low expression as brown color granules in hepatocyte (cytoplasm and nucleus) 400x.

that used bioactive materials, such as aloe vera, to reinforce hernioplasty in rams (**Atiyah and Alkattan, 2024; Zedan et al., 2025**). Additionally, a therapeutic strategy may be approved to regulate metabolism and hepatocyte proliferation, using MSCs to achieve successful liver regeneration (**Jeong et al., 2023**). Regarding the histopathological section, we observed some cellular metabolic disturbances in the control group in all time frames. This finding is consistent with lesions that can also be found in clinically normal dogs in various organs, such as the prostate gland in healthy dogs (**Abed et al., 2023**).

The histopathological changes observed on day 7 post-operation in estrogen-treated groups included the presence of normal hepatocytes, fibrosis, and infiltration of inflammatory cells. By day 14, changes were characterized by normal hepatocytes, pyknotic nuclei (increased number of Kupffer cells), normal architecture of liver tissue, and mild congestion of sinusoids (hyperplasia of Kupffer cells). At 30 days, the findings showed normal hepatocytes, normal sinusoids, and a normal central vein. As time progressed from day 7 to day 30 of the experiment, we observed a reduction in cellular disturbances. These findings aligned with what had been mentioned, that estradiol significantly contributes to liver regeneration. In male rats, plasma estradiol levels increase within the first six hours following hepatectomy. This elevation is likely critical for initiating the early phase of liver regeneration (**Eagon et al., 1985**).

Tumor necrosis factor alpha (TNF α) is an inflammatory cytokine that plays a crucial role in the body. This protein is produced by macrophages and monocytes and is responsible for initiating signaling events within cells, leading to apoptosis or necrosis. It also plays significant roles in infection response and cancer (**Idris and Naismith, 2000**). Inhibiting TNF α is a critical event, and the impaired healing response associated with the absence of SLPI may be relevant for the treatment or prevention of inhibited wound healing; this aligns with **Ashcroft et al. (2012)**. The research outcome in the treatment group with estrogen indicated that the improvement in the regeneration process and the reduced expression of TNF α were due to the application of estrogen. This had a positive impact on the regenerative response and inhibited the local inflammatory reaction by downregulating migrating inhibitory factors (**Ashcroft et al., 2003**).

CONCLUSION

It can be concluded that, the modified guillotine ligation technique may advantage the method for liver resection for smaller mass lesions, such as abnormal growth or abscess and hepatic cyst, and the use of

estrogen directly on hepatectomized tissue has beneficial value to improve the regenerative process of hepatic tissue in rabbits. The present study provides a new model rabbit for establishing the way to treat liver affections in pet animals.

Acknowledgment

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Conflict of interest

We have declared no conflicts of interest.

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