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Award Winners

A-8

Melatonin prevents wistar rats testes from bleomycin, etoposide, and cisplatin (BEP) chemotherapy-induced reproductive toxicity: A biochemical, immunohistochemical and apoptosis-related genes based evidence

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Background: Recently, the prevalence of testicular cancer, accounting for the most common cancer among young people of reproductive age (15-40 yr), has risen internationally. Bleomycin, Etoposide, and Cisplatin (BEP) chemotherapy has increased the 5-year survival rate of patients with testicular cancer at all stages of testicular germ cell tumors to 90-95%. However, nowadays there is growing concern that some cytotoxic regimens for cancer like BEP create a high incidence of male infertility and even long-term genotoxic effects, which emerge as a critical health issue. Melatonin is a well-known potent antioxidant with widespread clinical applications that recently has been giving increasing attention to its role in male sub/infertility.

Objective: In order to investigate the protective and alleviative effects of melatonin following BEPchemotherapy exposure on sperm characteristics and parameters, nitro-oxidative status, as well as histopathological, inflammatory, and apoptotic alternations in testes. Moreover, to elucidate whether exogenous melatonin attenuates BEP-induced damage in testicular cells and spermatogenesis in a dose-dependent manner?

Materials and Methods: 60 adult male Wistar rats (n = 10/group) were treated with one cycle of 21 days of 0.33 therapeutically relevant dose levels of BEP (0.5 mg/kg Bleomycin, 5 mg/kg Etoposide and 1 mg/kg Cisplatin) with or without melatonin. At the end of the study (day 35), body weight, testes weight, sperm parameters, testosterone hormone level, testicular histopathology, stereological parameters, testicular level of malondialdehyde, nitric oxide and total antioxidant capacity, the expression of apoptosis-associated genes such as Bcl2, Bax, Caspase3, p53 (Real-time PCR and immunohistochemistry), and the expression of pro-inflammatory cytokine TNF-α (immunohistochemistry) were evaluated.

Results: Our findings showed that melatonin restores the BEP-induced reduction in the body and testes weight ($p < 0.05$). The evaluation of quantitative analysis of the testes stereological procedures, QRT-PCR examination, and immunohistochemical staining revealed that melatonin reversed the BEP-induced impaired spermatogenesis ($p < 0.05$). Furthermore, melatonin rectified BEP-induced disturbance on sperm count, motility, viability, and morphology. Additionally, co-administration of 10 and 20 mg/kg of melatonin could restore BEP-induced alteration in serum testosterone level. Moreover, melatonin enhanced the antioxidant status of the testis by elevating total antioxidant capacity and ameliorating malondialdehyde and nitric oxide levels. More notably, QRT-PCR examination indicated that melatonin therapy suppressed BEP-induced apoptosis by modulating apoptosis-associated genes such as Bcl-2, Bax, Caspase-3, p53 in the testis ($p < 0.01$). In this continuum, the co-administration of 10 and 20 mg/kg of melatonin with the BEP regimen decreased

significantly the population of p53 and TNF-α positive cells by comparison to the BEP group. Also, melatonin with low and high doses could enhance the expression of Bcl-2 protein in spermatogenic cells line compared to the BEP-treated group.

Conclusion: This study demonstrated that melatonin protected testes against BEP-induced damage by preventing and ameliorating histopathological and stereological alterations, spermatotoxicity, nitro-oxidative stress, inflammation, and apoptosis. These findings can draw attention to the clinical application of melatonin and also suggest that melatonin may be an attractive agent for attenuating chemotherapy-associated male sub/infertility. This indolamine may also shorten the fertility recovery period in patients undergoing chemotherapy with the BEP regimen.

Key words: *BEP chemotherapy, Melatonin, Sperm, Male infertility, Apoptosis.*

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