

Original Article

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



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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, 24, and 72 hours after surgery). Then, the IL-2, IFN- γ , TNF- α , WBCs, and lymphocytes levels were determined at different time points. The data were analyzed by one-way ANOVA and the Pearson-test at 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 ($P \leq 0.05$).

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

Keywords: Interleukin-2, Interferon- γ , Tumor necrosis factor- α , Propranolol, Surgical stress

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Introduction

The function of innate and acquired immune defense mechanisms is to protect the body against pathogens. Studies have shown that surgery as a treatment affects specific and non-specific immune systems (Yagawa & Tanigawa, 2017). Operation results in metabolic, endocrine, and immunosuppression responses and causes complications such as infection and tumor metastasis (Shankar Hari & Summers, 2018). Surgical stress stimulates the hypothalamic-pituitary-adrenal (HPA) axis. Subsequently, it increases the secretion of adrenocorticotrophic (ACTH) and glucocorticoids such as cortisol, contributing significantly to 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 & 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 interleukin-2 (IL-2), interferon- γ (IFN- γ), tumor necrosis factor- α (TNF- α) 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 β 2-adrenergic receptors on the surface of immune cells, causes immunosuppressive effects (Shimba & Iku-ta, 2020). Adrenaline activates β 2 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 made 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) from the adrenal glands (Eckerling et al., 2021). Therefore, in light of the 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 β 2 receptors with general or specific antagonists (Amaro et al., 2020). Propranolol affects the immune system cells by blocking β 2 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, and so on (O'Connor & Thayer, 2021).

Thus, this study aims to investigate the effects of pre-operative administration of propranolol (by targeting catecholamines and inhibition of beta-adrenoceptor activity) on blood levels of IL-2, IFN- γ , 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

Study animals

Forty-five adult male albino Wistar rats (5 weeks old) were purchased from the Faculty of Pharmacy of Kermanshah University of Medical Sciences, Kermanshah City, Iran. 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 study (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.

Sample collection

Blood sampling was done 5 times 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). About 4-5 mL of blood was taken directly from the heart using a 22-gauge syringe to reduce

Table 1. Characteristics of the laboratory model used in the research (n=15)

Variables	DW	P4	P8
Age (m)	4	4	4
Average weight before surgery (g)	218±4.03	221±5.1	212±2.2
Duration of surgery (min)	30	30	30
Laparotomy (selective surgery)	+	+	+

Abbreviation: DW: Distilled water (control group); P4: Propranolol group (4 mg/kg); P8: Propranolol group (8 mg/kg); M: Month.

possible blood hemolysis. The blood was immediately transferred to two different tubes. Half of each sample was transferred to a tube containing EDTA anticoagulant for routine cell count and hematology tests. The other half was transferred to an anticoagulant-free tube for serum separation. The samples were centrifuged at 2000 rpm 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 µL sampler and kept at -20°C until measured using the ELISA method.

The serum level of measured cytokines was analyzed using the ELISA method with commercial kits for IL-2 (Diacclone Co, France), 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% (Daropaksh 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 this experiment, anesthesia was induced for 3.65 min. The appropriate duration of surgical anesthesia was provided (38.3 min) by intraperitoneal injection of propofol (100 mg/kg) and midazolam (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 to 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 abdomen was sutured in both layers using a simple continuous method (Catgut 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 start, 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 using Excel software, version 18.

Data analysis

All data were statistically analyzed using SPSS software, version 18. 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 ANOVA and LSD tests were used. The Pearson test was used to investigate the relationship between the differences of two factors at different blood sampling times. $P \leq 0.05$ was considered significant.

Results

Serum levels of measured cytokines

The results of the normality of the ELISA test are shown 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 by 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 (n=15)

Parameter (pg/mL)	Min	Max	Mean±SD	Skewness	Kurtosis
IL-2	3	597	352.67±148.72	-0.350	-0.641
TNF-α	6	871	305.80±294.01	0.900	-0.172
IFN-γ	1	712	275.76±170.95	0.987	0.425

Abbreviation: IL-2: Interleukin-2; TNF-α: Tumor necrosis factor-alpha; IFN- γ: Interferon-gamma.

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

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 these groups' samples taken three days after surgery. At the same time, the decrease in IL-2 level in the P8 group was significant 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 h 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 h samples ($P \leq 0.05$) (Figure 1).

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 h after surgery in group C, a significant decrease has been seen in its level in group P4 samples 6 h after surgery. In both groups, serum TNF-α levels returned to normal 72 h 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 normal until 24 h after surgery. The serum level of this cytokine showed a significant increase in the P8 group 72 h after surgery ($P \leq 0.05$) (Figure 2).

The serum level of IFN-γ in the C group did not show a significant change until 6 hours after surgery. A significant increase has been seen in the level of this cytokine in 24-h samples of this group ($P \leq 0.05$). There was a significant increase in 72-h samples compared to 6-h samples ($P \leq 0.01$, $P \leq 0.05$, respectively). In the 6-h samples, a significant rise in IFN-γ was seen in the P4 group ($P \leq 0.05$). In comparison, this increase has been seen 24 hours after

Table 3. The serum levels of investigated cytokines in different time points in the studied groups

Group	Parameter (pg/mL)	Before Surgery	Mean±SD			
			After Surgery			
			Immediately	6 h	24 h	72 h
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

Abbreviation: IL-2: Interleukin-2; TNF-α: Tumor necrosis factor-alpha; IFN- γ: Interferon-gamma; C: Control group; P4: Propranolol group (4 mg/kg); P8: Propranolol group (8 mg/kg).

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

Parameter (pg/mL)	Compared Groups	Mean Difference	Sig.
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

Abbreviation: IL-2: Interleukin-2; TNF-α: Tumor necrosis factor-alpha; IFN- γ: Interferon-gamma.

^aSignificance level of 95%, ^{ab}Difference in the significance of the drug effect.

surgery in the P8 group ($P \leq 0.05$). The P4 group had a higher level of IFN-γ in the 6-h samples compared to the control group and P8 group. At the same time, there was a significant increase in the 24-h samples of the P8 group compared to the C and P4 groups ($P \leq 0.01$) (Figure 3).

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 (Figures 4 and 5).

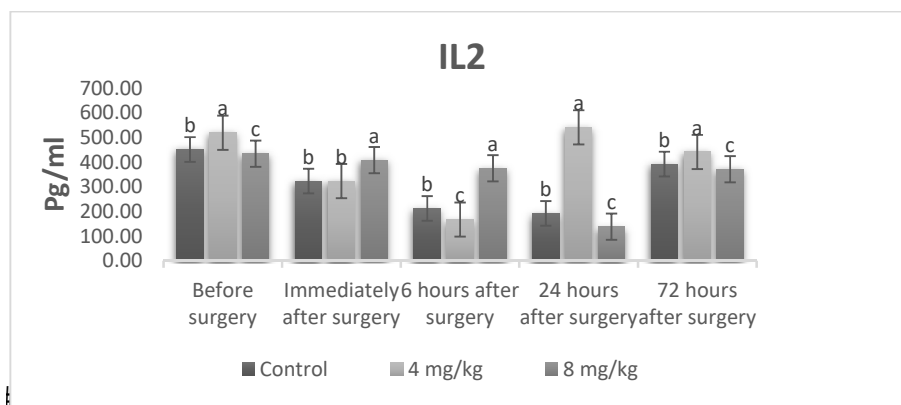


Figure 1. IL2 levels changes in the study period

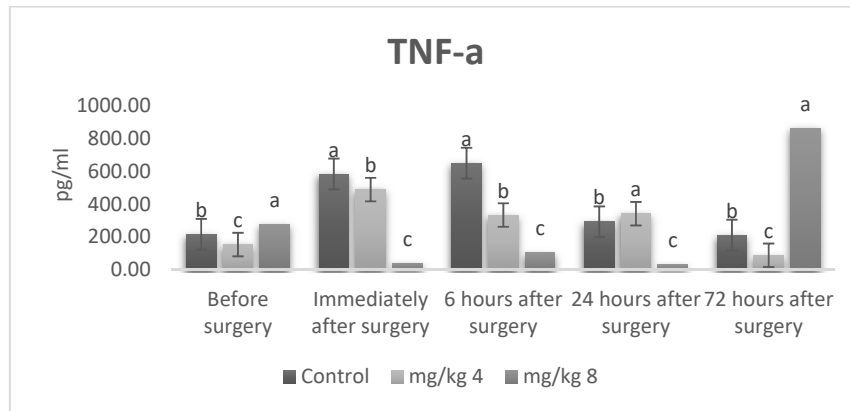


Figure 2. TNF-α levels changes in the during the study period

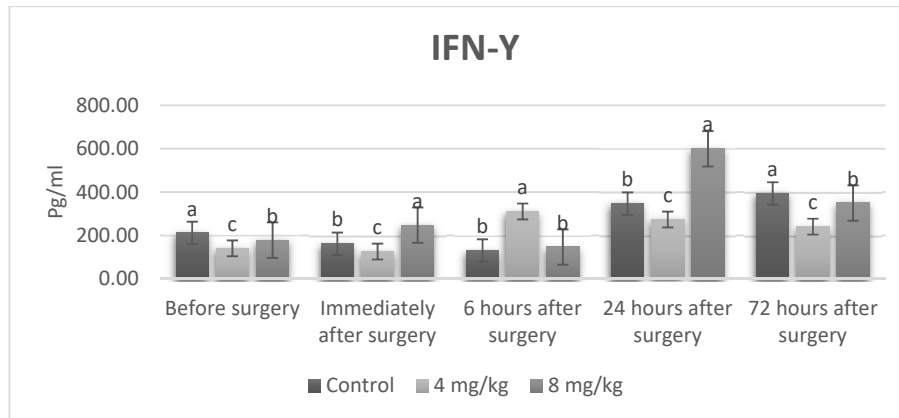


Figure 3. IFN-γ levels changes during the study period

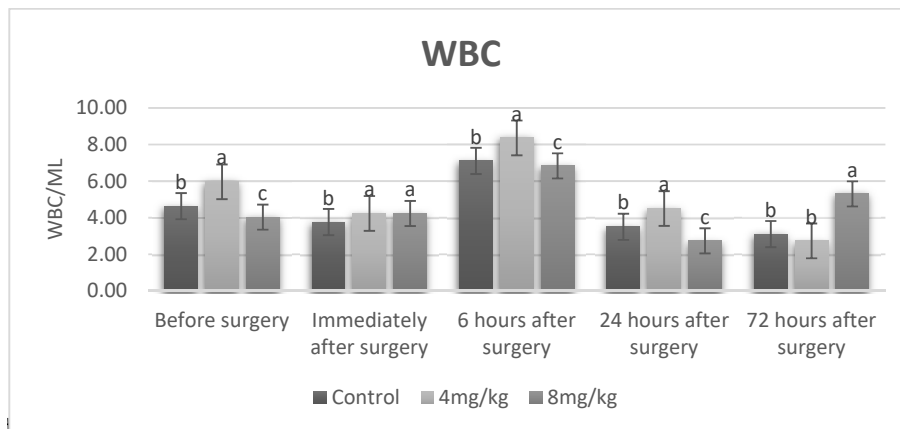


Figure 4. Changes in the total number of WBC during the study period

Discussion

The body’s reaction to various stimuli is called stress. Any factor that affects body tissue can change the homeostasis balance (Everly & Lating, 2019). The surgery

causes a type of stress called surgical stress. The response to surgical stress is a part of the systemic response and includes a wide range of neuroendocrine, metabolic, immunological, and hematological events (Hirose et al., 2022). The studies about the impact of surgical stress on

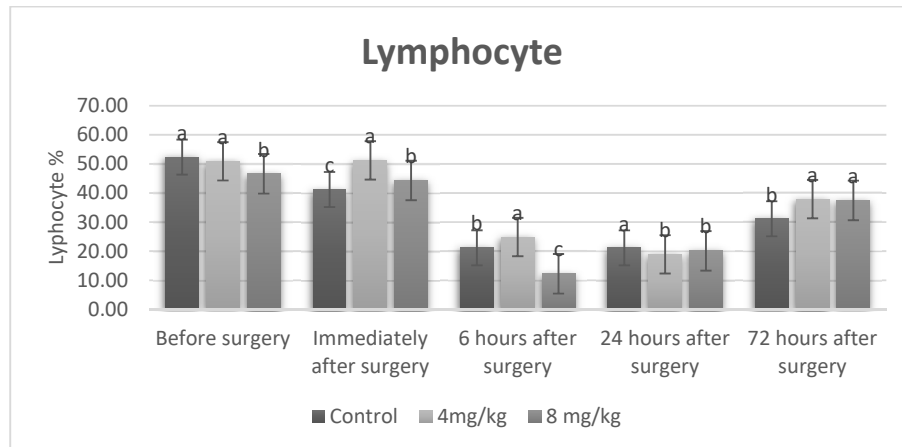


Figure 5. Changes in the number of lymphocytes during the study period

various body systems, especially the immune system, emphasize that this stress weakens the immune system and, therefore, directly impacts the surgery outcomes. 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). Studies have shown that releasing compounds, such as glucocorticoids and catecholamines, 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 post-surgery, avoiding immunosuppression, and increasing the likelihood of surgical success and patient treatment. The prescription of propranolol with a specific dose before operation maintains the body's homeostasis balance as one of the main aspects of the host's defense against surgical stress. Propranolol effectively prevents decreased TNF- α levels (Shaaban & El-Menshawly, 2021). The significance 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 6 hours.

Also, no significant decrease in IL-2 serum levels was observed in this 24 h sample. Propranolol has appropriate anti-anxiety effects by blocking adrenaline receptors (blocking beta sympathetic receptors) (Śmiałowska & Zięba, 2021). It reaches the maximum plasma concentration after 1 to 3 hours, and its half-life is 4 to 5 hours. However, its effect lasts longer than its half-life and may

continue up to 12 hours (Kalam & Rasool, 2020). Propranolol blocks β -2 receptors of immune cells in rats for 6-12 hours (Jean Wrobel et al., 2016). Therefore, it is probably not attached to its receptor in 24 h 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 h samples compared to the control and P4 groups. Contrary to 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 ones (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 did not show 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 the T cells. Meanwhile, in the 8 mg/kg receiving group, the blocking effects of catecholamines have been seen at least 6 hours after surgery. 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. The 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 7 days after surgery, the changes in serum levels of adrenaline and noradrenaline show higher levels of adrenaline up to 7 days after surgery (Eckertling & Ricon-Becker, 2021; Silva et al., 2022). Pantziarka et al. reported that propranolol performed better in preventing lung tumor metastasis with a dose of 1.5 mg/kg rather than the 4.5 mg/kg group. A study shows 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 a moderate amount 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, but 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 major surgeries with severe pro-inflammatory stages, the inhibition of TNF- α production increases post-surgical complications like infection and mortality (Ko & Rubenstein, 2018). The presence of β -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 decreasing 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, FOXP3+ (a necessary transcription factor for regulatory T cells) is at its lowest level in the pro-inflammatory step (Georgiev & Charbonnier, 2019). This event 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 finding aligns 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 h 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). Non-antibiotic use due to interference in the tests supported this hypothesis.

Clinical studies have shown that excessive inflammation after surgery increases the mortality rate 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 (Nikfarjam & Adineh, 2017). According to Chu et al.'s study, inhibition of TNF- α signaling pathways, such as NF- κ B and MAPK, reduces dysfunction after surgery in rats (Chu et al., 2013). Different studies have explored the role of TNF- α . T Kataoka et al. 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 propranolol's effect on TNF- α depends on doses. Low doses of propranolol 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, accompanied by a reduction in IFN- γ 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 (Martinez-Barricarte et al., 2018). IL-12 is the primary motive of IFN- γ production. Catecholamines, glucocorticoids, and prostaglandins reduce 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 response measurement (Zhou et al., 2016). In our study, it has been found that propranolol

improves lymphocyte proliferation, which enhances cellular immune responses. These responses are crucial 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 increase that can last for days. Glucocorticoids raise the population of circulating neutrophils through two mechanisms: An inhibitory effect on the expression of sialomucins in the vessel wall, causing the release of peripheral neutrophils into the bloodstream, and by inhibiting the expression of selectins and preventing the apoptosis of carp granulocyte cells. It seems that propranolol prevents the decrease of lymphocytes before surgery but does not affect 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 propranolol, has applications beyond its typical use in research. Stress pathway blockade by β_2 -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 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 and reduces the IFN- γ level by affecting adrenergic receptors. Using propranolol, changes in the immunogenic platform of infiltrated immune cells, such as Th1 in the surgical microenvironment, may effectively correct the body's cytokine patterns. 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 it.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Animal Ethics Committee of Razi University (Code: Razi. AEC, 396-2-031).

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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مقاله پژوهشی

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

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چکیده

زمینه مطالعه: جراحی با مکانیسم‌های مختلف باعث سرکوب سیستم ایمنی در دوره بعد از عمل می‌شود.

هدف: این مطالعه باهدف بررسی اثرات تجویز پروپرانولول قبل از جراحی بر سطوح خونی اینترلوکین-۲ (IL-2)، اینترفرون (IFN- γ)، فاکتور نکروز تومور- α (TNF- α) و پارامترهای خونی مانند گلبول‌های سفید (WBCs) و لنفوسیت‌ها انجام شد.

روش کار: ۴۵ سر موش صحرایی نر، نژاد ویستار به ۳ گروه تقسیم شدند. به گروه ۱ (کنترل نرمال) نرمال سالین تزریق شد. به گروه‌های ۲ و ۳ به ترتیب ۴ میلی‌گرم بر کیلوگرم پروپرانولول (P4) و ۸ میلی‌گرم بر کیلوگرم پروپرانولول (P8) به صورت زیرجلدی تزریق شد. نمونه خون (قبل، بلافاصله، ۶، ۲۴ و ۷۲ ساعت بعد از جراحی) جمع‌آوری شد. سطح WBCs، TNF- α ، IFN- γ ، IL-2 و لنفوسیت‌ها تعیین شد. داده‌ها با استفاده از تحلیل واریانس یک‌طرفه و آزمون پیرسون با سطح معنی‌داری ($P \leq 0.05$) تجزیه و تحلیل شدند.

نتایج: نتایج نشان داد سطح IL-2 در گروه‌های P8 و P4 با اختلاف معنی‌داری نسبت به گروه کنترل بالاتر بود ($P \leq 0.05$).

TNF- α در گروه P8 نسبت به گروه P4 و شاهد کاهش معنی‌داری داشت ($P \leq 0.05$). گروه P4 سطح پایین‌تری از IFN- γ در مقایسه با گروه P8 و شاهد اختلاف معنی‌داری نشان داد ($P \leq 0.05$).

نتیجه‌گیری نهایی: به نظر می‌رسد پروپرانولول اثرات تعدیل‌کننده ایمنی قابل توجهی بر پاسخ‌های ایمنی دارد. بنابراین، استفاده حین جراحی از پروپرانولول ممکن است عملکرد سیستم ایمنی را بهبود بخشد.

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

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