The Role of Vitamin E (alfa-tocopherol) on Testosterone level in sprague dawley rats following cisplatin treatment

by Dian Kartika Rezia

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THE ROLE OF VITAMIN E (α-TOCOPHEROL) ON TESTOSTERONE LEVEL IN SPRAGUE DAWLEY RATS FOLLOWING CISPLATIN TREATMENT

[1]Dian Kartika Rezia, [1]Lukman Hakim, [1] Wahjoe Djatisoesanto.

[1]Department of Urology, Faculty of Medicine/Universitas Airlangga, Soetomo General Hospital, Surabaya.

ABSTRACT

Objective: *To observe the difference of testosterone levels in adult male Sprague Dawley rats treated with combination of cisplatin and vitamin E compared to those treated with cisplatin only.* ***Material & Methods:*** *We used 24 adult male Sprague Dawley rats weight 200–300 grams and randomly assigned into 4 groups (n=6). Rats in negative control group (NC) were given intraperitoneal normal saline injection, while the positive control (PC) group were injected with cisplatin 5 mg/kgBW at the end of the 3rd week. Two other groups, P1 and P2, were injected with cisplatin 5 mg/kgBW and given vitamin E orally 50 mg/kgBW and 200 mg/kgBW, respectively. Cardiac blood was aspirated at the end of the 7th week and processed for analysis of testosterone levels.* ***Results:*** *Werecorded a significantly lower testosterone levels in rats treated only with cisplatin 5 mg/kgBW (CP) compared to those in CN group (p=0.006), and those receiving combination of cisplatin and vitamin E 50 mg/kgBW (p=0.003) and 200 mg/kgBW (p=0.001). Though not significant, testosterone levels were higher in P2 group than in P1 group (p=0.702).* ***Conclusion:*** *Exposure to cisplatin can lower testosterone levels in white rats, and the administration of vitamin E gives protection against such effect.*

Keywords: *Cisplatin, chemotherapy, vitamin E, antioxidant, testosterone, testis.*

ABSTRAK

Tujuan: *Untuk mengetahui perbedaan kadar testosterone pada tikus Sprague Dawley yang diberikan kombinasi obat cisplatin dan vitamin E dibandingkan dengan tikus Sprague Dawley yang hanya mendapatkan cisplatin.* ***Bahan & Cara:*** *Dua puluh empat tikus putih jantan dewasa Strain Sprague Dawley dengan berat badan antara 200–300 gram dikelompokkan menjadi 4 grup (n=6). Grup kontrol negatif (CN) diberikan injeksi NaCl 0.9% 1cc secara intraperitoneal, sedangkan pada grup kontrol positif (CP) diberikan injeksi cisplatin 5 mg/kgBB pada akhir minggu ke-3. Dua grup lainnya masing-masing diberikan injeksi cisplatin 5 mg/kgBB dan vitamin E dengan dosis 50 mg/kgBB (P1) atau 200 mg/kgBB (P2). Aspirasi darah kardiak dilakukan di akhir minggu ke-7 dan diproses untuk analisa kadar testosteron.* ***Hasil:*** *Didapatkan kadar testosterone yang lebih rendah secara signifikan pada kelompok yang hanya diberikan injeksi cisplatin 5 mg/kgBB intraperitoneal dibandingkan dengan kelompok CN yang hanya diberikan NaCl 0.9% intraperitoneal (p=0.006), kelompok yang mendapatkan cisplatin 5 mg/KgBB dan vitamin E 50 mg/kgBB (p=0.003), dan kelompok yang mendapatkan cisplatin 5 mg/KgBB dan vitamin E 200 mg/kgBB (p=0.001). Meskipun secara statistik tidak signifikan (p=0.702), kadar testosteron pada kelompok yang mendapatkan cisplatin 5 mg/KgBB dan vitamin E 200 mg/kgBB lebih tinggi dibandingkan dengan kelompok yang mendapatkan cisplatin 5 mg/KgBB dan vitamin E 50mg/kgBB.* ***Simpulan:*** *Paparan cisplatin menurunkan kadar testosteron pada tikus putih, dan pemberian vitamin E dapat memperbaiki pengaruh cisplatin terhadap kadar testosteron darah.*

Kata Kunci: *Cisplatin, kemoterapi, vitamin E, antioksidan, testosterone, testis.*

Correspondence: Dian Kartika Rezia; c/o: Department of Urology, Faculty of Medicine/Universitas Airlangga, Soetomo General Hospital, Surabaya. Jl. Mayjen. Prof. Dr. Moestopo 6-8 Surabaya 60286. Phone: +62 31 5501318; Fax: +62 31 5024971. Mobile phone: 083857857353. Email: diankrezia@gmail.com.

INTRODUCTION

Reports estimated about 14.1 million new cancer cases and 8.2 million cancer-related deaths worldwide in 2012. Of those figures, 57% of new cases and 65% of deaths were reported in developing countries. The differences in these numbers between developed and developing countries are probably due to the different clinical features of patients, as well as diagnostics and therapeutics facilities.[1] One

percent of new cancer cases in the United States were accounted for juvenile (0-14 years) and adolescence (15-19 years). Testicular cancer is marked on the fourth place for adolescence malignancy in the US.[2]

Cisplatin is one of the most potent and commonly used chemotherapy agent, especially in testicular, bladder, cervix, nasopharyngeal, and lung cancers.[3-5]Despite its wide potency, cisplatin is also known to have numerous toxicity, including on testicular tissues.[3,6,7]Studies have described negative effect of cisplatin on testicular tissue, both on its spermatogenic and steroidogenic functions. A study by Kilarkaje demonstrated a disturbance in the synthesis of testosterone in rats receiving 3 cycles of BEP with or without antioxidant administration.[8-10]

Intracellular cisplatin causes an increase in reactive oxygen species (ROS) which will induce numerous chain reactions including apoptosis and cell necrosis. Physiologically, spermatozoa will produce a small amount of ROS for intracellular regulation, capacity, and acrosome reactions. However, if produced excessively, ROS in testicular tissue will cause damage to cellular elements and DNA fragmentation.[11,12] Testicular tissue is highly sensitive of ROS and free radicals. Binding of free radical to a testicular component (spermatogonium, Sertoli cells, or Leydig cells) can induce lipid peroxidation and other chain reactions leading to apoptosis and cell necrosis.[11] Previous studies have demonstrated a dysfunction of Leydig cells after exposure to cisplatin, both in short or long-term, though not all show marked decrease in testosterone levels.[13-16]

Vitamin E is known to be a potent chain-breaking antioxidant, as well as lipid-soluble. Traber and Stevens stated that vitamin E indirectly prevents the formation of free radicals, or the early oxidation of fatty acids, and stopping the lipid peroxidation chain-reaction.[17,18] Administration of vitamin E (α-tocopherol) is expected to prevent lipid peroxidation reaction in cell membrane caused by ROS as a byproduct of cisplatin, thus an improved level of testosterone.

OBJECTIVE

This study is aimed to observe the difference in testosterone levels in white rats (Sprague Dawley strain) receiving combination of cisplatin and vitamin E compared to those receiving only cisplatin.

MATERIAL & METHODS

In this laboratory experimental study we analyzed serum testosterone level after rats were given treatments. Twenty-four adult male rats (strain Sprague Dawley) weight 200-300 grams were assigned randomly into 4 experimental groups (n=6). Rats in the Negative Control (NC) group were given distilled water orally for 7 weeks and injected 1 ml of normal saline at intraperitoneally at the end of the 3rd week. Rats in the Positive Control (PC) group were given distilled water orally for 7 weeks, and were injected 1 ml of cisplatin (Kalbe Farma, Indonesia) 5 mg/kgBW intraperitoneally at the end of the 3rd week.

In therapy group 1 (P1) and therapy group 2 (P2) rats were respectively given 0.5 ml vitamin E 50 mg/kgBW and 200 mg/kgBW orally for 7 weeks, and were injected 1 ml of cisplatin 5 mg/kgBW intraperitoneally at the end of the 3rd week. The vitamin E doses were based on a previous study by Gevrek and Erdemir, which showed the same level of protection against oxidative stress on testis and sperm, without any significant side effects reported.[19] At the end of the 7th week cardiac blood was aspirated and then tested for testosterone level using ELISA. This study has been ethically approved by the Veterinary Faculty of Universitas Airlangga, Surabaya.

RESULTS

We studied 24 male adult rats aged 10-12 weeks, which characteristics are shown in table 1.

Shapiro-Wilk analysis showed a normal data for testosterone levels in each group, and with a homogenous variance ($p>0.05$). Based on those results, we analyzed the data further using one-way ANOVA, as shown in table 2. Our data showed a significant difference in testosterone levels between groups ($p<0.05$), thus we used the LSD post hoc test to compare each groups.

We found a significantly lower testosterone levels ($p<0.05$) in the positive control group (CP) compared to the negative control group (CN). Testosterone levels were also significantly lower in the CP group compared to those in the P1 and P2 groups ($p=0.003$ and $p=0.001$, respectively). Although statistically insignificant, we also found that the testosterone levels in P2 group were lower than in P1 ($p=0.702$).

Table 1. Basic sample characteristics.

Weight	Mean ± SD	p
Pre Treatment (gram)		
CN	248.33 ± 18.34	0.57[a]
CP	252.50 ± 23.18	
P1	249.17 ± 30.07	
P2	263.33 ± 27.33	
Testis Weight (gram)		
CN	1.40 ± 0.18	0.74[a]
CP	1.33 ± 0.21	
P1	1.31 ± 0.22	
P2	1.25 ± 0.23	

CN : Control Negative
CP : Control Positive (Cisplatin 5 mg/kgBB)
P1 : Cisplatin 5 mg/kgBB + Vitamin E 50 mg/kgBB
P2 : Cisplatin 5 mg/kgBB + Vitamin E 200 mg/kgBB
a : Kruskal-Wallis Test
* : statistically significant if p<0.05

Table 2. Comparison of testosterone levels among groups.

Group	n	Mean ± SD	p
CN	6	6.353 ± 0.229	0.004*
CP	6	5.899 ± 0.070	
P1	6	6.406 ± 0.259	
P2	6	6.461 ± 0.370	

* p<0.05 = statistically significant

Table 3. LSD post hoc analysis of testosterone levels between groups.

Comparison between groups	Mean Difference	CI 95%		p value
		Lower Bound	Upper Bound	
CN vs CP	0.454	0.147	0.762	0.006*
CN vs P1	-0.052	-0.360	0.255	0.726
CN vs P2	-0.109	-0.417	0.198	0.466
CP vs P1	-0.507	-0.814	-0.199	0.003*
CP vs P2	-0.564	-0.872	-0.257	0.001*
P1 vs P2	-0.057	-0.364	0.250	0.702

* p<0.05 = statistically significant

DISCUSSION

Cisplatin, or Cisdiammine dichlorido platinum (II), is considered one of the most widely used chemotherapy agents. Its potency has been known for testicular cancer, and other types of cancers.[3-5] Unfortunately, along with its benefits as anti-tumor agent, this drug also causes several toxicities in both short and long-term use on various organs and is known to be dose-related. The most commonly occurred toxicity is on the kidneys, which is caused by severe degeneration of the glomeruli and distal tubules.[20,21] Other studies also reported other long-term toxicities such as ototoxicity, neurotoxocity, and myelosuppression.[3,5,6]

In testicular tissues, cisplatin have also been reported to cause both spermatogenic and steroidogenic dysfunction.[8-10] Oxidative stress caused by an

increase in concentration of ROS and RNS as the product of cisplatin on testicular tissue is marked by elevated lipid peroxidation and a reduction of anti-oxidant system, leading to changes in the tissue histologically.[22,23] Animal subjects exposed to cisplatin are reported to suffer from testicular damage indicated by germinal cells apoptosis, Leydig cells dysfunction, and a decrease in steroidogenic function. Cisplatin is known to inhibit the synthesis of nucleic acid in germinal cells, resulting in disruption of spermatogenesis, while also causing LH receptors dysfunction and damaging Leydig cells viability - which results in the decreased testosterone production - both to be blamed for infertility at a later point. A study by Ciftci detailed the spermatogenic dysfunctions caused by cisplatin as azoospermia, dysmorphology of the sperm, decreased sperm motility, and disrupted spermatogenesis.[13,22,24,25]

In the current study, single intraperitoneal administration of cisplatin 5 mg/kgBB caused a significant decrease of testosterone levels compared to control group ($p<0.05$). This result is similar with a study by Aydiner et al., which showed a marked decrease in testosterone level, followed by an increase in Leutenizing Hormone (LH) level on the 3rd and 21st day after administration of cisplatin. Ultrastructural damages of the Leydig cells, such as dilatation of the endoplasmic reticulum (ER) and increase in lipid and lipofusion inclusions, as well as mitochondrial structural disorganizations were observed under electron microscopy on the 3rd until the 21st day after cisplatin injection.[26]

As has been understood, the chain reaction of testosterone biosynthesis takes place in the mitochondria, as well as the smooth endoplasmic reticulum. A study by Maines (1990) demonstrated a significantly decreased level of P450scc as well as its activity in rats treated with cisplatin.[27] Garcia (2012) demonstrated cisplatin exposure on cultured testicular interstitial cells in several modified microenvironment. It was also found that cisplatin causes an acute significant decrease in P450scc enzyme which was followed by a decrease in testosterone synthesis. The decrease, as explained in the study, was unlikely to be caused by the down-regulation of the enzyme which has a slow turnover. Moreover, Cisplatin did not seem to have any effect on the P450scc mRNA levels. Thus, it was concluded that the inhibition of the steroid synthesis is caused by a ROS-mediated mechanism.[28]

Marked improvements were found in testosterone levels of rats receiving vitamin E. In this study we found a significantly higher level of testosterone with the administration of vitamin E 50 mg/kgBW (P1) compared to those only injected with cisplatin 5 mg/kgBW (CP) (6.406 ± 0.259 vs. 5.899 ± 0.070, $p=0.003$). The same result was also seen in the group receiving higher dose of vitamin E (P2) compared to CP (6.461 ± 0.370 vs. 5.899 ± 0.070, $p=0.001$). However, the higher dose of vitamin E administered did not seem to give significantly better improvement of testosterone levels ($p=0.702$).

Platinum molecules from cisplatin will bind to the intracellular DNA and produce reactive oxygen species (ROS), which will cause several chain reactions, including lipid peroxidation.[3,6] Vitamin E (α tocopherol) is potent lipid-soluble antioxidant and works as a potent chain-breaking scavenger for peroxyl radicals and inhibits the propagation of free radicals in cell membrane and plasma lipoprotein. The OH atom from α tocopherol is phenolic, and binds to a peroxyl radical to form hydroperoxide. Tocopheroxyl radical formed in this reaction is relatively stable, non-radical, and inactive.[18,29] Traber and Stevens stated that vitamin E indirectly prevents the formation of free radicals, or the early oxidation of fatty acids, and stopping the lipid peroxidation chain-reaction.[17] However, in a high concentration α tocopherol may also induce the formation of lipid hydroperoxide, which can bind to a lipid free radical and eventually cause membrane damage as well.[18,30]

A study by Umeda in 1978 demonstrated an activation of smooth ER development in rat's Leydig cells with administration of vitamin E. Furthermore, Umeda reported in his study in 1982 that there was a significant increase of testosterone levels in both plasma and testicular tissue after administration of vitamin E in a long-term.[31,32] This might explain the basic mechanism of testosterone improvement in rats treated with cisplatin. Vitamin E works as an antioxidant which prevents lipid peroxidation and damage to Leydig cells and its components, thus ensuring the biosynthesis of testosterone. Moreover, vitamin E also induces the development of smooth ER which plays an important role in testosterone biosynthesis.

Despite the obvious positive effect of vitamin E on testosterone levels in mice, this study does not fully represent the actual condition of patients with malignancy receiving cisplatin therapy.

Firstly, because it was designed as a post-test only study, we cannot compare the testosterone levels before and after the administration of vitamin E, with and without cisplatin, and vice versa. Secondly, we only administered a single dose of cisplatin, instead of multiple dose with interval as dictated on chemotherapy protocols.

CONCLUSION

Administration of vitamin E helps recover the negative effect caused by cisplatin on testosterone levels.

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