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Can dehydroepiandosterone prevent chemotherapy-related damage? Investigation of protective effects of dehydroepiandosterone against paclitaxel-induced toxicity damage in rat ovaries

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ABSTRACT

Our aim is to evaluate whether dehydroepiandosterone has a protective effect on paclitaxel-induced ovarian damage. Group 1 (the control group): No treatment was administered. Intact ovarian tissue was removed and blood samples were taken for anti-mullerian hormone (AMH) test. Group 2 (the paclitaxel group): Rats received paclitaxel intraperitoneally at a single dose of 7.5 mg/kg. Group 3 (the paclitaxel + DHEA group): Rats received paclitaxel intraperitoneally at a single dose of 7.5 mg / kg at baseline and DHEA subcutaneously for 10 days at a dose of 60 mg / kg daily. Rats in groups 2 and 3 were sacrificed at the end of 10 days, ovarian tissues were removed and blood samples were taken for AMH test. The edema score was higher in the paclitaxel+DHEA group than in the normal group. Vasculary congestion score was higher in the paclitaxel and paclitaxel+DHEA groups than in the normal group. Cellular degeneration score was higher in paclitaxel group than normal group. Total score was higher in the paclitaxel and paclitaxel+DHEA groups than in the normal group. In the paclitaxel group, the number of tertiary follicles and ovarian volume were lower than in the normal group. Primordial follicles, secondary follicles, tertiary follicles, AMH level and ovarian volume of paclitaxel+DHEA group were lower than normal group. In conclusion DHEA was found to increase damage in paclitaxel-treated rats, leading to a decrease in follicle counts and AMH.

1. Introduction

The incidence of cancer has recently shown a steady increase (Siegel et al., 2018). World Health Organization estimates that 1.4 million women of reproductive age will be diagnosed with cancer annually by 2030 (Lyttle Schumacher et al., 2017). In parallel with these

increasing numbers, new populations have emerged in recent years that include cancer survivors and individuals exposed to harmful side effects of treatments such as young adults, and their numbers are likely to continue to increase (Sonigo and Beau, 2019). Young cancer patients may have to undergo chemotherapy treatment, and most of them may experience fertility loss (Ili et al., 2019).

Paclitaxel is a natural product derived from the bark and needles of Pacific yew tree, Taxus brevifolia (Massey et al., 2019; Zhu and Chen, 2019). This drug is a microtubule inhibitor that promotes polymerization and inhibits the separation of microtubules (Bang and Na, 2019). It has high activity against epithelial ovarian cancer, and exhibits notable penetration capacity in cells up to 80 cell layers (Dwivedi et al., 2019). It is one of the most successful and widely used natural anticancer drugs owing to its unique anticancer mechanism (Wani et al., 1971). It is commonly used in the treatment of solid tumors including ovarian, breast, head, neck and non-small cell lung cancers (Yucebilgin et al., 2004; Bang and Na, 2019).

It is an extremely important drug in terms of side effects. Poor water solubility, severe toxicity and lack of selective antitumor activity are factors limiting its clinical application (Wani et al., 1971; Bernabeu et al., 2016; Holden and Varcoe, 2019; Moku and Layek, 2019; Zajdel and Wilczok, 2019). Several studies have shown that menstrual irregularities and amenorrhea may develop following anthracycline-based chemotherapy (Davis et al., 2005; Fornier et al., 2005; Abusief et al., 2010). Animal studies have revealed that paclitaxel damages healthy mature oocytes by inducing cell death, and impacts the short-term reproductive potential in a dose-dependent manner (Yucebilgin et al., 2004; Tarumi et al., 2009). Further, paclitaxel damages the primordial follicles that constitute a large portion of the ovarian reserve (Nicosia et al., 1985; Meirow et al., 2007).

Dehydroepiandrosterone (DHEA) is an important pro-hormone in the ovarian follicular steroidogenesis (Tartagni et al., 2015). It increases follicular insulin-like growth factor-1 (IGF-1) levels that promote folliculogenesis by increasing the effect of gonadotropin and by reducing follicular arrest (Ubaldi et al., 1996; Bosch et al., 2003; Al-Azemi et al., 2012). It has been shown that, in this way, it can improve the quantitative and qualitative ovarian response (Jayaprakasan et al., 2014).

Several studies have shown the useful effect of DHEA on ovarian reserve. At reproductive centers in 45 countries worldwide, DHEA is used to improve outcomes in approximately one-third of the in vitro fertilization cycles (Zhang et al., 2014). In two separate studies, it was reported that DHEA support can improve oocyte retrieval (Tsui et al., 2015) and an improvement in pregnancy rate (Tsui et al., 2015). A meta-analysis of eight studies reported between 2006 and 2014 concluded that DHEA supplementation increased pregnancy rates without resulting in a significant improvement in oocyte retrieval or quality (Li et al., 2015; Klinge et al., 2018).

In this experimental study, we aimed to investigate whether DHEA has protective effects on paclitaxel -related ovarian damage.

2. Material and methods

This study was conducted at the Animal Testing Laboratory of University in July 2019, after the approval of the ethics committee.

Care of rats

Norvegicus species in our study, Wistar albino genus, 10-12 weeks, and female rats weighing 190 to 216 grams were used. The rats received light at least 12 hours per day in a cage of four animals, at a temperature of 21 to 23 degrees Celsius, at a moisture content of 40-50%, they reached the standard rodent pellet without restriction and drank tap water without restriction.

Study groups

Group 1 (the control group): These rats underwent a laparotomy procedure at baseline and the ovaries were removed. Blood was drawn from the inferior vena cava for AMH testing.

Group 2 (the paclitaxel group): Rats received paclitaxel intraperitoneally at a dose of 7.5 mg/kg at baseline (Yucebilgin et al., 2004) and underwent an oophorectomy procedure at the end of day 10 of the study. After sacrificing the rats, at least 2-3 ml of blood was collected for AMH testing. Then laparotomy was performed and both ovaries were excised for histopathological examination.

Group 3 (the paclitaxel + DHEA group): Rats received paclitaxel intraperitoneally at a dose of 7.5 mg/kg at baseline. In addition, they received DHEA (Cayman Chemical, Michigan, USA, CAS registry no: 53-43-0, item no:15728) subcutaneously for 10 days at a dose of 60 mg/kg daily as dissolved in 0.1 ml of sesame oil (Wang et al., 2014; Hassa et al., 2015). After sacrificing the rats, at least 2-3 ml of blood was collected for AMH testing. Then laparotomy was performed and both ovaries were excised for histopathological examination.

Paclitaxel

Robotic chemotherapy drug preparation device in our hospital prepared the drugs under conditions in accordance with international standards. Double HEPA air cleaning system, waste safety system, dose measurement to ISO 5, class 100 and GMP class A standards.

Surgical procedures

Animals were decapitated before laparotomy. Surgical procedures were performed after iodized solution

cleaning. In order to prevent the drying effect of the air, the treatments were carried out in less than 5 minutes. Ovaries were excised with scissors (Fig. 1).

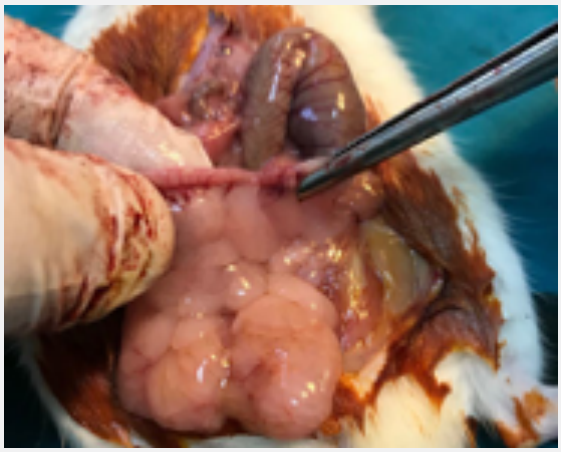

Fig. 1. Excision of the ovary.

Histopathological examinations

The extracted ovarian tissue was placed in 10% formalin and taken to the laboratory for pathological examination. Paraffin blocks were prepared for approximately 24 hours and tissue sections of five micrometers were taken. Follicular activity was evaluated by taking five random samples from each ovarian tissue. The preparations were first stained with hematoxylin eosin and then examined with a light microscope (Olympus Clinical Microscope, Tokyo, Japan) and a microtome blade was used for the preparation of paraffin blocks (Leica, Nussloch, Germany).

Histopathological damage scores were performed according to the evaluations of Celik et al. (Celik et al., 2004). Tissues that appeared completely normal with no changes were evaluated as grade 0. Grade 1 indicated mild edema, mild vascular congestion, absence of hemorrhage or leukocyte infiltration; Grade 2 indicated moderate edema, moderate vascular congestion, absence of hemorrhage or leukocyte infiltration; Grade 3 indicated severe edema, severe vascular occlusion, minimal hemorrhage and minimal leukocyte infiltration, Grade 4 indicated severe edema, severe vascular occlusion, hemorrhage and leukocyte infiltration (Fig. 2).

All follicles were counted to assess ovarian reserve. Primordial, primary, secondary (pre-antral), tertiary (antral) and atretic follicles were counted (Fig. 3, 4). Follicles were evaluated as described by Parlakgumus et al. (Parlakgumus et al., 2014). Primordial follicle is described as an oocyte surrounded with only one layer of flattened ovarian follicular epithelial cell layer, primer follicle is surrounded with one or more layer of cuboidal granulosa cells. Secondary/ pre-antral follicle is surrounded with more than two cell layers and consists of antrum folliculi and zona pellucida. Tertiary follicle is defined if there are antrum, stratum granulosum and surrounding cumulus oophorus layers. Atretic follicle; the basement that separated the oocyte from granulosa cells often thickens to become the glassy membrane. Fibrous material replaces the granulosa cells and loss of cohesion may also occur in granulosa cells.

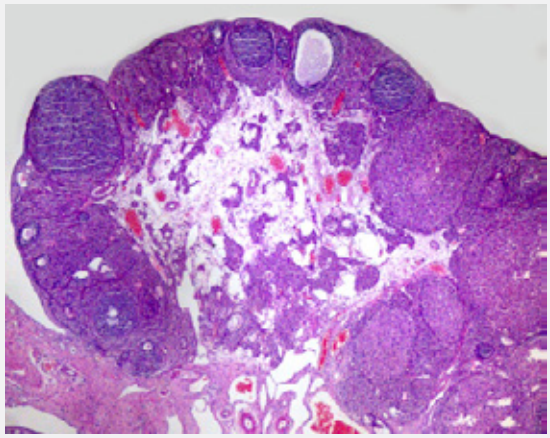

Fig. 3. Edema in medulla x100 hematoxylin-eosin.

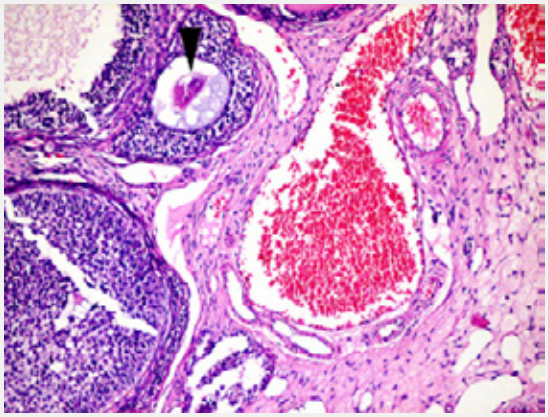

Fig. 2. Distinct dilated vessels x200 hematoxylin-eosin.

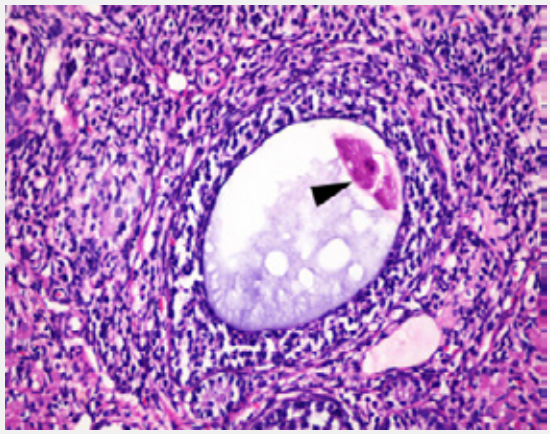

Fig. 4. Defragmented oocyte x400 hematoxylin-eosin.

AMH assays

The laboratory technician was blinded by not knowing which blood belonged to which animal, and all samples were analyzed in the same experiment. Blood samples were taken into lithium heparinized tubes (BD Vacutainer Plasma tubes, Manchester, UK). Blood was centrifuged before 30 minutes (15 minutes at 1000 G). Serum was first removed and the remaining plasma was transferred to an Eppendorf tube and stored at -20°C until the day of analysis. The sensitivity of the AMH kit was 0.10 g/mL, with a detection range of 0.16 to 10 ng / mL (Elabscience®, Rat AMH kit; Houston, Texas, USA).

Statistical analysis

Statistical analysis was performed with the help of SPSS version 17.0 program. The suitability of the variables to normal distribution was examined by histogram graphs and Kolmogorov-Smirnov test. Mean, standard deviation, median and IQR values were used to present descriptive analyzes. Non-parametric variables were evaluated between the two groups and Mann Whitney U Test was used. Spearman Correlation Test was used to analyze the measured data with each other. The cases where the p-value was less than 0.05 were evaluated as statistically significant results.

3. Results

Histopathological damage scores were compared between the groups. The edema score was higher in the paclitaxel+DHEA group than in the normal group. Vascular congestion score was higher in the paclitaxel and paclitaxel+DHEA groups than in the normal group. Cellular degeneration mean score in normal ovary group is 0.00±0.00, in paclitaxel group 0.63±0.52 and in paclitaxel+DHEA group 0.25±0.46. Cellular degeneration score was higher in paclitaxel group than normal group (Table 1).

Total damage score was calculated by summing all the scores of edema, vascular congestion, inflammation, cellular degeneration and hemorrhage. Total score was higher in the paclitaxel and paclitaxel+DHEA groups than in the normal group (Table 1).

Follicle numbers and AMH values were compared according to the groups. In the paclitaxel group, the number of tertiary follicles and ovarian volume were lower than in the normal group. Primordial follicles, secondary follicles, tertiary follicles, AMH level and ovarian volume of paclitaxel+DHEA group were lower than normal group (Table 2).

Correlation between AMH and rat weight, ovarian volume, total damage score, number of atretic follicles,

Table 1. Comparison of histopathological damage scores of normal ovary vs paclitaxel, paclitaxel + DHEA (Mann Whitney U Test).

		Normal ovary	Paclitaxel	p*	Paclitaxel+DHEA	p**
Edema	Mean SD	0.00±0.00	0.38±0.52	0.063	1.50±0.76	0.001
	Median- IQR	0.00(0.00-0.00)	0.00(0.00-1.00)		2.00(1.00-2.00)	
Vascular congestion	Mean SD	0.00±0.00	0.50±0.53	0.025	1.50±1.07	0.003
	Median- IQR	0.00(0.00-0.00)	0.50(0.00-1.00)		2.00(0.50-2.00)	
Inflammation	Mean SD	0.00±0.00	0.13±0.35	0.317	0.00±0.00	1.000
	Median- IQR	0.00(0.00-0.00)	0.00(0.00-0.00)		0.00(0.00-0.00)	
Cellular degeneration	Mean SD	0.00±0.00	0.63±0.52	0.009	0.25±0.46	0.143
	Median- IQR	0.00(0.00-0.00)	1.00(0.00-1.00)		0.00(0.00-0.50)	
Hemorrhage	Mean SD	0.13±0.35	0.00±0.00	0.317	0.00±0.00	0.317
	Median- IQR	0.00(0.00-0.00)	0.00(0.00-0.00)		0.00(0.00-0.00)	
Total damage score	Mean SD	0.13±0.35	1.63±1,19	0.009	3.25±1.83	0.002
	Median- IQR	0.00(0.00-0.00)	2.00(0.50-2.50)		4.00(2.00-4.50)	

Table 2. Comparison of normal ovary vs paclitaxel, paclitaxel + DHEA groups in terms of follicle count and AMH values (Mann Whitney U Test).

		Normal ovary	Paclitaxel	p*	Paclitaxel +DHEA	p**
Primordial follicle	Mean SD	12.75±1.91	8.63±5.10	0.063	3.87±2.30	0.001
	Median- IQR	12.50(11.50-14.00)	10.00(3.50-12.00)		3.00(2.00-5.50)	
Primary follicle	Mean SD	10.50±2.33	14.75±8.84	0.792	8,13±3,98	0.224
	Median- IQR	11.00(8.50-12.00)	12.00(7.00-23.50)		8.50(4.50-11.00)	
Secondary (pre-antral) follicle	Mean SD	12.25±1.83	10.75±3.15	0.365	7.88±3.64	0.017
	Median- IQR	12.50(10.50-13.50)	11.00(9.00-13.50)		8.50(4.50-10.50)	
Tertiary (antral) follicle	Mean SD	21.50±3.21	15.00±3.96	0.010	17.00±5.15	0.050
	Median- IQR	22.00(19.50-23.50)	14.00(12.50-15.50)		18.50(12.00-21.00)	
Athretic follicle	Mean SD	0.25±0.46	0.63±0.52	0.143	0.25±0.46	1.000
	Median- IQR	0.00(0.00-0.50)	1.00(0.00-1.00)		0.00(0.00-0.50)	
AMH (ng/mL)	Mean SD	3.42±0.79	2.95±0.73	0.294	2.07±0.80	0.010
	Median- IQR	3.37(2.64-4.06)	2.95(2.55-3.47)		2.02(1.45-2.70)	
Ovary volume (mm^3)	Mean SD	55.49±9.14	39.14±8.22	0.003	37.99±12.91	0.008
	Median- IQR	54.12(50.19-55.53)	39.05(33.07-42.40)		36.23(28.74-45.35)	
Rat weight (grams)	Mean SD	197.25±13.60	203.38±6.57	0.247	204.00±7.33	0.139
	Median- IQR	193.0(189.0-207.0)	205.50(201.0-207.0)		203.0(198.0-209.0)	

secondary + tertiary follicles were evaluated for each group. Accordingly, there is a strong positive correlation between AMH and ovarian volume in normal group (Table 3).

Table 3. Correlations between rat weights, ovary volume, total damage score, number of atretic follicles, and AMH levels (Spearman Correlation Test *p<0,050 **p<0,010).

	Normal	Normal ovary	Paclitaxel
Rat weight (grams)	AMH	Paclitaxel AMH	Paclitaxel +DHEA
Ovary volume (mm3)	AMH	-0.500	0.476
Total damage score	0.082	-0.309	-0.466
Atretic follicle count	0.000	0.169	-0.630
Pre-antral + antral follicle count	-0.072	-0.024	0.252

4. Discussion

Paclitaxel binds and stabilizes cellular microtubules that cause cell death. It also initiates apoptosis by various mechanisms (Wang et al., 2000). However, the mechanisms that lead to chemotherapy-induced follicular destruction of follicles have not yet been elucidated and require further research (Gucer et al., 2001). Previous studies have shown that paclitaxel application in mice causes depletion of the follicular reserve. This effect of paclitaxel causes premature ovarian failure and infertility in young patients (Gucer et al., 2001). We performed histopathological evaluations to examine the damage of paclitaxel to the ovarian tissue. We determined that there was a significant increase in vascular congestion, cellular degeneration, and total damage scores in paclitaxel-treated tissues compared with those observed in normal ovarian tissues. We determined that there was increase in edema, vascular congestion and total damage scores in the group receiving the paclitaxel+DHEA treatment (Table 1). When ovarian volumes were examined, we identified a significant decrease in ovarian volumes in both groups (Table 2). We observed that paclitaxel caused damage to ovarian tissue in both groups, however this damage did not change with DHEA supplementation.

Moreover, it has also been documented that combined chemotherapy regimens exert a significant cytotoxic effect on the ovaries and that a combination of paclitaxel and cisplatin has a maximum cytotoxic effect on both primordial and mature follicles (Ozcelik et al., 2010). In mature oocytes, paclitaxel induces meiotic maturation delay and spindle defect, which results in aneuploid oocytes. In addition, mature follicles show higher susceptibility to chemotherapy-induced damage (Gucer et al., 2001). In their first study conducted on mice in 2000, Gucer et al. identified the damage caused by the use of paclitaxel on primordial cells in the ovaries. They observed that this damage developed in all doses of 2.5, 5.0, and 7.5 mg/kg of paclitaxel (Gucer et al., 2001).

In the study conducted by Yucebilgin et al., rats that received 7.5 mg/kg paclitaxel and 5 mg/kg cisplatin underwent oophorectomy after seven days, and there was a significant decrease in ovarian follicles in both groups. In our study, we examined the ovarian follicles and observed a significant decrease in the antral follicles in the paclitaxel group compared with the normal ovary group. In the paclitaxel+DHEA group, we found that there was a decrease in primordial, preantral and antral follicles. We determined that the addition of DHEA was associated with an increase in follicular damage (Table 2). We think that DHEA could not prevent primordial follicle damage because it did not prevent the increase in edema, vascular congestion and total damage scores. Primordial follicles are known to be sensitive to chemotherapy. In previous studies, as a result of applying chemotherapy, primordial follicles decreased because of the damage (Ozcelik et al., 2010) The ovarian toxicity of taxane-based chemotherapies remains unclear and the dose dependence of this toxicity is uncertain, partially due to the fact that an adequate evaluation of ovarian toxicity through animal studies is lacking. Paclitaxel is an important agent for breast cancer as well as for gynecological malignancies, and the use of paclitaxel as a neoadjuvant chemotherapy is an important treatment strategy. Therefore, whether the incidence of amenorrhea is dependent on paclitaxel dose is an important issue for the treatment of young women (Tarumi et al., 2009). Taraumi et al. identified a decrease in the primordial and antral follicle counts as a result of the use of paclitaxel. They found that the number of tertiary follicles also increased. In hormonal assessments, estradiol and progesterone hormone levels did not vary depending on paclitaxel. Based on their study results, they reported that paclitaxel damaged antral follicles, but did not affect less mature follicles (Tarumi et al., 2009). In this study, no AMH evaluation was carried out. AMH has been confirmed in many studies as a reliable molecular biomarker of ovarian reserve (Broer et al., 2011; Iliodromiti and Nelson, 2015; Cheng et al., 2019). Reduction of AMH to minimal levels may be correlated with reduced ovarian follicle count (Stracquadanio et al., 2018). Although there are numerous ovarian reserve tests with varying predictive capabilities, antral follicle count and anti-mullerian hormone levels have been determined to provide the best diagnostic accuracy for constantly predicting poor ovarian reserve (Jayaprakasan et al., 2010). We investigated the effect of the use of paclitaxel on AMH. In conclusion, we determined that the AMH levels of rats that were administered paclitaxel alone were similar to those of normal rats, whereas there was a decrease in AMH levels in rats who received paclitaxel+DHEA. We determined that the addition of DHEA was associated with an increase in AMH decline (Table 2).

DHEA, a precursor of estradiol and testosterone, has been recognized as a potential intervention to enhance supplementation, improve the ovarian status, and improve assisted reproductive technique results in women with low ovarian response (Tsui et al., 2014). Although DHEA is more widely used in patients with poor response, many different opinions remain among many clinicians. Most of the published studies are based on retrospective and/or observational data, and their results can be biased (Yeung et al., 2014). However, initial reports on DHEA supplementation in patients with low ovarian response remain controversial due to the lack of large-scale, well-designed confirmatory studies (Barad and Gleicher, 2006; Barad et al., 2009). Based on the result of our study that investigated whether DHEA supplementation in addition to paclitaxel would reduce ovarian damage, it was determined that DHEA supplementation has an overall negative effect because rats treated with paclitaxel+DHEA experienced a decrease in ovarian volume, an increase in histopathological damage scores, a decrease in AMH levels, and a greater decrease in follicle counts compared with the group using paclitaxel alone.

In the paclitaxel+DHEA group, we found that there was a decrease in primordial, preantral and antral follicles. The addition of DHEA was associated with an increase in follicular damage.

It was determined that DHEA does not exert any positive effect in reducing ovarian damage caused by the use of paclitaxel in rats and that on the contrary, it has a negative effect on follicle counts and AMH levels, which are the most important indicators of infertility.

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