Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

Investigating the protective potential of dinoprost in a rat model of ischemia-reperfusion

Savas Karakus[a,*], Mustafa Ozkaraca[b]

[a] *Cumhuriyet University, Faculty of Medicine, Department of Obstetrics and Gynaecology, Sivas, Türkiye*
[b] *Cumhuriyet University, Faculty of Veterinary Medicine, Department of Pathology, Sivas, Türkiye*

ARTICLE INFO

Keywords:
Dinoprost
Ischemia/reperfusion injury
Rat ovary
Tissue damage

Received: Sep 26, 2023
Accepted: Nov 21, 2023
Available Online: 27.11.2023

DOI:
10.5455/annalsmedres.2023.09.264

Abstract

Aim: This study investigates the protective effects of Dinoprost against Ischemia/ Reperfusion (I/R) damage in the rat ovary, focusing on the expression of cyclooxygenase-2 (COX-2), Interleukin-1β (IL1β), and Tumor Necrosis Factor-α (TNF-α). Additionally, the impact of Dinoprost on reducing hemorrhage in the ovarian tissue is evaluated.

Materials and Methods: A total of 24 rats were randomly divided into four groups: Control, Ischemia (Isch), I/R, and Dino+I/R. Ischemia was induced by clamping the ovarian blood supply, followed by reperfusion. Dinoprost was administered before reperfusion in the Dino+I/R group. COX-2, IL1β, and TNF-α expression levels were assessed through histochemical and immunochemical analyses. Hemorrhage in the ovarian tissue was also examined.

Results: The Dino+I/R group exhibited a significant decrease in COX-2 expression compared to the Isch and I/R groups ($p<0.05$). However, there were no significant changes in the expression levels of IL1β and TNF-α among the groups. Notably, the Dino+I/R group showed significantly reduced hemorrhage compared to the Isch and I/R groups ($p<0.05$).

Conclusion: Dinoprost demonstrated a protective effect against I/R damage in the rat ovary, primarily by attenuating COX-2 expression and reducing hemorrhage. These findings suggest the potential therapeutic utility of Dinoprost in mitigating ovarian I/R injury, emphasizing its role in preserving ovarian function and fertility.

Introduction

Ischemia/reperfusion (I/R) injury, characterized by the temporary deprivation of blood flow followed by the subsequent restoration of circulation, is a phenomenon that can have profound implications in various organ systems. In reproductive health and ovarian physiology, I/R injury represents a critical challenge, as the ovary is particularly vulnerable to ischemic insults due to its high metabolic activity and extensive vascular supply. This phenomenon has been associated with various pathological conditions, including ovarian torsion, cystectomy, and assisted reproductive technologies such as ovarian transplantation. I/R injury in the ovary can lead to follicular atresia, impaired hormone production, and compromised fertility, all of which have substantial clinical ramifications [1, 3].

The diagnosis of ovarian torsion, which causes ischemia, is challenging. Following the diagnosis of torsion, a surgical procedure called detorsion operation is necessary to prevent damage to the ovarian tissue. In cases of ovarian torsion, various drug treatments have been attempted to prevent damage to the ovary, both due to ischemia and as a result of mediators that emerge after detorsion of the ovary [3,4]. Anti-inflammatory treatments such as prostaglandin E2 (PG E2) have also been used in many studies during and after ischemia to protect tissues from damage caused by mediators associated with reperfusion [5-7].

Prostaglandins (PGs) belong to the eicosanoid family, which consists of oxygenated C20 fatty acids and are generated by virtually all cell types within the organism [8]. Unlike being stored within cells, these lipid mediators are synthesized from arachidonic acid through the catalytic activity of Cyclooxygenase (COX) enzymes. This synthesis can occur constitutively or in response to cell-specific injuries, stimuli, or signaling molecules [8,9].

Recent research highlighting the potential applications of cyclooxygenase-2 (COX-2) inhibitors in cancer chemotherapy [10] and neurodegenerative conditions such as Parkinson's and Alzheimer's diseases [11] continues to fuel inves-

*Corresponding author:
Email address: karakussavas@yahoo.com (Savas Karakus)

tigations into the development of COX-2 inhibitors. Four primary bioactive prostaglandins are produced in vivo: Prostaglandin D2 (PG D2), Prostaglandin E2 (PG E2), Prostaglandin I2 (PG I2), and Prostaglandin F2 alpha (PGF2α). PGs play a pivotal role in producing the inflammatory response, with their biosynthesis markedly elevated in inflamed tissues, contributing to the emergence of the cardinal manifestations of acute inflammation [12].

The investigation of Dinoprost's potential therapeutic utility in mitigating ovarian I/R injury is important due to the clinical relevance of preserving ovarian function and fertility in various medical scenarios. In recent years, considerable research has been devoted to identifying strategies to mitigate the detrimental effects of I/R injury in the ovary. One such avenue of investigation is the utilization of Dinoprost (also known as a synthetic analog of PG F2α, a naturally occurring lipid molecule with potent physiological roles in the female reproductive system [13]. Dinoprost has garnered attention for its potential therapeutic applications in alleviating I/R injury due to its anti-inflammatory and cytoprotective properties [5,14]. However, the precise mechanisms underlying its protective effects in the context of ovarian I/R injury remain a subject of active investigation.

This study aims to contribute to our understanding of Dinoprost's efficacy in mitigating I/R damage in the rat ovary by focusing on the expression and localization of key inflammatory mediators, namely COX-2, Interleukin-1β (IL-1β), and Tumor Necrosis Factor-α (TNF-α). COX-2 is an enzyme responsible for PG synthesis and is often implicated in inflammatory responses. COX-2 is a key enzyme involved in the production of pro-inflammatory PGs. IL-1β and TNF-α are prominent cytokines that are pivotal in orchestrating inflammatory cascades. By employing histochemical and immunochemical techniques, the study aims to elucidate the alterations in the spatial distribution and levels of these markers in response to Dinoprost treatment during ovarian I/R injury.

Materials and Methods

A total of sixty female rats belonging to the Wistar Albino strain, weighing 200-250 grams, were employed in this study. Procuring these animals was facilitated through the Animal Research Laboratory at Cumhuriyet University. Subsequently, they were accommodated within a controlled environment with a 12-hour light-dark cycle, maintaining a temperature of 21±2°C. Before commencing the experimental procedures, the rats underwent 15 days of acclimatization to the laboratory conditions. Throughout the study, they were afforded unrestricted access to standard laboratory chow and water. It is crucial to note that this research endeavor adhered rigorously to the ethical principles established by Cumhuriyet University (Approval No: 14.07.2023-612).

Experimental groups

The rats were randomly divided into four experimental groups, each consisting of six animals:

Control Group (Ctrl): After anesthetizing all the experimental animals, the bilateral ovaries were removed four hours after opening and closing the abdomen.

Ischemia Group (Isch): Rats in this group underwent ovarian ischemia. The procedures for this group were as follows:

- The rats were anesthetized using.
- A midline abdominal incision was made, and both bilateral ovaries were identified.
- The ovaries were subjected to Isch by rotating them 360 degrees around their own axes.
- After 4 hours of Isch, the bilateral ovaries were removed.

Ischemia/Reperfusion Group (I/R): Rats in this group underwent both ischemia and reperfusion. The procedures for this group were as follows:

- Ischemia was induced as described by the Isch Group.
- After 4 hours of ischemia, the ovaries were subjected to 4 hours of reperfusion.
- Subsequently, the bilateral ovaries were removed.

Dinoprost + Ischemia/Reperfusion Group (Dino+I/R): Rats in this group received Dinoprost treatment prior to reperfusion. The procedures for this group were as follows:

- The rats were given a solitary 6 mg/kg dosage.
- In the test group, they were subjected to daily subcutaneous doses of Dinoprost (6 mg/kg) for three consecutive days prior to the onset of ischemia.
- Ischemia was induced as described by the Isch Group. Furthermore, it was administered to rats in the Dino+I/R group subcutaneously 30 minutes before reperfusion.
- After 4 hours of reperfusion, the bilateral ovaries were removed.

The primary endpoint variables of the study were defined as the expression levels of cyclooxygenase-2 (COX-2), Interleukin-1β (IL1β), and Tumor Necrosis Factor-α (TNF-α), as well as the extent of hemorrhage in the ovarian tissue. The expression levels were determined through immunohistochemical staining, while the extent of hemorrhage was evaluated through histopathological examination. To ensure the ethical and responsible use of animals in research, the committee recommended reducing each group to 6 rats. This approach was adopted to minimize the overall use of rats.

Surgical procedure

Rats were anesthetized using Xylazine (10 mg/kg) (Alfazyne 2%, Ege Vet San. Tic, İzmir, Turkey) and Ketamine hydrochloride (50 mg/kg) (Pfizer Ltd, in Turkey) obtained and maintained on a temperature-controlled surgical platform. A midline abdominal incision was made, and the ovaries were carefully exposed. Ischemia was induced by occluding the ovarian blood supply using atraumatic vascular clamps for 4 hours. Reperfusion was initiated by removing the clamps and restoring blood flow to

the ovaries. In the Dinoprost Treated Group, Dinoprost (6 mg/kg) (Zoetis Türkiye, in Turkey) was administered subcutaneously 30 minutes before reperfusion. Euthanasia was performed by an overdose of anesthetic usage at the end of the experimental procedures.

Histopathological method

At the end of the reperfusion period, rats were euthanized. Ovarian tissues were carefully dissected and collected for further analysis. Tissues were subjected to routine alcohol-xylene processing procedures and taken into paraffin blocks, and subsequently, histological examination was performed to assess morphological changes, tissue damage, and apoptosis. Sections of 5 µm thickness taken to poly-lysine-coated slides were stained with hematoxylin-eosin, and 6 random areas were performed in terms of hemorrhage according to Table 1.

Immunohistoliogical method

Sections of 5 µm thickness, obtained on polylysine-coated slides, underwent xylene and alcohol series, followed by a wash with PBS. Subsequently, endogenous peroxidase inactivation was achieved by treating the sections with 3% H_2O_2 for 10 minutes. In order to expose antigens in the tissues, antigen retrieval solution was applied to the sections for 2 sessions of 5 minutes each at 500 watts. Afterward, the tissues, which were rinsed with PBS, were incubated overnight at +4 ºC with COX-2 (Abcam, Catalog no. ab-15191), IL1β (Santa Cruz, Catalog No. sc-52012), and TNF-α (Santa Cruz, Catalog No. sc-133192) primary antibodies at a dilution ratio of 1/200.

As for the subsequent stage, the Large Volume Detection System: anti-polyvalent, HRP (Thermofischer, Catalog no: TP-125-HL) was employed, following the guidelines provided by the manufacturer. DAB (3,3'-Diaminobenzidine) served as the chromogen. After counterstaining with Mayer's Hematoxylin, the sections were cover-slipped using Entellan and examined under a light microscope. Immunopositivity during the examination was semiquantitatively evaluated, with categorizations of negative (-), weak (+), moderate (++), and strong (+++).

Statistical analysis

The normality of the data distribution was assessed using the Shapiro-Wilk test. The results indicated that some variables did not follow a normal distribution ($p<0.05$). Therefore, nonparametric statistical methods were employed to analyze histopathological and immunohistochemical data. The Kruskal-Wallis test, a nonparametric statistical method, was used to assess the differences among the groups in the histopathological evaluation of ovary tissues. The Mann-Whitney U test, another nonparametric test, was utilized to identify the specific group responsible for the observed differences in the histopathological evaluation. The data were presented as mean ± standard error of the mean (SEM) for both histopathological and immunohistochemical findings. SPSS 20.00, a statistical analysis software, was used for the data analysis. The significance level (p-value) was set at 0.05 to determine the groups' presence of statistically significant differences.

Results

Histopathological findings

Histopathological evaluation revealed statistically significant differences between the groups (Table 1).

The tables above display the histopathological examination of ovary tissues in the rats, control, Isch, I/R, and Dino+I/R groups. In the visual observation of the control group, it was observed that the ovaries displayed a histological appearance within the normal range. Control groups significantly reduced compared to the Isch

Table 1. The categorization of hemorrhage based on the extent of the whole area affected.

Hemorrhage
No (-)
Whole area <10% (+)
Whole area 10-30% (++)
Whole area 30%>(+++)

Table 2. The groups and their respective hemorrhage values.

Groups (n)	Hemorage
Control (6)	0.00 (0.000.25)^{a}
Isch(6)	3.00 (3.00-3.00)^{b}
I/R(6)	3.00 (2.75-3.00)^{cb}
DINO+I/R(6)	2.00 (2.00-2.00)^{dcb}

p<0.001**

Data were presented as median (Q1-Q3) p<0,001**, p a,b,c,d <0,05* Kruskal Wallis test, Dunn Test.

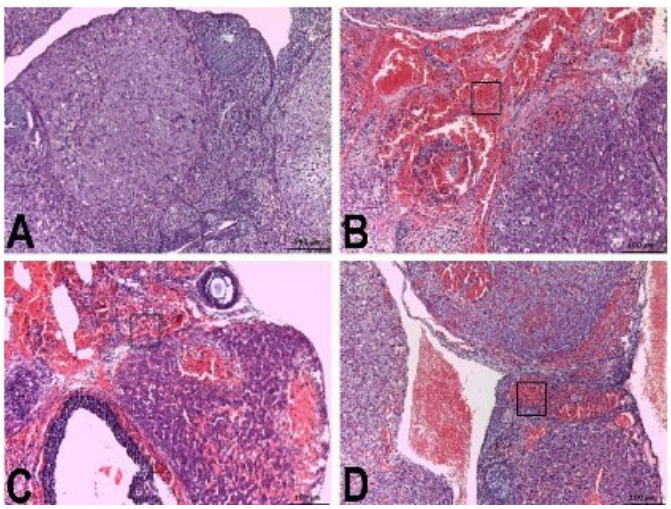

Figure 1. A- Control group. Normal histological appearance, B- (Isch) group. At severe level, Hemorrhage (□), C- (I/R) group. At severe level, Hemorrhage (□), D- (Dino+I/R) group. Moderate level Hemorrhage (□), H-E.

Table 3. Expression of COX-2, IL1β, and TNF-α in gifferent groups.

Groups (n)	COX-2	IL1β	TNF-α	p
Control (6)	0.00 (0.00-0.25)^{aA}	0.00(0.00-0.25)^{aA}	0.00(0.00-0.25)^{aA}	0.999
Isch(6)	3.00 (2.75-3.00)^{bA}	2.00(2.00-2.00)^{bB}	3.00(2.00-3.00)^{bAB}	0.030*
I/R(6)	3.00 (3.00-3.00)^{cA}	2.00 (2.00-2.25)^{bB}	3.00 (2.75-3.00)^{cbdAB}	0.015*
DINO+I/R(6)	2.00(2.00-2.25)^{bc}	2.00(2.00-2.00)^{c}	2.00(2.00-2.25)^{db}	0.015*
p	<0.001**	<0.001**	<0.001**	^{A,B}p<0.05*

$^{a, b,c}$P<0. 001**, ^{A,B}p <0.05* Kruskall Wallis, Dunn test, Friedman test, Wilcoxon t test.

Data were presented as median (Q1-Q3).

A, B and capital letters indicate comparisons from right to left.

A, b, c, d and lowercase letters indicate comparisons from top to bottom.

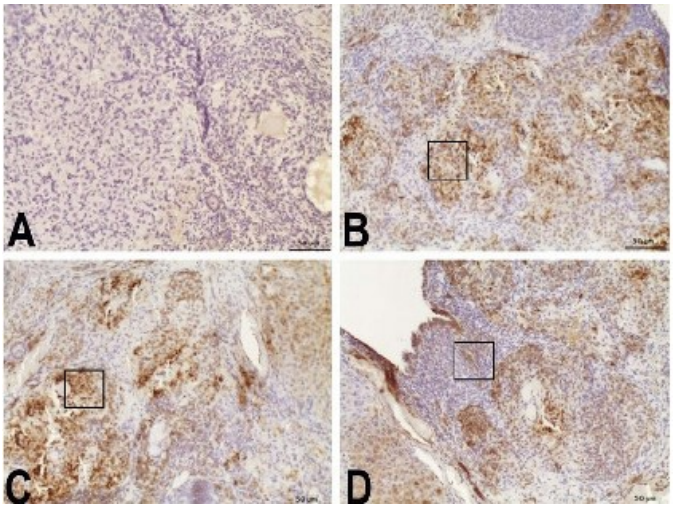

Figure 2. A- Control group. Immune negativity, B- (Isch) group. Severe-level, C- (I/R) group. Severe-level, D- (Dino+I/R) group. Moderate-level COX-2 immune positivity (□), IHC.

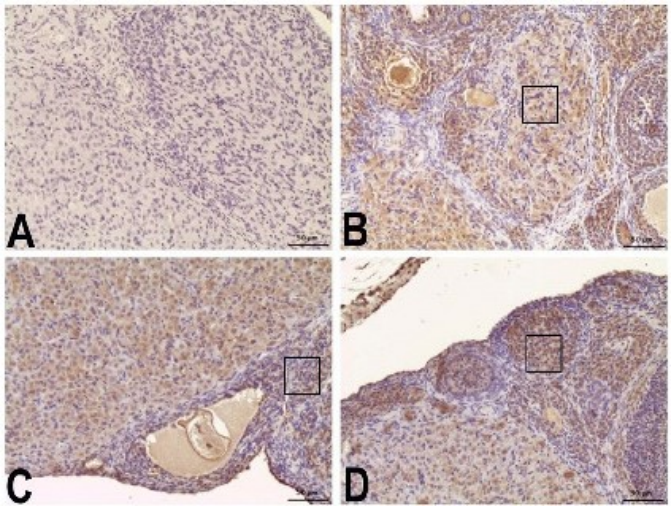

Figure 3. A- Control group. Immune negativity, B- (Isch) group. Severe-level, C- (I/R) group. Severe-level, D- (Dino+I/R) group. Severe-level IL1β immune positivity (□), IHC.

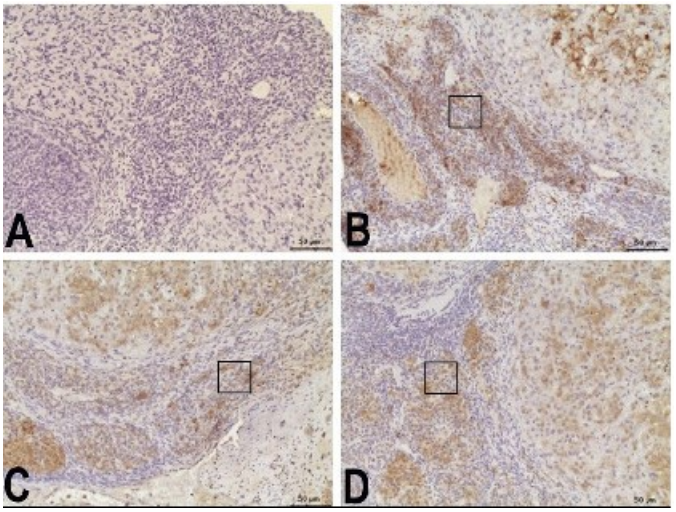

Figure 4. A- Control group. Immune negativity, B- (Isch) group. Moderate-level, C- (I/R) group. Moderate-level, D- (Dino+I/R) group. Moderate-level TNF-α immune positivity (□), IHC.

group, I/R group, and Dino+I/R group concerning the hemorrhagical score ($p<0.05$). The Dino+I/R group significantly decreased the hemorrhagic score compared to the Isch group and I/R group ($p<0.05$). The hemorrhagia scores were significantly lower in the rats' control and Dino+I/R group compared to the Isch group and I/R group ($p<0.05$) (Table 2). However, there were no significant differences between the Isch and I/R groups concerning hemorrhegia ($p>0.05$). The control group exhibited ovaries with a histological appearance, which is considered normal. In contrast, both the Isch and I/R groups displayed severe hemorrhage in the ovarian tissue. In the Dino+I/R group, hemorrhage was mild (Figure 1).

Immunohistochemical findings

Immunohistochemical staining with COX-2, IL1β, and TNF-α showed statistically significant differences (Table 3).

Table 3 shows that the expression levels of COX-2, IL1β, and TNF-α were significantly increased in the Isch, I/R, and DINO+I/R groups compared to the control group. The DINO+I/R group had lower expression levels of COX-2 compared to the Isch and I/R groups, but the differences

in IL1β and TNF-α expression levels between these groups were not significant.

COX-2 staining showed severe immunopositivity in the Isch and I/R groups, while DINO+I/R was moderately positive. On the other hand, staining with IL1β revealed severe immunopositivities in all application groups, whereas staining with TNF-α revealed moderate immunopositivities in all application groups (Figure 2-4).

Discussion

The present study investigates the protective potential of Dinoprost in a rat model of Ischemia-Reperfusion (I/R) injury on ovarian tissue. The results showed a significant decrease in COX-2 expression and reduced hemorrhage in the Ischemia-Reperfusion Dinoprost (Dino+I/R) group compared to the Ischemia (Isch) and I/R groups. Additionally, the Dino+I/R group exhibited moderate-level immune positivity for IL1β and TNF-α, indicating a potential therapeutic effect of Dinoprost in mitigating ovarian I/R injury and preserving ovarian function and fertility.

PGs hold a pivotal position in instigating the inflammatory response. Their biosynthesis experiences a substantial upsurge within inflamed tissue, thereby contributing to the emergence of the hallmark features associated with acute inflammation. Within the context of an inflammatory response, both the magnitude and the pattern of PG generation undergo dramatic alterations. Typically, PG production remains minimal in non-inflamed tissues; however, it experiences an immediate surge during the onset of acute inflammation, preceding the recruitment of leukocytes and the infiltration of immune cells.

PG production relies upon the activity of PG synthases, commonly called COXs. These enzymes are bifunctional, encompassing both cyclooxygenase and peroxidase functions, and they exist in distinct isoforms known as COX-1 and COX-2 [15]. COX-1, widely distributed in most tissues, contributes to the physiological generation of PGs for maintaining normal homeostasis. In contrast, COX-2, induced by cytokines, mitogens, and growth factors, primarily governs PG production at inflammatory sites [16]. Notably, COX-2 is extensively implicated in prostanoid synthesis. This enzyme plays a significant role in the body's responses to inflammation and pain and is associated with oxidative stress. It is activated when the body is exposed to pro-inflammatory cytokines and stressors. Given the documented increase in COX-2 expression in the brain and PG levels in cerebrospinal fluid in Alzheimer's disease, coupled with the observed correlation between COX-2 protein levels in the brain and clinical dementia and the severity of amyloidosis, there is a suggestion that the inhibition of COX-2 by NSAIDs may play a role in the perceived protection in this context [17].

In an investigation conducted by Matsuyama M. et al. [18], they examined COX-1 and COX-2 expression levels in rats subjected to a 90-minute occlusion of their renal artery and vein using a hemostasis clip. The rats were euthanized at different times, specifically at 0, 1.5, 3, 5, 12, and 24 hours after the reperfusion period began. The study results indicated that COX-2 expression reached its highest levels on the endothelial cells of the renal tissue at 3 and 5 hours after reperfusion, as detected through immunohistochemical staining. This finding suggests a direct association between increased COX-2 expression and the severity of renal I/R injury.

A notable investigation by Hamada et al. [19] involving COX-2-deficient mice has yielded significant insights suggesting an active involvement of COX-2 in liver I/R injury. Their findings indicate that COX-2-deficient mice exhibited a considerable reduction in liver damage following an I/R insult. Furthermore, these livers exhibited elevated levels of the anti-inflammatory cytokine IL-10, thereby tilting the immune response balance towards a Th2 response in COX-2-deficient mice. The absence of COX-2 expression led to diminished levels of CXCL2, a chemokine responsible for neutrophil activation, resulting in reduced infiltration of MMP-9-positive neutrophils and impaired macrophage activation during the later stages of liver I/R injury. The expression of IL-2 mRNA, which belongs to the Th1-type cytokine category, was significantly diminished in the presence of COX-2. It is worth noting that COX-2 plays a pivotal role as a prominent inflammatory mediator [20]. This observation raises the prospect of leveraging COX-2-derived prostanoid pathways as a promising avenue for therapeutic interventions in the context of liver I/R injury. Our research underscores the potential utility of Dinoprost as a therapeutic candidate for inflammatory conditions. The administration of Dinoprost may reduce the migration of neutrophils and lymphocytes to the site of inflammation, ultimately mitigating tissue damage and injuries associated with inflammation. These findings shed light on the multifaceted anti-inflammatory mechanisms employed by Dinoprost. The downregulation of COX-2 by Dinoprost suggests its capacity to modulate the PG pathway, thereby exerting anti-inflammatory effects.

Additionally, there have been observations of elevated concentrations of PGF2α in melanoma tumor cells compared to healthy tissues [14]. This increased PGF2α presence appears to confer a protective effect on these cells, potentially rescuing them from undergoing apoptosis. Furthermore, the concurrent use of PG antagonists has been shown to enhance the action of non-steroidal anti-inflammatory drugs [21]. PGF2α, the PG in question, has also been implicated in promoting the migration and invasiveness of colorectal tumor cells [22,23]. Within colorectal carcinoma cells, stimulation by PGF2α has been associated with heightened migratory and invasive capabilities [23]. Moreover, the PGF2α-cognate receptor pathway has been shown to augment cell proliferation, angiogenesis, and migration in carcinoma cells by activating the Extracellular Signal-regulated Kinase pathway, particularly in endometrial cancer [24,25]. In our study, cell death in ovarian tissue may have been less after dinoprost administration.

In addition to its direct effects on inflammation, PGF2α has also been shown to interact with immune cells. Maehara et al. [5] conducted a study focusing on PGF2α influence on macrophage polarization. They found that PGF2α played a role in encouraging the transformation of macrophages into an anti-inflammatory M2 phenotype. The generation of anti-inflammatory cytokines, including interleukin-10, marked this transformation. This shift in

macrophage polarization suggests a broader immunomodulatory role for PGF2α in regulating the immune response to inflammation.

PGF2α is a bioactive lipid mediator that regulates various physiological processes, such as blood pressure homeostasis [26]. Its biosynthesis is markedly induced under oxidative stress, hypercholesterolemia, smoking, or inflammation, as observed during rheumatic disease [27] and type 1 or 2 diabetes mellitus [28,29]. Excessive angiogenesis also occurs in diabetic nephropathy [30]. The PGF2α/PTGFR axis may be involved in the pathogenesis of diabetic retinopathy.

Zhao et al. [31] investigate the molecular mechanism through which PGF2α promotes the proliferation of retinal microvascular endothelial cells. Their study unveiled an elevation in circulating PGF2α metabolites among type 2 diabetic patients with proliferative retinopathy. Additionally, they observed an upregulation of the PGF2α receptor in retinal endothelial cells using a mouse model of oxygen-induced retinopathy. These findings led them to propose that PGF2α played a role in promoting the proliferation and tube formation of human retinal microvascular endothelial cells. In our study, it was observed that the administration of Dinoprost may have led to an increase in upregulated endothelial cells and excessive angiogenesis, ultimately contributing to the mitigation of tissue damage. These discoveries underscore the multifaceted mechanisms through which Dinoprost operates.

Cure et al. [4] investigated a study to explore the potential protective benefits of Adalimumab in reducing oxidative stress and cellular damage in rat kidney tissue following I/R injury. They assessed the levels of IL-6, TNF-α, and IL-1β expression in a rat model after the administration of ADA. Their investigation revealed that the levels of IL-1β and TNF-α decreased in the group treated with ADA compared to both the I/R group and the Ctrl group. Our study showed no statistical difference in terms of IL-1β and TNF-α. IL-1β and TNF-α are well-established pro-inflammatory cytokines known to play key roles in the inflammatory response associated with I/R injury. They are typically upregulated in response to tissue injury, and their expression is often used as markers of inflammation [32]. However, While the study did not find significant differences in IL-1β and TNF-α expression, it is essential to consider that PGE2 may exert its protective effects through alternative pathways. PGF2α can modulate the release of other cytokines, promote tissue repair, and influence immune cell behavior [12].

The study's findings have several practical implications, particularly in the potential use of Dinoprost in clinical settings to protect the ovary from ischemia-reperfusion (I/R) injury. The study demonstrated that Dinoprost administration prior to reperfusion in a rat model of I/R injury resulted in a significant decrease in cyclooxygenase-2 (COX-2) expression and reduced hemorrhage in the ovarian tissue. These effects suggest the therapeutic utility of Dinoprost in mitigating ovarian I/R injury, emphasizing its role in preserving ovarian function and fertility.

In a clinical context, using Dinoprost could be explored as a preventive measure during surgical procedures that may induce ovarian I/R injury, such as ovarian torsion or cystectomy. Additionally, Dinoprost may be considered a protective agent in assisted reproductive technologies, including ovarian transplantation, where I/R injury can compromise the procedure's success.

Future research directions should focus on investigating the long-term effects of Dinoprost administration and determining the optimal dosage and timing of its administration. Understanding the duration of Dinoprost's protective effects and the most effective treatment regimen will be crucial in translating these findings into clinical practice.

Furthermore, elucidating the underlying mechanisms of Dinoprost's protective effects in the context of ovarian I/R injury is essential. The study's focus on COX-2, interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α) provides valuable insights into the inflammatory response associated with I/R injury. However, additional research is needed to fully understand the role of Dinoprost in modulating these inflammatory mediators and its impact on overall tissue preservation.

The present study has some limitations. First, it was conducted using a rat model, and the results may not directly translate to human physiology. Further investigations are needed to validate the findings in human subjects. Another limitation of the study includes a small sample size due to the maximum of 6 allowed for rat experiments and the use of nonparametric tests due to the number of groups being less than 10. Additionally, in-depth molecular studies should elucidate the underlying mechanisms of Dinoprost's effects on COX-2, IL1β, and TNF-α expression. Overall, this research provides valuable insights into the potential therapeutic applications of Dinoprost in the field of reproductive medicine.

Limitations

The study's limitations include the small sample size and the use of a rat model, which may not fully represent the human condition.

Conclusion

The results demonstrated that DINO administration significantly reduced the number of hemorrhages and the expression of COX-2, IL1β, and TNFα in the I/R and DINO+I/R groups compared to the I/R group. Additionally, the DINO+I/R group showed a lower number of hemorrhages and a lower expression of COX-2, IL1β, and TNF-α compared to the I/R group, indicating the potential protective effects of DINO against I/R injury. Further research is needed to validate these findings and explore the underlying mechanisms of DINO's protective effects.

Conflict of interest

No conflict of interest is reported by the authors.

Ethical approval

Ethical approval was received for this study from Sivas Cumhuriyet University Animal Experiments Local Ethics Committee (Approval No: 14.07.2023-612).

References

1. Kalogeris T, Baines C, Krenz M, Korthuis RJ. Cell biology of ischemia/reperfusion injury. Int Rev Cell Mol Biol. 2012;298:229–318.
2. Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. N Engl J Med. 2007;357(11):1121-35.
3. Kartal B, Bozkurt MF, Alimoğullari E, Saçık U. The protective effect of erythropoietin on ischemia- reperfusion injury caused by ovarian torsion-detorsion in the experimental rat model. J Histotechnol. 2023;46(2):57-64.
4. Cure MC, Cure E, Kalkan Y, et al. The Protective Effect of Adalimumab on Renal Injury in a Model of Abdominal Aorta Cross-Clamping. Adv Clin Exp Med. 2016;25(2):219-26.
5. Maehara T, Fujimori K. Contribution of FP receptors in M1 macrophage polarization via IL-10-regulated nuclear translocation of NF-κB p65. Biochim Biophys Acta Mol Cell Biol Lipids. 2020;1865(5):158654.
6. Westman M, Korotkova M, af Klint E, et al. Expression of microsomal prostaglandin E synthase 1 in rheumatoid arthritis synovium, Arthritis Rheum. 2004;50(6):1774-80.
7. Miyoshi H, VanDussen KL, Malvin NP, et al. Prostaglandin E2 promotes intestinal repair through an adaptive cellular response of the epithelium. EMBO J. 2017;36(1):5-24.
8. Smith WL. The eicosanoids and their biochemical mechanisms of action. Biochem J. 1989;259(2):315-24.
9. Berenbaum F. Pro-inflammatory cytokines, prostaglandins, and the chondrocyte: mechanisms of intracellular activation. Joint Bone Spine. 2000;67(6):561-4.
10. Vosooghi M, Amini M. The discovery and development of cyclooxygenase-2 inhibitors as potential anticancer therapies. Expert Opin Drug Discov. 2014;9(3):255-67.
11. Jordan F, Quinn TJ, McGuinness B, et al. Aspirin and other non-steroidal anti-inflammatory drugs for the prevention of dementia. Cochrane Database Syst Rev. 2020;4(4):CD011459.
12. Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. Arterioscler Thromb Vasc Biol. 2011;31(5):986-1000.
13. Sugimoto Y, Inazumi T, Tsuchiya S. Roles of prostaglandin receptors in female reproduction. J Biochem. 2015;157(2):73-80.
14. Bie Q, Dong H, Jin C, et al. 15d-PGJ2 is a new hope for controlling tumor growth. Am J Transl Res. 2018;10(3):648-58.
15. Smith WL, DeWitt DL, Garavito RM. Cyclooxygenases: Structural, cellular, and molecular biology. Annu Rev Biochem. 2000;69:145–82.
16. Hase T, Yoshimura R, Matsuyama M, et al. Cyclooxygenase-1 and -2 in human testicular tumours. Eur J Cancer. 2003;39(14):2043-9.
17. Vuolteenaho K, Moilanen T, Moilanen E. Non-steroidal anti-inflammatory drugs, cyclooxygenase-2 and the bone healing process. Basic Clin Pharmacol Toxicol. 2008;102(1):10-14.
18. Matsuyama M, Nakatani T, Hase T, et al. The expression of cyclooxygenases and lipoxygenases in renal ischemia-reperfusion injury. Transplant Proc. 2004;36(7):1939-42.
19. Hamada T, Tsuchihashi S, Avanesyan A, et al. Cyclooxygenase-2 deficiency enhances Th2 immune responses and impairs neutrophil recruitment in hepatic ischemia/reperfusion injury. J Immunol. 2008;180(3):1843-53.
20. Kim SF, Huri DA, Snyder SH. Inducible nitric oxide synthase binds, S-nitrosylates, and activates cyclooxygenase-2.Science. 2005;310(5756):1966-70.
21. Thyagarajan A, Saylae J, Sahu RP. Acetylsalicylic acid inhibits the growth of melanoma tumors via SOX2-dependent-PAF-R-independent signaling pathway. Oncotarget. 2017;8(30):49959-72.
22. Wang YJ, Xie XL, Liu HQ, et al. Prostaglandin F2α synthase promotes oxaliplatin resistance in colorectal cancer through prostaglandin F2α-dependent and F2α-independent mechanism. World J Gastroenterol. 2023;29(39):5452-5470.
23. Qualtrough D, Kaidi A, Chell S, et al. Prostaglandin F(2alpha) stimulates motility and invasion in colorectal tumor cells. Int J Cancer. 2007;121(4):734-40.
24. Sales KJ, List T, Boddy SC, et al. A novel angiogenic role for prostaglandin F2alpha-FP receptor interaction in human endometrial adenocarcinomas. Cancer Res. 2005;65(17):7707-16.
25. Wallace AE, Sales KJ, Catalano RD, et al. Prostaglandin F2alpha-F-prostanoid receptor signaling promotes neutrophil chemotaxis via chemokine (C-X-C motif) ligand 1 in endometrial adenocarcinoma. Cancer Res. 2009;69(14):5726-33.
26. Yu Y, Lucitt MB, Stubbe J, et al. Prostaglandin F2alpha elevates blood pressure and promotes atherosclerosis. Proc Natl Acad Sci U S A. 2009;106(19):7985-90.
27. Basu S, Whiteman M, Mattey DL, Halliwell B. Raised levels of F(2)-isoprostanes and prostaglandin F(2alpha) in different rheumatic diseases. Ann Rheum Dis. 2001;60(6):627-31.
28. Helmersson J, Vessby B, Larsson A, Basu S. Association of type 2 diabetes with cyclooxygenase-mediated inflammation and oxidative stress in an elderly population. Circulation. 2004;109(14):1729-34.
29. Basu S, Larsson A, Vessby J, et al. Type 1 diabetes is associated with increased cyclooxygenase- and cytokine-mediated inflammation. Diabetes Care. 2005;28(6):1371-5.
30. Nakagawa T, Kosugi T, Haneda M, et al. Abnormal angiogenesis in diabetic nephropathy. Diabetes. 2009;58(7):1471-8.
31. Zhao Y, Lei Y, Ning H, et al. PGF2α facilitates pathological retinal angiogenesis by modulating endothelial FOS-driven ELR+ CXC chemokine expression. EMBO Mol Med. 2023;15(1):e16373.
32. Topdagi Yilmaz EP, Tanyeli A, Ekinci Akdemir FN, et al. The therapeutic effect of naringin on ovarian and lung damages created by adnexal torsion/detorsion: A biochemical study. Annals of Medical Research.2020;27(9):2438-42