DOI:10.22059/IJVM.2023.356822.1005374 Iranian Journal of Veterinary Medicine Original Article

Online ISSN: 2252-0554

Evaluating Immunomodulatory Effects and Cytokine Changes by Propranolol Following Surgical-Induced Stress in Male Rats

Milad Azarhosh[1], Ali Ghashghaei [2], Mehrdad Pooyanmehr [3*], Ali Maleki[4], Samad Alimohammadi [3]

1. Graduated of Veterinary Medicine, Faculty of Veterinary Medicine, Razi University, Kermanshah, Iran

2. Department of Clinical Sciences, Faculty of Veterinary Medicine, Razi University, Kermanshah, Iran

3. Department of Basic Sciences and Pathobiology, Faculty of Veterinary Medicine, Razi University, Kermanshah, Iran

4. Medical Biology Research Center, Health Technology Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran

Abstract

Background: Surgery through different mechanisms causes immunosuppression in the postoperative period.

Objectives: This study aimed to investigate the effects of preoperative administration of Propranolol on blood levels of Interleukin-2 (IL-2), Interferon-γ (IFN-γ), Tumor Necrosis Factor-α (TNF-α), and hematological parameters such as white blood cells (WBCs) and lymphocytes**.**

Methods: Forty-five Wistar male rats were divided into three groups. Group 1 (normal control) was injected with normal saline. Groups 2 and 3 were injected subcutaneously with 4 mg/kg of the Propranolol (P4) and 8 mg/kg of the Propranolol (P8), respectively. Blood samples were collected (before, immediately, 6, 2,4, and 72 hours after surgery). The levels of IL-2, IFN-γ, TNF-α, WBCs, and lymphocytes were determined. The data were analyzed by one-way ANOVA and Pearson test with a significant level of $P \leq 0.05$.

Results: The results showed a higher level of IL-2 in the P8 and P4 groups with a significant difference compared to the control group($P \leq 0.05$). TNF-α was decreased significantly in the P8 compared to the P4 and control groups ($P \leq 0.05$). The P4 has shown a lower level of IFN- γ compared to the P8 and control groups with a significant difference ($P \leq 0.05$).

Conclusions: It appears that Propranolol has considerable immunomodulatory effects on immune responses. Therefore, perioperative use of Propranolol may improve immune system function.

Keywords: IL-2, IFN- γ, TNF- α, Propranolol, Surgical Stress

Introduction

The practical function of innate and acquired immune defense mechanisms protects the body against pathogenic agents. Studies have shown that surgery affects specific and non-specific immune systems as a treatment (Yagawa & Tanigawa, 2017). It leads to metabolic, endocrine, and immunosuppression responses and is involved in causing complications such as infection and even tumor metastasis (Hari & Summers, 2018). Surgical stress causes the Hypothalamic-Pituitary-Adrenal (HPA) axis stimulation. Subsequently, it increases the secretion of Adreno-Cortico-Thropin (ACTH) and Glucocorticoids such as Cortisol, which carry out a significant role in the surgical effects on the immune system. The increase in ACTH and Cortisol is commensurate with the severity of surgical stress and may continue several days after surgery (Marko and Hamrahian, 2010). In the immunosuppression caused by surgery, cellular immunity

is often affected, and the number of circulating lymphocytes is decreased during surgery. The extent of this reduction depends on the type of surgery. When lymphocyte differentiation to T and B cells is concerned, T lymphocytes are more affected than B lymphocytes (Kim et al., 2018). T lymphocytes include T helper (Th1 and Th2) and cytotoxic T. Th1 produces pro-inflammatory cytokines such as IL-2, TNF-α, and IFN-γ and induces cell-mediated immune responses (Santos et al., 2018).

Glucocorticoids suppress cell-mediated immunity. The catecholamine's release (adrenaline and noradrenaline) of sympathetic nerve terminals, through the reaction with β2-adrenergic receptors on the surface of immune cells, causes immunosuppressive effects(Shimba & Ikuta, 2020). Adrenaline activates β2 receptors in T lymphocytes and prevents T cell proliferation by reducing IL-2 expression and secretion(Nishioka et al., 2022).IL-2 increases T cell colony proliferation and differentiation. In addition, it is involved in activating natural killer (NK) cells, cytotoxic T, B cells, and macrophages(Kolios &Tsokos, 2021). TNF-α induces cellular immunity by a direct cytotoxic effect on cancer and chronically infected cells(Li et al., 2020). IFN-γ is also one of the essential cytokines in cellular immunity, mainly produced by T helpers, and a small amount is produced by cytotoxic T and NK cells. IFN-γ stimulates the production of other cytokines and the practical functions of monocytes, including adhesion, phagocytosis, respiratory burst, and nitric oxide production. In addition, it is effective on mononuclear phagocytes, NK cells, and neutrophil stimulation(Jorgovanovic & Song, 2020).

Pro-inflammatory cytokines stimulate the HPA axis, eventually releasing Cortisol (a stress hormone) in the adrenal glands (Eckerling et al.,2021). Therefore, in light of function of glucocorticoids in suppressing the immune system after surgery, it seems possible to prevent immunosuppression by blocking glucocorticoid receptors or inhibiting their synthesis. On the other hand, the effects of catecholamines on immune system cells and their compounds may be accompanied by blocking β2 receptors with general or specific antagonists (Amaro et al., 2020). Propranolol affects the immune system cells by blocking β2 receptors(Murugan & Rousseau, 2021). As a dominant event, immune system suppression after surgical stress affects pro-inflammatory cytokines (including, the most important ones, IL-2, TNF-α, and IFN-γ) and the occurrence of various clinical disorders such as tumor progression, metastasis, wound healing deferment, septic complications, augmentation of mortality, et. c(O'Connor, & Thayer, 2021).
Thus, this study aims to investigate the effects of preoperative administration of Propranolol (by targeting catecholamines and inhibition of beta-adrenoceptor activity) on blood levels of Interleukin-2 (IL-2), Interferon-γ (IFN-γ), Tumor Necrosis Factor-α (TNF-α), and hematological

parameters such as white blood cells (WBCs) and lymphocytes after the induction of surgical stress in male rats via ELISA method.

Materials and Methods

Animals

The research proposal was approved by the Animal Ethics Committee of Razi University with the number: Razi. AEC, 396-2-031. Forty-five adult male albino Wistar rats (5 weeks old) were purchased from the Faculty of Pharmacy of Kermanshah University of Medical Sciences and Medical Services. The adaptation period of these rats was one week. Based on this, they were tampered with four times daily for 15 minutes to prevent additional stress during surgery while adapting. Rats were divided into the control group (C), the group receiving 4 mg/kg Propranolol (P4), and the group receiving 8 mg/kg Propranolol (P8) to start the examination (Jang et al., 2017) (Table 1). Animals had free access to food and water during the study period. The weights of the rats were measured and recorded daily during the adaptation period to check their general health status.

Table 1. Characteristics of the laboratory model used in the research

	DW	**P4**	**P8**
Number	15	15	15
Age (months)	4	4	4
Average weight before surgery (gr)	218±4.03	221±5.1	212±2.2
Duration of surgery (minutes)	30	30	30
Laparotomy (selective surgery)	+	+	+

Note: Abbreviation Groups: Control **DW** (Distilled water), **P4**(propranolol 4 mg/kg), **P8**(propranolol 8mg/kg)

Sample collection

Blood sampling was done during three days (T0, before surgery; T1, immediately after surgery; T2, 6 hours after surgery; T3, 24 hours after surgery; T4, 72 hours after surgery). 4-5 ml of blood was taken directly from the heart using a 22-gauge syringe to reduce possible blood hemolysis. The blood was transferred to two different tubes immediately. Half of each sample was transferred to a tube containing EDTA anticoagulant for routine cell count and hematology

tests, while the other half was transferred to an anticoagulant-free tube for serum separation. The samples were centrifuged with 2000 rounds per second for 3 minutes after clot processing. All blood samples were analyzed by CBC analyzer (Mindary, model; BC 600). The serum samples were transferred to a sterile micro tube by a 1000 µ/l sampler and kept at minus 20 degrees centigrade until measured using the ELISA method.

The serum level of measured cytokines was analyzed using the ELISA method with commercial kits for IL-2 (Diaclone Co, France) and TNF-α and IFN-γ (Booster Co, China). The results were read by Eliza Reader (Bioteck Co; Elx800 model, USA).

Medicines

Propofol 1% (Braun, Germany; Alborz Daro, Co) and Midazolam 0.5% (Daropakhsh Co) were used to anesthetize rats. Also, the injectable Propranolol (Polfa Warszawa, Poland, Sina Arat Gostar, Co) was used with a concentration of 0.1%.

Anesthesia, surgery, and research design

In the experiment, anesthesia was induced for 3.65 minutes. The appropriate duration of surgical anesthesia was provided (38.3 minutes) by intraperitoneal injection of propofol with a dose of 100 mg/kg and midazolam with a quantity of 3 mg/kg. (each ml of midazolam and propofol diluted with 4 ml of sterile distilled water with a concentration of 0.1%). After the induction of surgical anesthesia, the rats were placed on the laparotomy glass on their back, and their hands and feet were attached by hypoallergenic glue. Then, using Metz scissors, a 2-3 cm incision was cut in the midline of the abdomen. After cutting the skin, abdominal muscles, and peritoneum, the intestines were gently removed and placed between moist sterile gauze. The intestines were gently massaged with sterile gauze for 15 minutes with moisture preservation. Then, they were slowly returned to their anatomical location, and the abdomens were sutured in both layers using a simple continuous method (Catcote thread 0.4 for the abdominal muscles and fascia and nylon thread 0.3 for the skin). The rats were transferred to a heating blanket immediately after the surgery to prevent a decrease in body temperature reduction during the recovery period. Creating similar conditions based on the numbering of each rat was one of the crucial factors of the research schedule. Accurate calculation of well-timed injection of drugs, the amount of anesthetic and Propranolol, the precise timing of surgery startation, the equal duration of laparotomy surgery for each rat, the termination of surgery, and the recovery period were

determined before the surgery. All schedules were created by Excel software and formula writing.

Data analysis

All data were statistically analyzed by SPSS version 18 software. First, the data related to the serum level of cytokines were checked for normality. Then, to check the significance level of the average data of blood sampling times and the significant changes of each group alone, one-way and LSD tests were used. Pearson's test was used to investigate the relationship between the differences between two factors at different blood sampling times. A significance level of $P \leq 0.05$ was considered.

Results

Serum levels of measured cytokines

The results of the normality of the ELISA test were shown by using the skewness and kurtosis test in the range of (2<x<-2) (Table 2). Also, the significant difference in the results of the serum levels of the investigated cytokines in the one-way parametric test during the study period is shown (Table 3).

Table 2. Investigating the normality of cytokine data by kurtosis and skewness test

Parameter pg/ml	Number	Minimum	Maximum	Average	Deviations	Skewness	Kurtosis
IL-2	15	3	597	352.67	148.72	-0.350	-0.641
TNF-α	15	6	871	305.80	294.01	0.900	-0.172
IFN-γ	15	1	712	275.76	170.95	0.987	0.425

Table 3. The results of measuring the serum levels of investigated cytokines according to timing in the studied groups

Group	Parameter pg/ml	before surgery	immediately After surgery	6 hours after surgery	24 hours after surgery	72 hours after surgery
C	**IL-2**	451±82	323±104	212±32	192±44	392±68

	TNF-α	217±62	584±114	650±89	293±88	212±33
	IFN-γ	212±13	162±53	131±41	347±108	394±92
P4	**IL-2**	519±67	323±156	167±191	541±77	441±120
	TNF-α	154±56	489±171	334±118	342±95	89±64
	IFN-γ	141±67	126±27	311±171	274±131	141±50
P8	**IL-2**	434±107	408±78	375±155*	138±35	371±27
	TNF-α	278±64	41±34	105±9	32±5	863±6
	IFN-γ	179±72	248±85	147±66	600±112	350±154

Note: Abbreviation Groups: **C**(control), **P4** (propranolol 4 mg/kg), **P8** (8 mg/kg propranolol)

Examining the data of the LSD test with multiple examinations of all the studied groups has shown a significant level of 95% and 99% in some of the measured parameters (Table 4).

Table 4. Significant results of multiple studies of the studied groups at different blood sampling times*

Parameter pg/ml	Compared groups	Mean difference	Significant
IL-2	before surgery in the control group compared to the P4 and P8 groups	259[ab]	0.004
	immediately after surgery in the control group compared to the P4 and P8 groups	196[a]	0.025
	6 hours after surgery in the control group compared to the P4 and P8 groups	315[ab]	0.000
	24 hours after surgery in the control group compared to the P4 and P8 groups	207[a]	0.018
	72 hours after surgery in the control group compared to the P4 and P8 groups	349[ab]	0.000
TNF-α	before surgery in the control group compared to the P4 and P8 groups	367[ab]	0.000
	immediately after surgery in the control group compared to the P4 and P8 groups	433[ab]	0.000

	6 hours after surgery in the control group compared to the P4 and P8 groups	335[ab]	0.001
	24 hours after surgery in the control group compared to the P4 and P8 groups	237[ab]	0.001
	72 hours after surgery in the control group compared to the P4 and P8 groups	155[a]	0.026
IFN-γ	before surgery in the control group compared to the P4 and P8 groups	216[ab]	0.009
	immediately after surgery in the control group compared to the P4 and P8 groups	237[ab]	0.004
	6 hours after surgery in the control group compared to the P4 and P8 groups	452[ab]	0.000
	24 hours after surgery in the control group compared to the P4 and P8 groups	249[ab]	0.003
	72 hours after surgery in the control group compared to the P4 and P8 groups	830[ab]	0.000

Note: The letter an indicates a significance level of 95% and the letter b indicates a significance level of 99%.

There was a significant difference between the serum level of IL-2 before surgery and its serum level 6 and 24 hours after surgery in groups C and P4 ($P \leq 0.05$). This difference was insignificant in the samples taken three days after surgery in these groups. At the same time, the decrease of IL-2 level in the P8 group was substantial only 24 hours after surgery ($P \leq 0.05$). A significant difference was observed between the P4 and P8 groups in the samples taken 6 hours after the surgery by comparing the studied groups at each time of blood sampling. In contrast, the two treatments had no significant difference from the control group ($P \leq 0.05$). A significant difference was observed in the 24-hour samples of the P4 group compared to the control group. This significant difference has also been seen between P4 and P8 groups ($P \leq 0.05$). No significant difference has been seen between the studied groups by examining the 72-hour samples ($P \leq 0.05$) (Figure 1).

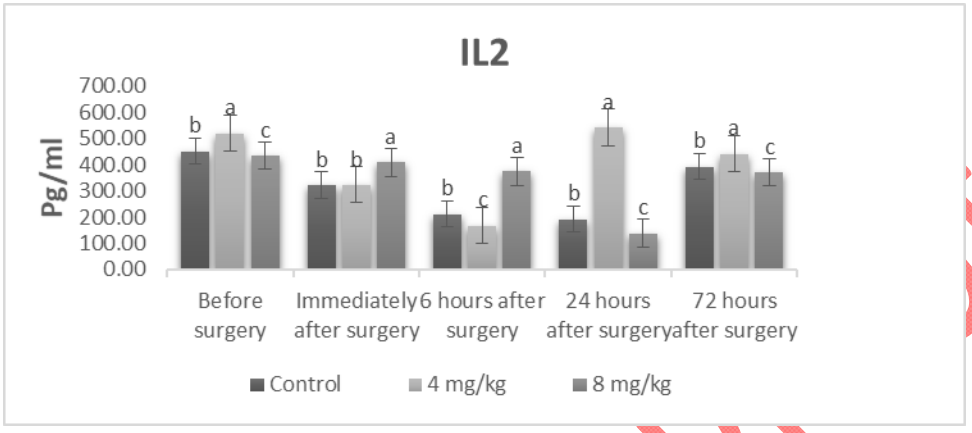

Figure 1. IL2 levels changes in the study period

The serum level of TNF-α in groups C and P4 has significantly increased after surgery. While the level of TNF-α has remained high until 6 hours after surgery in group C, a significant decrease has been shown in its level in group P4 samples 6 hours after surgery. In both groups, serum TNF-α levels returned to normal average 72 hours after surgery ($P \leq 0.05$). Unlike the other two groups, group P8's level of TNF-α decreased significantly after surgery and remained below the normal average until 24 hours after surgery. The serum level of this cytokine showed a significant increase in the P8 group 72 hours after surgery ($P \leq 0.05$) (Figure 2).

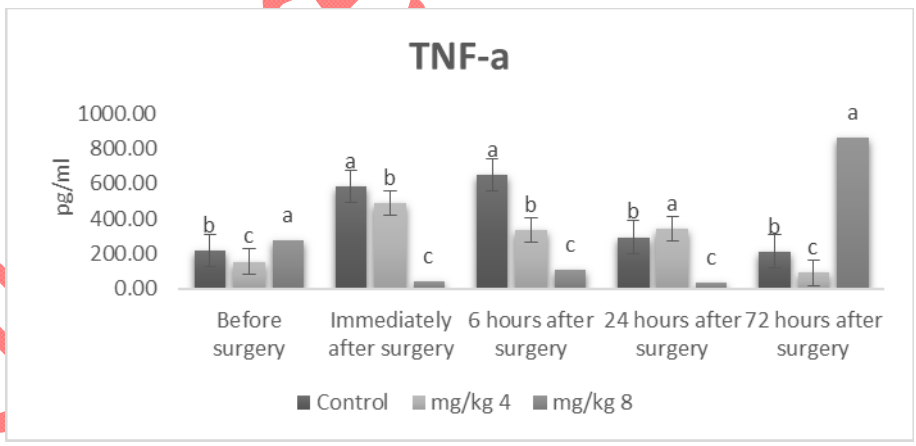

Figure 2. TNF-α levels changes in the during the study period

The serum level of IFN-γ in the C group hasn't shown a significant change until 6 hours after surgery. While a significant increase has been seen in the level of this cytokine in 24-hour samples of this group ($P \leq 0.05$). There was a significant increase in 72-hour samples compared to 6-hour samples ($P \leq 0.01$, $P \leq 0.05$). In the 6-hour samples, a significant increase in IFN-γ was seen in the P4 group ($P \leq 0.05$). In comparison, this increase has been seen 24 hours after surgery in the P8 group ($P \leq 0.05$). The P4 group had a higher level of IFN-γ in the 6-hour samples compared to the control group and P8 group. At the same time, there was a significant increase in the 24-hour samples of the P8 group compared to the C and P4 groups ($P \leq 0.01$) (Figure 3).

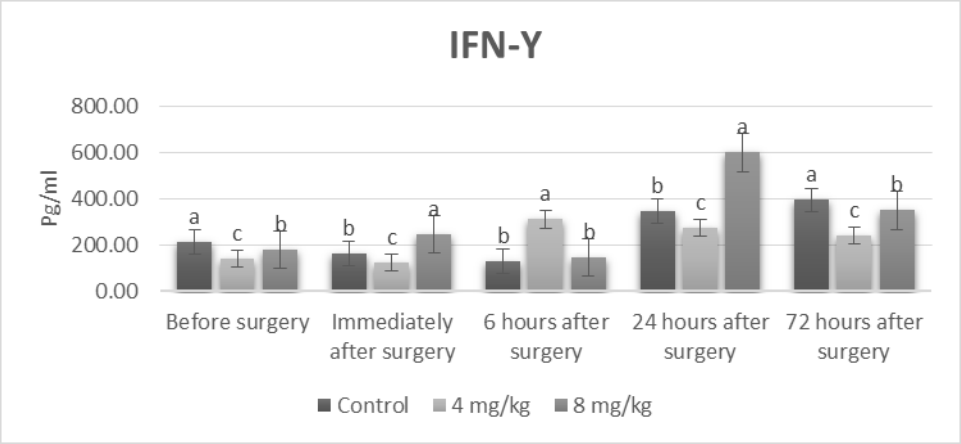

Figure 3. IFN-γ levels changes in the during the study period

Also, leukocytes and lymphocytes increased in all groups immediately after surgery for 6 hours. However, there were fluctuations and differences during 72 hours in the two treatment groups compared to the control group (Figure 4,5).

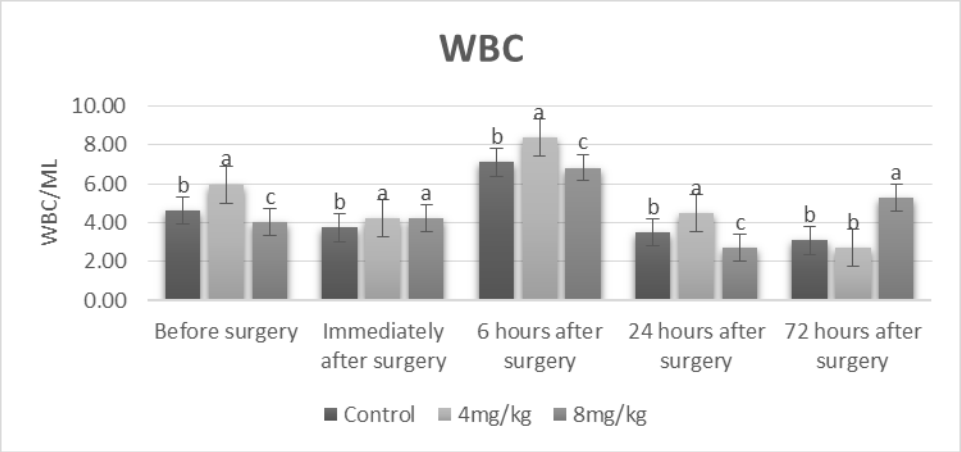

Figure 4. Changes in the total number of white blood cells during the study period

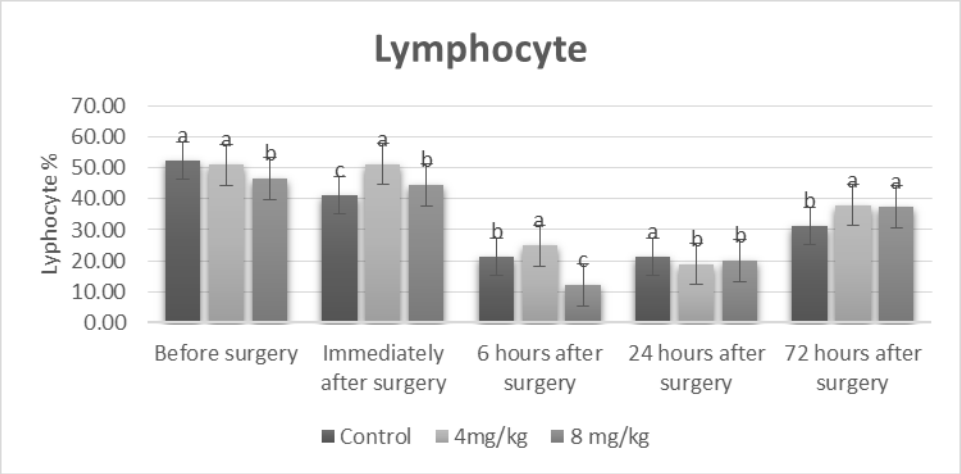

Figure 5. Changes in the number of lymphocytes during the study period

Discussion

The body's reaction to various stimuli is called a stress reaction. Any factor that affects body tissue can affect the homeostasis balance (Everly & Lating, 2019). The surgery causes a type of stress called surgical stress. The surgical stress response is a part of the systemic response to

surgery and includes a wide range of neuroendocrine, metabolic, immunological, and hematological effects (Hirose et al., 2022). The studies about the impact of surgical stress on various body systems, especially the immune system, emphasize that this stress weakens the immune system and, therefore, directly impacts the surgery. Several experimental studies have reported that surgical stress is associated with impaired innate and acquired immune responses (Helander et al., 2019; Wang et al., 2022). Various studies have shown that releasing compounds such as glucocorticoids and catechol amines are among the main factors that weaken the immune system under surgical stress (Jaya & Tantri,2021; Zuo et al., 2019). Understanding the molecular mechanisms underlying these events can be facilitated by preventing excessive immune system changes in the post-surgery period, preventing immunosuppression, and increasing the likelihood of surgical success and patient treatment. The prescription of Propranolol with a specific dose in the pre-surgery period leads to the homeostasis maintenance of the body as one of the main aspects of the host's defense against the stress caused by surgery. Propranolol effectively prevents the decrease of TNF-α levels (Shaaban & El-Menshawy,2021). The importance of cellular immunity and natural killer cells, which require IL-2 for survival, has been identified in immune system defense (Hsieh & Hernandez, 2021). The results of the present study have shown a decrease in the serum level of IL-2 in the control group for at least 72 hours. The difference was however insignificant. The P4 group demonstrated a significant decrease in IL-2 immediately following surgery, which persisted for six hours. Also, no significant decrease in IL-2 serum levels was observed in this 24-hour sample. Propranolol has appropriate anti-anxiety effects by blocking adrenaline receptors (blocking beta sympathetic receptors)(Śmiałowska & Zięba, 2021). It reaches the maximum plasma density after 1 to 3 hours, and its half-life is 4 to 5 hours. But its effect time is longer than its half-life and may last up to 12 hours(Kalam & Rasool, 2020). Propranolol blocks beta-2 receptors of immune cells in rats for 6-12 hours (Wrobel et al., 2016). Therefore, it is probably not attached to its receptor in 24-hour samples, and all effects are directly induced on immune cells. At the same time of blood sampling, the P8 group reached the minimum serum level of IL-2, which is probably caused by the effect of catecholamines on immune system cells. Also, the P8 group has shown a higher level of IL-2 with a significant difference in the 6-hour samples compared to the control and P4 groups. In contrast with the P8 group, the lower effect of Propranolol in the P4 group in the samples 6 hours after surgery, could be due to the impact of the lower dose of the drug compared to the P8 group.

By examining and comparing the pre-surgery samples with the post-surgery samples (blood collection time 2), we saw a significant decrease in the IL-2 serum level in the control group and P4. However, the P8 group hasn't shown a noticeable change. This issue probably indicates the lower effect of Propranolol at a dose of 4 mg/kg in inhibiting the catecholamine effect on T cells. While in the 8 mg/kg receiving group, the blocking effects of catecholamines have been seen at least 6 hours after surgery, the blocking effects of catecholamines have been seen at least 6 hours after surgery in the 8 mg/kg receiving group. The P4 group reached the highest IL-2 serum level 24 hours after surgery. This difference may be due to the P4 group's experience of less stress than the control group. Afew changes in serum adrenaline and noradrenaline levels in women under the stress of breast cancer surgery have shown that the highest serum levels are immediately after surgery and up to 24 hours later. The data have demonstrated the reduction of IL-2 does not occur before the end of the surgery, while the level of catecholamines reaches its maximum level (Silva et al., 2022).

The time difference is probably caused by the time required for catecholamine to affect its receptor on the surface of lymphocytes and decrease the transcription of the IL-2 gene (Alhussien & Dang, 2020). In breast cancer patients who underwent surgery, during the period (before surgery until seven days after surgery), the changes in serum levels of adrenaline and noradrenaline show higher levels of adrenaline up to seven days after surgery (Eckerling & Ricon-Becker, 2021; Silva et al., 2022). Pantziarka et al. have shown that Propranolol performs better in preventing lung tumor metastasis (LTR) with a dose of 1.5 mg/kg rather than the 4.5 mg/kg group. A study showed that apoptosis of T lymphocytes, which in this case have the highest rate of apoptosis 24 hours after surgery, is directly related to the reduction of IL-2 (Pantziarka et al., 2016). Propranolol leads to the proliferation increment of T lymphocytes and increases human peripheral blood cells (Zhou et al., 2016). Propranolol increases IL-2 receptor expression in human lymphocytes in vitro(Sharashenidze et al., 2021). IL-2 is used as a Th1 cytokine for cancer immunotherapy. Furthermore, studies have shown that IL-2 induces antitumor responses in chemotherapy-resistant cancers such as melanoma and renal carcinoma(Sahin et al., 2020).

TNF-α is a pro-inflammatory cytokine mainly produced by activated macrophages. Although the average level of TNF-α is essential for regulating immune responses, the continuation of the immune response can cause some inflammatory diseases due to its excessive production. TNF-α

is one of the most abundant primary mediators in inflamed tissue and is rapidly released after trauma (Germolec & Shipkowski, 2018). An increase in the level of cytokine TNF-α after surgery is a sign of the post-surgery pro-inflammatory phase. In the control and P4 groups, the level of this cytokine increased, and a significant decrease in the level of TNF-α was seen just in the P8 group up to 24 hours after surgery (Shahzamani et al., 2019). Although inhibition of TNF-α production in the pro-inflammatory stage is successful in surgeries with severe pro-inflammatory stages, such as major surgeries, the inhibition of TNF-α production increases post-surgical complications in cases like infection and mortality (Ko & Rubenstein, 2018). The presence of beta-adrenergic receptors on monocytes and macrophages has been proven, and these cells are the main sources of TNF-α production. Thus, a higher dose of Propranolol effectively prevents the increase of TNF-α (Droho & Cuda, 2019), while a lower amount of Propranolol could inhibit the TNF-α increment after surgery until 6 hours. The benefits of preventing the increase of TNF-α levels after surgery are discussed.

Although limiting the level of TNF-α prevents the development of the acute inflammatory phase and aids in tissue repair, it also increases the possibility of post-surgical infections (Lopetuso et al., 2017). One day after surgery, the level of Foxp3+ (a necessary transcription factor for regulatory T cells) is at its lowest level in the pro-inflammatory step (Georgiev & Charbonnier, 2019). This shows the suppression of regulatory T cells at least 24 hours after surgery and can justify the pro-inflammatory step after surgery. The pro-inflammatory phase is essential after surgery. The reduction of pro-inflammatory cytokines indicates the decline of the pro-inflammatory step after surgery. Reducing the pro-inflammatory step can be one of the causes of infection(Bouchard et al., 2016). It seems that preventing the increment of pro-inflammatory cytokines worsens the prognosis of surgery and increases the possibility of post-surgical infections(Brujeni, 2022). Not only have studies shown that suppressing the production of TNF-α and IL-2 does not enhance performance, but also that the mortality rate and complications after surgery will be higher if the sTNF-R75 antibody is administered (Amodeo et al., 2018; Bartekova & Radosinska, 2018). This issue is entirely in line with the results obtained from this research because high doses of Propranolol have increased the possibility of post-surgical infections by preventing the development of the pro-inflammatory phase. Thus, in the 72-hour samples of the P8 group, the increase in the total number of white blood cells after 24 hours was probably indicative of post-surgery infection in this group (data not shown). Antibiotics non-use due to interference in the tests strengthened this hypothesis.

Clinical studies have shown that excessive inflammation after surgery causes mortality increment based on the excessive secretion of TNF-α. However, it can also increase the failure of multiple organs (Freitas et al., 2018; Schmatz et al., 2017). With the results of TNF-α increment in some inflammatory autoimmune diseases, neutralizing or blocking its receptors is a primary strategy in treating these diseases(Abd Nikfarjam & Adineh, 2017). According to Chu et al.'s study, inhibition of TNF-α signaling pathways such as NF-κB and MAPK reduced dysfunction after surgery in rats (Chu et al., 2013). Different studies have been mentioned about TNF-α. T Kataoka et al. have reported a significant increment in TNF-α levels in patients undergoing surgery, which is similar to the results of our study(Kataoka et al., 2004). Also, studies have shown that Pro's effect on TNF-α depends on doses. Low doses of Pro stimulate the synthesis and release of TNF-α, but high doses suppress TNF-α levels. (Hajighasemi & Mirshafiey, 2016; Zanelatto et al., 2018).On the other hand, in patients with major and minor traumatic injuries, cellular immunity is suppressed and is accompanied by a reduction in IFN-g and IL-2 production (Boddie & Currie, 2003). Therefore, stress hormones and histamine secretion caused by major and minor injuries may contribute to the severe suppression of the immune system and the emergence of infection in these conditions by inducing a change in Th2 and Th1 cell transcription (Zhao et al., 2018).

The interaction between stress and the immune system is undoubtedly complicated. Studies have shown that stress hormones differentially regulate signaling pathways and patterns of Th1/Th2 intracellular biochemical events and cytokine secretion types 1/ 2 (Chen et al., 2022; Zhao et al., 2018). The reduction of IFN-γ due to the incomplete production of IL-12 in monocytes has begun during tampering and preparation for surgery (initial stress). It can go on up to 3 days after minor surgeries(Martínez-Barricarte et al., 2018) . IL-12 is the primary motive of IFN-γ production. Catecholamines, glucocorticoids, and prostaglandins have effects on the reduction of IL-12 serum levels caused by surgery (Bain & Myles, 2022; Matzner et al., 2019). An increment of IFN-γ has been observed in the P4 group 6 hours after surgery. In contrast, this increment occurred in the control and P8 groups 24 hours after surgery. Therefore, the lower dose of Propranolol has had a better performance in preventing the IFN-γ level reduction. Propranolol, a non-specific β-adrenergic blocking drug, competitively prevents the catecholamines from binding receptors and suppresses cancer cells. In the study of Matzner et al., blocking adrenergic receptors directly affects the production of IL-12. Therefore, the IFN-γ level increment can be

attributed to the Propranolol effects on adrenergic receptors on Th1 cells in the treatment groups (Matzner et al., 2019).

Our finding aligns with previous studies that have shown that the administration of Propranolol causes IFN-γ levels increment(Ashrafi & Shapouri, 2017). IFN-γ is predominantly secreted by innate cells (NK cells) and adoptive cells (Th1 and CTLs cells) and also stimulates Th1 immune responses (Wang et al., 2016). It seems that Propranolol acts as a Th1 activating agent by stimulating the production of IFN-γ (Th1 cytokine). While reducing surgical stress, it is effective in healing the effects of surgery and shortening the recovery period(Amiri, et al., 2021).

Further, Lymphocyte cell proliferation is an index to cellular immune responses measurement (Zhou et al., 2016). In our study, it has been found that Propranolol improves lymphocyte proliferation, which means it enhances cellular immune responses. Cellular immune responses play a crucial role in controlling and healing surgical wounds (Alazawi et al., 2016). Our results confirm the role of Propranolol. Improving cellular immune responses and cytokine production is essential in the proper surgical process (Muire et al., 2020). Besides, leukocytes have increased in all groups 6 hours after surgery. Investigating the effect of changes in the number of lymphocytes and the total number of white blood cells has shown a correlation between lymphocyte changes. This increase can result from the trauma caused by surgery related to the pro-inflammatory phase following the increase in lymphocyte changes compared to the shift in the number of other immune cell components such as neutrophils and monocytes. As a pre-surgery response, Glucocorticoid levels are increased and can last for days. Glucocorticoids have increased the population of circulating neutrophils through two mechanisms (including an inhibitory effect on the expression of sialomucins in the vessel wall, causing the release of peripheral neutrophils into the bloodstream, and also by inhibiting the expression of selectins and preventing the apoptosis of Carp granulocyte cells). It seems that Propranolol prevents the decrease of the number of lymphocytes before surgery, but has no effect on their population after surgery. Its inability to inhibit the reduction of lymphocytes is probably because of its short half-life (6-12 hours). On the other hand, the decline in the number of lymphocytes can be due to a reduction in the proliferation rate of lymphocytes or to the location of lymphocytes in different organs (lymphatic and blood) compared to blood lymphocytes and lymphatic organs.

Conclusion

Safe drug usage, such as that of Propranolol, has applications beyond its typical use in research. Stress pathway blockade by b2-AR and, or H2 antagonists may help enhance Th1 responses, manage infection, and post-surgical recovery. Propranolol prevents the suppression of IL-2 by inhibiting the synthesis of corticosteroids and helps to improve the suppression of the immune system during and after surgery. Inhibition of TNF-α production increases post-surgery problems such as infection and mortality. Propranolol is effective in preventing TNF-α level reduction. Propranolol also impacts Th1 cells that, reduce the level of IFN-γ by affecting adrenergic receptors. A few changes in the immunogenic platform of infiltrated immune cells, such as Th1 in the surgical microenvironment, may effectively correct the body's cytokine patterns using Propranolol. Propranolol seems to be potent immunomodulatory and capable of inducing cellular immune responses. Although Propranolol accelerates healing by shifting the immune system towards a pattern of Th1 immunological mechanisms in surgical stress, further studies would be helpful to confirm this.

Ethical Considerations

Compliance with ethical guidelines this study was extracted from a doctoral dissertation and all experimental procedures were approved by the Faculty of Veterinary Medicine, University of Razi Local Ethics Committee (AEC, 396-2-031).

Funding

This study was a general doctoral dissertation and funded by Faculty of Veterinary Medicine, Razi University.

Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgments

The authors wish to express their appreciation to everyone that assists us in this study.

References

Abd Nikfarjam, B., Adineh, M., Hajiali, F., & Nassiri-Asl, M. (2017). Treatment with rutin-a therapeutic strategy for neutrophil-mediated inflammatory and autoimmune diseases:-anti-inflammatory effects of rutin on neutrophils. *Journal of pharmacopuncture*,52,(1)20 . [DOI: 10.3831/KPI.2017.20.003]

Alazawi, W., Pirmadjid, N., Lahiri, R., & Bhattacharya, S. (2016). Inflammatory and immune responses to surgery and their clinical impact. *Annals of surgery, 264(1)*, 73-80. [DOI:10.1097/SLA.0000000000001691]

Alhussien, M. N., & Dang, A. K. (2020). Interaction between stress hormones and phagocytic cells and its effect on the health status of dairy cows: A review. *Veterinary world, 13(9)*, 1837. [DOI: 10.14202/vetworld.2020.1837-1848]

Amaro, F., Silva, D., Reguengo, H., Oliveira, J. C., Quintas, C., Vale, N., Fresco, P. (2020). β-adrenoceptor activation in breast mcf-10a cells induces a pattern of catecholamine production similar to that of tumorigenic mcf-7 cells. *International journal of molecular sciences, 21(21)*, 7968. [DOI:10.3390/ijms21217968]

Amiri, I. A., Pedram, M., Tavakoli, A., Vajhi, A., Rezaii, J., Ashegh, H., & Dezfouli, M. M. (2021). Laparoscopic Versus Conventional YU Pyloroplasty in Dogs: A Comparative Study of Pain, Stress, and Duration. *Iranian Journal of Veterinary Medicine*. [DOI:10.22059/IJVM.2021.304157.1005098]

Amodeo, G., Bugada, D., Franchi, S., Moschetti, G., Grimaldi, S., Panerai, A., Sacerdote, P. (2018). Immune function after major surgical interventions: the effect of postoperative pain treatment. *Journal of pain research, 11*, 1297. [PMID]

Ashrafi, S., Shapouri, R., & Mahdavi, M. (2017). Immunological consequences of immunization with tumor lysate vaccine and propranolol as an adjuvant: a study on cytokine profiles in breast tumor microenvironment. *Immunology Letters, 181*, 63-70. [DOI:10.1016/j.imlet.2016.11.014]

Bain, C., Myles, P., Corcoran, T., & Dieleman, J. (2022). Postoperative systemic inflammatory dysregulation and corticosteroids: a narrative review. *Anaesthesia*, *78*(3), 356-370. [DOI:10.1111/anae.15896]

Bartekova, M., Radosinska, J., Jelemensky, M., & Dhalla, N. S. (2018). Role of cytokines and inflammation in heart function during health and disease. *Heart failure reviews, 23(5)*, 733-758. [DOI:10.1007/s10741-018-9716-x]

Boddie, D., Currie, D., Eremin, O., & Heys, S. D. (2003). Immune suppression and isolated severe head injury: a significant clinical problem. *British journal of neurosurgery, 17(5), 405-417.* [DOI:10.1080/02688690310001611198]

Bouchard, L. C., Antoni, M. H., Blomberg, B. B., Stagl, J. M., Gudenkauf, L .M., Jutagir, D. R., . . . Derhagopian, R. P. (2016). Post-surgical depressive symptoms and pro-inflammatory cytokine elevations in women undergoing primary treatment for breast cancer. *Psychosomatic medicine, 78(1),* 26. [DOI: 10.1097/PSY.0000000000000261]

Brujeni, G. N. (2022). Novel Insights into Infection and Immunity. *Iranian Journal of Veterinary Medicine*, *16*(2).[DOI: 10.22059/IJVM.2022.337927.1005234]

Chen, X., Bi, M., Yang, J., Cai, J., Zhang, H., Zhu, Y., Zhang, Z. (2022). Cadmium exposure triggers oxidative stress, necroptosis, Th1/Th2 imbalance and promotes inflammation through the TNF-α/NF-κB pathway in swine small intestine. *Journal of hazardous materials, 421,* 126704. [DOI:10.1016/j.jhazmat.2021.126704]

Chu, W., Li, M., Li, F., Hu, R., Chen, Z., Lin, J., & Feng, H. (2013). Immediate splenectomy down-regulates the MAPK–NF-κB signaling pathway in rat brain after severe traumatic brain injury. *Journal of Trauma and Acute Care Surgery, 74(6),* 1446-1453. [DOI:10.1097/TA.0b013e31829246ad]

Droho, S., Cuda, C. M., Perlman, H., & Lavine, J. A. (2019). Monocyte-derived macrophages are necessary for beta-adrenergic receptor-driven choroidal neovascularization inhibition. *Investigative ophthalmology & visual science, 60(15),* 5059-5069. [DOI:10.1167/iovs.19-28165]

Eckerling, A ,.Ricon-Becker, I., Sorski, L., Sandbank, E., & Ben-Eliyahu, S. (2021). Stress and cancer: mechanisms, significance and future directions. *Nature Reviews Cancer, 21(12),* 767-785. [DOI:10.1038/s41568-021-00395-5]

Everly, G. S., & Lating, J. M. (2019). The anatomy and physiology of the human stress response. In A clinical guide to the treatment of the human stress response (pp. 19-56): *Springer Science+ Business Media.* [DOI: 10.1007/978-1-4939-9098-62]

Freitas, W. R., Oliveira, L. V. F., Perez, E. A., Ilias, E. J., Lottenberg, C. P., Silva, A. S., Ribeiro-Alves, M. (2018). Systemic inflammation in severe obese patients undergoing surgery for obesity and weight-related diseases. *Obesity Surgery, 28(7),* 1931-1942. [DOI:10.1007/s11695-017-3104-9]

Georgiev, P., Charbonnier, L.-M., & Chatila, T. A. (2019). Regulatory T cells: the many faces of Foxp3. Journal of clinical immunology, 39(7), 623-640. [DOI:10.1007/s10875-019-00684-7]

Germolec, D. R., Shipkowski, K. A., Frawley, R. P., & Evans, E. (2018). Markers of inflammation. *Immunotoxicity Testing,* 57-79. [DOI: 10.1007/978-1-4939-8549-45]

Hajighasemi, F., & Mirshafiey, A. (2016). Regulation of inflammatory cytokines in human immunocompetent cells by propranolol in vitro. In: *Eur Respiratory Soc.* [DOI:10.1183/13993003.congress-2016.PA1083]

Hari, M. S., & Summers, C. (2018). Major surgery and the immune system: from pathophysiology to treatment. *Current Opinion in Critical Care, 24(6),* 588-593. [DOI: 10.1097/MCC.0000000000000561]

Helander, E. M., Webb, M. P., Menard, B., Prabhakar, A., Helmstetter, J., Cornett, E. M., Kaye, A. D. (2019). Metabolic and the surgical stress response considerations to improve postoperative recovery. *Current pain and headache reports, 23(5),* 1-8. [DOI:10.1007/s11916-019-0770-4]

Hirose, M., Okutani, H., Hashimoto, K., Ueki, R., Shimode, N., Kariya, N., Tatara, T. (2022). Intraoperative Assessment of Surgical Stress Response Using Nociception Monitor under General Anesthesia and Postoperative Complications: A Narrative Review. *Journal of Clinical Medicine, 11.*6080,(20). [DOI:10.3390/jcm11206080]

Hsieh, E. W., & Hernandez, J. D. (2021). Clean up by aisle 2: roles for IL-2 receptors in host defense and tolerance. *Current Opinion in Immunology, 72,* 298-308. [DOI:10.1016/j.coi.2021.07.010]

Jaya, A. G. P. S., Tantri, A. R., Heriwardito, A., & Mansjoer, A. (2021). Single-centre, double-blind, randomised, parallel-group, superiority study to evaluate the effectiveness of general anaesthesia and ultrasound-guided transversus thoracis muscle plane block combination in adult cardiac surgery for reducing the surgical stress response: *clinical trial protocol. BMJ open,* 11(11), e051008. [DOI:10.1136/bmjopen-2021-051008]

Jorgovanovic, D., Song, M., Wang, L., & Zhang, Y. (2020). Roles of IFN-γ in tumor progression and regression: A review. Biomarker research, 8(1), 1-16. [DOI:10.1186/s40364-020-00228-x]

Kalam, M. N., Rasool, M. F., Rehman, A. U., & Ahmed, N. (2020). Clinical pharmacokinetics of propranolol hydrochloride: a review. Current Drug Metabolism, 21(2), 89-105. [DOI:10.2174/1389200221666200414094644]

Kataoka, T., Enomoto, F., Kim, R., Yokoi, H., Fujimori, M., Sakai, Y., Ikeda, K. (2004). The effect of surgical treatment of obstructive sleep apnea syndrome on the plasma TNF-α levels. *Tohoku journal of experimental medicine, 204(4),* 267-272 [DOI:10.1620/tjem.204.267]

Kim, R. (2018). Effects of surgery and anesthetic choice on immunosuppression and cancer recurrence. *Journal of translational medicine, 16(1),* 1-13. [DOI:10.1186/s12967-018-1389-7]

Ko, F. C., Rubenstein, W. J., Lee, E. J., Siu, A. L., & Sean Morrison, R. (2018). TNF-α and sTNF-RII are associated with pain following hip fracture surgery in older adults. *Pain Medicine, 19(1),* 169-177. [DOI:10.1093/pm/pnx085]

Kolios, A. G., Tsokos, G. C., & Klatzmann, D. (2021). Interleukin-2 and regulatory T cells in rheumatic diseases. Nature Reviews Rheumatology, 17(12), 749-766. [DOI:10.1038/s41584-021-00707-x]

Li, W., Hu, X., Wang, S., Jiao, Z., Sun, T., Liu, T., & Song, K. (2020). Characterization and anti-tumor bioactivity of astragalus polysaccharides by immunomodulation. *International Journal of Biological Macromolecules, 145,* 985-997. [DOI:10.1016/j.ijbiomac.2019.09.189]

Lopetuso, L. R., Gerardi, V., Papa, V., Scaldaferri, F., Rapaccini, G. L., Gasbarrini, A., & Papa, A. (2017). Can we predict the efficacy of anti-TNF-α agents? *International journal of molecular sciences, 18(9),* 1973. [DOI:10.3390/ijms18091973]

Marko, N. F., Hamrahian, A. H., & Weil, R. J. (2010). Immediate postoperative cortisol levels accurately predict postoperative hypothalamic–pituitary–adrenal axis function after transsphenoidal surgery for pituitary tumors. *Pituitary, 13(3),* 249-255. [DOI:10.1007/s11102-010-0227-6]

Martínez-Barricarte, R., Markle, J. G., Ma, C. S., Deenick, E. K., Ramírez-Alejo, N., Mele, F., Mansouri, D. (2018). Human IFN-γ immunity to mycobacteria is governed by both IL-12 and IL-23. *Science immunology, 3(30),* eaau6759. [DOI: 10.1126/sciimmunol.aau6759]

Matzner, P., Sorski, L., Haldar, R., Shaashua, L., Benbenishty, A., Lavon, H., Rosenne, E. (2019). Deleterious synergistic effects of distress and surgery on cancer metastasis: abolishment through an integrated perioperative immune-stimulating stress-inflammatory-reducing intervention. *Brain, Behavior, and Immunity, 80,* 170-178. [DOI:10.1016/j.bbi.2019.03.005]

Mikulska, J., Juszczyk, G., Gawrońska-Grzywacz, M., & Herbet, M. (2021). HPA Axis in the pathomechanism of depression and schizophrenia: New therapeutic strategies based on its participation. *Brain Sciences, 11(10),* 1298. [DOI:10.3390/brainsci11101298]

Muire, P. J., Mangum, L. H., & Wenke, J. C. (2020). Time course of immune response and immunomodulation during normal and delayed healing of musculoskeletal wounds. *Frontiers in immunology, 11,* 1056. [DOI:10.3389/fimmu.2020.01056]

Murugan, S., Rousseau, B., & Sarkar, D. K. (2021). Beta 2 Adrenergic receptor antagonist propranolol and opioidergic receptor antagonist naltrexone produce synergistic effects on breast cancer

growth prevention by acting on cancer cells and immune environment in a preclinical model of breast cancer. *Cancers, 13(19),* 4858. [DOI:10.3390/cancers13194858]

Nishioka, R., Nishi, Y., Choudhury, M. E., Miyaike, R., Shinnishi, A., Umakoshi, K., Yano, H. (2022). Surgical stress quickly affects the numbers of circulating B-cells and neutrophils in murine septic and aseptic models through a β2 adrenergic receptor. *Journal of Immunotoxicology, 19(1),* 8-16. [DOI:10.1080/1547691X.2022.2029630]

O'Connor, D. B., Thayer, J. F., & Vedhara, K. (2021). Stress and health: A review of psychobiological processes. *Annual review of psychology, 72,* 663-688. [DOI:10.1146/annurev-psych-062520-122331]

Pantziarka, P., Bouche, G., Sukhatme, V., Meheus, L., Rooman, I., & Sukhatme, V. P. (2016). Repurposing Drugs in Oncology (ReDO),Propranolol as an anti-cancer agent. *ecancermedicalscience, 10.* [DOI: 10.3332/ecancer.2016.680]

Sahin, D., Arenas-Ramirez, N., Rath, M., Karakus, U., Hümbelin, M., van Gogh, M., Boyman, O. (2020). An IL-2-grafted antibody immunotherapy with potent efficacy against metastatic cancer. *Nature communications, 11(1),* 1-12. [DOI:10.1038/s41467-020-20220-1]

Santos, J. M., Cervera-Carrascon, V., Havunen, R., Zafar, S., Siurala, M., Sorsa, S., Hemminki, A. (2018). Adenovirus coding for interleukin-2 and tumor necrosis factor alpha replaces lymphodepleting chemotherapy in adoptive T cell therapy. *Molecular therapy, 26(9),* 2243-2254. [DOI:10.1016/j.ymthe.2018.06.00]

Schmatz, R., Bitencourt, M. R., Patias, L. D., Beck, M., Alvarez, G. d. C., Zanini, D., Leal, C. A. (2017). Evaluation of the biochemical, inflammatory and oxidative profile of obese patients given clinical treatment and bariatric surgery. *Clinica Chimica Acta, 465,* 72-79. [DOI:10.1016/j.cca.2016.12.012]

Shaaban, N. R. A., El-Menshawy, S. S., Salem, A. E., & Othman, S. S. M. Protective Effects of Propranolol and Carvedilol on ExperimentallyInduced Ulcerative Colitis in Male Albino Rat. *European Journal of Molecular & Clinical Medicine, 8(03),* 2021. [PMID] [PMCID]

Shahzamani, M., Tehrani, R. B., Dabbagh, A., Fani, K., Foroughi, M., & Pourmohsen, M. (2019). Effect of combined conventional ultrafiltration and modified ultrafiltration on serum interleukin-6 and TNF-α levels in pediatric cardiac surgery patients. *Journal of Cellular & Molecular Anesthesia, 4(1),* 3-7. [DOI:10.22037/jcma.v4i1.26197]

Sharashenidze, T., Mamamtavrishvili, N., Enukidze, M., Machavariani, M., Gabunia, T., & Sanikidze, T. (2021). EFFECT OF PROPRANOLOL ON CYTOKINE PROFILE IN AN EXPERIMENTAL MODEL OF HUMAN T LYMPHOCYTES (JURKAT CELLS) IN VITRO. *Georgian Medical News(311),* 169-172. [PMID: 33814413]

Shimba, A., & Ikuta, K. (2020). Control of immunity by glucocorticoids in health and disease. *Paper presented at the Seminars in immunopathology*. [DOI:10.1007/s00281-020-00827-8]

Silva, D., Quintas, C., Gonçalves, J., & Fresco, P. (2022). Contribution of adrenergic mechanisms for the stress-induced breast cancer carcinogenesis. *Journal of Cellular Physiology, 237(4),* 2107-2127. [DOI:10.1002/jcp.30707]

Śmiałowska, M., Zięba, B., & Domin, H. (2021). A role of noradrenergic receptors in anxiolytic-like effect of high CRF in the rat frontal cortex. *Neuropeptides, 88,* 102162. [DOI:10.1016/j.npep.2021.102162]

Wang, Y.-T., Kong, Y., Song, Y., Han, W., Zhang, Y.-Y., Zhang, X.-H., Huang, X.-J. (2016). Increased type 1 immune response in the bone marrow immune microenvironment of patients with poor graft function after allogeneic hematopoietic stem cell transplantation. *Biology of Blood and Marrow Transplantation, 22(8)*, 1376-1382. [DOI:10.1016/j.bbmt.2016.04.016]

Wang, Y., Qu, M., Qiu, Z., Zhu, S., Chen, W., Guo, K., Zhang, H. (2022). Surgical stress and cancer progression: new findings and future perspectives. *Current Oncology Reports,* 1-11. [DOI:10.1007/s11912-022-01298-w]

Wrobel, L. J., Bod, L., Lengagne, R., Kato, M., Prévost-Blondel, A., & Le Gal, F.-A. (2016). Propranolol induces a favourable shift of anti-tumor immunity in a murine spontaneous model of melanoma. *Oncotarget, 7(47),* 77825. [DOI: 10.18632/oncotarget.12833]

Yagawa, Y., Tanigawa, K., Kobayashi, Y., & Yamamoto, M. (2017). Cancer immunity and therapy using hyperthermia with immunotherapy, radiotherapy, chemotherapy, and surgery. *Journal of Cancer Metastasis and Treatment, 3,* 218-230. [DOI: 10.18632/oncotarget.12833]

Zanelatto, F., Dias, E., Teixeira, J., Sartori, C., Parada, C., & Tambeli, C. (2018). Anti-inflammatory effects of propranolol in the temporomandibular joint of female rats and its contribution to antinociceptive action. *European journal of pain, 22(3), 572-582.* [DOI:10.1002/ejp.1143]

Zhao, H., Wang, Y., Shao, Y., Liu, J., Wang, S., & Xing, M. (2018). Oxidative stress-induced skeletal muscle injury involves in NF-κB/p53-activated immunosuppression and apoptosis response in copper (II) or/and arsenite-exposed chicken. *Chemosphere,* 210, 76-84. [DOI:10.1016/j.chemosphere.2018.06.165]

Zhou, L., Li, Y., Li, X., Chen, G., Liang, H., Wu, Y., Ouyang, W. (2016). Propranolol attenuates surgical stress–induced elevation of the regulatory T cell response in patients undergoing radical mastectomy. *The Journal of Immunology, 196(8),* 3460-3469. [DOI:10.4049/jimmunol.1501677]

Zuo, Y., Zhao, L., Zeng, M., Yang, Q., Chen, X., & Yang, T. (2019). The effects of vitamin-rich carbohydrate pretreatment on the surgical stress response and S-1,β after splenectomy in elderly rats. *BMC anesthesiology, 19(1),* 1-6. [DOI:10.1186/s12871-019-0748-0]

بررسی اثرات تعدیل کننده ایمنی و تغییرات سیتوکینی توسط پروپرانولول به دنبال استرس ناشی از جراحی در موش‌های صحرایی نر

میلاد آذرهوش[1]، علی قشقایی[2]، مهرداد پویانمهر[3*]، علی ملکی[4]، صمدعلیمحمدی[3]

1 – دانش آموخته دکتری عمومی دامپزشکی، دانشکده دامپزشکی، دانشگاه رازی، کرمانشاه، ایران

2 -گروه علوم بالینی، دانشکده دامپزشکی، دانشگاه رازی، کرمانشاه، ایران.

3 -گروه علوم پایه و پاتوبیولوژی، دانشکده دامپزشکی، دانشگاه رازی، کرمانشاه، ایران.

4- مرکز تحقیقات زیست پزشکی، پژوهشکده فناوری بهداشت، دانشگاه علوم پزشکی کرمانشاه ، کرمانشاه ، ایران

چکیده

زمینه مطالعه: جراحی با مکانیسم های مختلف باعث سرکوب سیستم ایمنی در دوره بعد از عمل می شود.

اهدف: این مطالعه با هدف بررسی اثرات تجویز پروپرانولول قبل از جراحی بر سطوح خونی اینترلوکین- 2(IL-2) ، اینترفرون - γ (IFN-γ)، فاکتور نکروز تومور- α (TNF-α) و پارامترهای خونی مانند گلبول های سفید (WBCs) و لنفوسیت ها انجام شد.

روش کار: چهل و پنج سر موش صحرایی نر نژاد ویستار به سه گروه تقسیم شدند. به گروه 1 (کنترل نرمال) نرمال سالین تزریق شد. به گروه های 2 و 3 به ترتیب 4 میلی گرم بر کیلوگرم پروپرانولول (P4) و 8 میلی گرم بر کیلوگرم پروپرانولول (P8) به صورت زیر جلدی تزریق شد. نمونه خون (قبل ، بلافاصله ، 6، 24 و 72 ساعت بعد از جراحی) جمع آوری شد. سطح IL-2 ، IFN-γ، TNF-α، WBCsو لنفوسیت ها تعیین شد. داده ها با استفاده از آنالیز واریانس یک طرفه و آزمون پیرسون با سطح معنی داری $P\leq 0/05$ تجزیه و تحلیل شدند.

نتایج: نتایج نشان داد سطح IL-2 در گروه‌های P8 و P4 با اختلاف معنی‌داری نسبت به گروه کنترل بالاتربود($P\leq 05/0$). TNF-α درگروه P8 نسبت به گروه P4 و شاهد TNF-α کاهش معنی‌داری داشت($P\leq 05/0$) . گروه P4 سطح پایین تری را در مقایسه با گروه P8 و شاهد از IFN-γ با اختلاف معنی داری نشان داد($P\leq 05/0$).

نتیجه گیری: به نظر می رسد پروپرانولول اثرات تعدیل کننده ایمنی قابل توجهی بر پاسخ های ایمنی دارد. بنابراین، استفاده حین جراحی از پروپرانولول ممکن است عملکرد سیستم ایمنی را بهبود بخشد.

کلمات کلیدی: IL-2، IFN-γ، TNF-α، پروپرانولول، استرس جراحی