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Original Research Article

Effect of melatonin on hematological indices in cyclophosphamide induced hematotoxicity in mice

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ABSTRACT

Background: Cyclophosphamide use is often limited by associated hematotoxicity. This study investigated the effects of melatonin on haematological indices in cyclophosphamide-induced hematotoxicity in mice.
Methods: Ninety mice weighing between 20-25 gm were randomly divided equally into nine groups (A-I). Group A (saline control) received 2 ml/kg intraperitoneal (i.p.) normal saline with 10 ml/kg distilled water orally, groups B, C and D (melatonin control) received i.p. normal saline with melatonin at 5, 10 and 20 mg/kg orally, respectively. Group E (cyclophosphamide control) received 150 mg/kg/day i.p. cyclophosphamide with 10 ml/kg distilled water orally, while group F received 150 mg/kg/day cyclophosphamide with standard drug, (erythropoietin control) at 100 IU/kg. Group G, H and I (treatment groups) received 150 mg/kg/day cyclophosphamide with melatonin at 5, 10 and 20 mg/kg/day orally. Cyclophosphamide was administered on days 1 and 2 only, oral administrations occur once daily for 14 days. On day 15, animals were sacrificed and blood collected by cardiac puncture for assessment of haematological parameters; white blood cell count (WBC), red blood cell count (RBC) and platelets (PLT).
Results: The results showed a significant increase in WBC in groups C D, G and H (melatonin control; 10 mg/kg. 20 mg/kg and melatonin treatment; 5 mg/kg and 10 mg/kg) and a significant ($p=0.001$) decrease in group E (cyclophosphamide control) compared to A (saline control). RBC increased significantly in groups B and D (melatonin control; 5 mg/kg and 20 mg/kg) and significantly decreased in group E (cyclophosphamide control) compared to group A (saline control). Compared to group E (cyclophosphamide control), RBC increased significantly in groups F-I (erythropoietin standard, melatonin treatment). PLT increased significantly in groups B, C, (melatonin control; 5mg/kg and 10 mg/kg) G, H and I (melatonin treatment) compared with groups A (saline control) and E (cyclophosphamide control) ($p=0.001$).
Conclusions: Melatonin has potential to attenuate cyclophosphamide-induced hematotoxicity in mice.

Keywords: Melatonin, Cyclophosphamide, Adverse effects, Erythropoietin

INTRODUCTION

Hematotoxicity is one of the serious adverse events associated with cancer chemotherapy such as cyclophosphamide. It often causes deleterious effects on hematopoietic system with consequent cytopenia(s).[1] Depending on the cell line(s) affected, it may manifest with anaemia, neutropenia, and thrombocytopenia. These manifestations usually cause a halt in continued administration of systemic chemotherapy until they are addressed, constituting a major challenge in the management of cancers.[2] To mitigate these effects, several measures which include dose reduction, postponement of courses of drugs until the side effects abate, colony stimulating factors like erythropoietin, darbopoietin, granulocyte-colony stimulating factor,

granulocyte monocyte colony stimulating factor, various cytokines, platelet transfusions have been tried with some success.[2-9] However, some of these agents are expensive and not readily available particularly in developing countries. Therefore, there is increasing demand for cheaper, more efficient and less toxic compounds to ameliorate or prevent these toxic effects.

Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone secreted principally by the pineal gland.[10] It is also synthesized in both plants and animal.[11] Some of the physiologic functions of melatonin that have been established include mediation of dark signal and serving as antioxidant.[10] Also, melatonin is believed to have immunomodulatory effects; it enhances innate and cellular immunity and stimulates the production of some cells of the immune system.[12] Also, some works have reported protective effects of melatonin on cyclophosphamide induced toxicities of some organs, for example reproductive organs, lung, liver and kidney.[13-16]

Considering that melatonin has been shown to modulate hematopoiesis and the immune-hematopoietic system, it possible that it may have ameliorative effect on cyclophosphamide-induced hematotoxicity. Hence, this study seeks to examine the effects of melatonin on hematological indices in cyclophosphamide-induced hematotoxicity.

METHODS

Materials

Plastic cages, electronic precision balance (Mettler Toledo), 10 ml, 5 ml and 1 ml sterile disposable syringes and needles, oral cannula, petri dish, cotton wool, universal bottles, dissecting set, slides and cover slips.

Drugs and reagents

Melatonin (5 mg tablets), cyclophosphamide (500 mg vial), erythropoietin (2000 IU/2 ml), distilled water and normal saline. Assay kits for superoxide dismutase, glutathione peroxidase, catalase, lipid peroxidation (malondialdehyde) were sourced from BioVision Inc. USA. All other reagents used were of analytical grade.

Animals

Adult Swiss mice weighing between 20-25 gm were used for this study. Animals were sourced from the animal house. They were housed in plastic cages located in temperature-controlled quarters (22-25 degree Celsius) with lights on at 7:00 am daily. All mice were fed commercial standard chow (TOP FEEDS Nigeria LTD). Animals were allowed access to food and water ad libitum. All experimental procedures were conducted in accordance with Ladoke Akintola University of Technology institutional protocols and within the provisions for animal care and use prescribed in the scientific procedures on living animals, European Council Directive (EU2010/63).

Experimental methodology

Ninety healthy adult mice weighing 20-25 gm were randomly divided into nine groups of ten (10) animals each. Animals in group A served as normal control, and were administered vehicle [normal saline at 2 ml/kg intraperitoneal injection (i.p) with distilled water 10 ml/kg daily (oral)], mice in group B, C and D served as melatonin control and were administered i.p. normal saline with one of three doses of melatonin (5, 10 and 20 mg/kg respectively).[13,17] Group E (cyclophosphamide control) received i.p. dose of cyclophosphamide (150 mg/kg/day) with oral distilled water, while groups F, received standard drug erythropoietin at 100 IU/kg.

Animals in groups G, H and I were administered i.p. injection of cyclophosphamide and oral doses of melatonin at 5, 10 and 20 mg/kg body weight respectively. Vehicle and melatonin were given daily for 14 days; while cyclophosphamide was daily for the first two days only. Standard drug was administered once weekly for two weeks. Animals were weighed weekly and on day 15, all animals were euthanized by cervical dislocation and blood was taken via cardiac puncture for assessment of haematological parameters.

Determination of body weight

Body weights of animals in all groups were measured weekly using electronic Mettler weighing balance (Mettler Toledo Type BD6000, Switzerland).

Hematological tests

Blood samples collected were analysed using the Hematology Autoanalyzer Systems (Sysmex Hematology Systems®, Model XE-2100, Sysmex Incorporation, USA). The following hematological parameters were determined: red blood cell count (RBC), hemoglobin (Hb) and packed cell volume (PCV), white blood cell count (WBC) and differentials, and platelet count

Statistical analysis

Statistical analysis was carried out using Chris Rorden'sez ANOVA for windows. Data obtained were subjected to analysis of variance (ANOVA) and post-hoc tests (Tukey HSD). Results were expressed as Mean±SEM, $p<0.05$ was taken as the accepted level of significant difference from control.

RESULTS

Effect of melatonin on body weight of the mice

Figure 1 shows effect of melatonin on body weight of the mice. The change in body weight was measured as the

difference between final weight and initial weight divided by initial weight. There was a significant ($p< 0.05$) weight loss observed in groups E-I compared to mice in group A (control). Compared to group E (cyclophosphamide control), there was a decrease in weight loss in groups F-I. While compared to standard drug Erythropoietin (group F) a decrease in weight loss was observed in groups H and I.

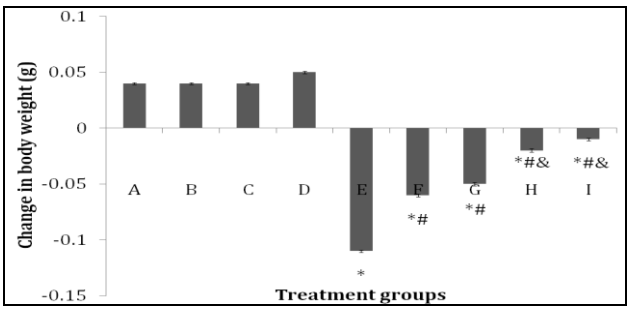

Figure 1: Effect of melatonin on change in body weight.

Each bar represents mean±SEM, *p<0.05 versus A#p<0.05 versus E, &p<0.05 versus F. Number of mice per treatment group (A-D) = 10, E=5, F=10, G=6, H=8, I=8. Group A-Normal control, B-D: Melatonin control at (5, 10 and 20 mg/kg) respectively, E: Cyclophosphamide control, F: Erythropoietin control, G-I: cyclophosphamide+ melatonin at (5, 10 and 20 mg/kg).

Effect of melatonin on complete white blood count (CBC) in CYP-induced hematotoxicity

Figure 2 shows the effect of melatonin on complete white cell count (CBC) in cyclophosphamide-induced hematotoxicity. There was a significant ($p<0.001$) increase in complete WBC in groups C, D, G and H and a significant decrease in group E compared to group A (control). Compared to group E (cyclophosphamide control) there was a significant increase in complete CBC in groups F to I. While compared to standard drug erythropoietin (group F), complete CBC increased significantly in groups G and H.

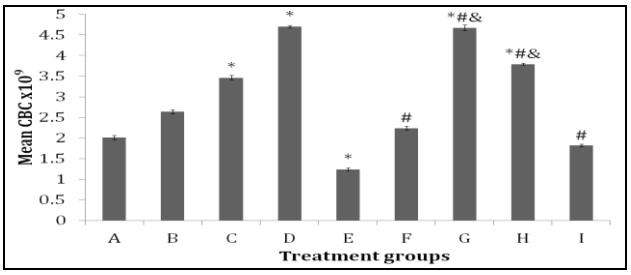

Figure 2: Effect of melatonin on complete white cell count (CBC).

Each bar represents mean±SEM, *p<0.05 versus A#p< 0.05 versus E, &p<0.05 versus F. Number of mice per treatment group (A-D) = 10, E=5, F=10, G=6, H=8, I=8. Group A-Normal control, B-D: Melatonin control at (5, 10 and 20 mg/kg) respectively, E: Cyclophosphamide control, F: Erythropoietin control, G-I: cyclophosphamide + melatonin at (5, 10 and 20 mg/kg).

Effect of melatonin on differential white blood cells in CYP-induced hematotoxicity

Table 1 (differential white cell count) show the effects of melatonin on white blood cells in cyclophosphamide-induced hematotoxicity. Granulocytes increased significantly ($p<0.001$) in groups B, G and decreased in group E compared to group A (control). Compared to group E (cyclophosphamide control) there was a significant increase in granulocytes in group G. While compared to standard drug erythropoietin (group F), granulocytes increased significantly in group G.

Table 1: Effect of melatonin on differential white cells in cyclophosphamide-induced hematotoxicity.

Groups	Granulocytes x10⁹	Mid cells x10⁹	Lymphocytes x10⁹
A	0.21±0.05	0.24±0.06	1.59±0.45
B	0.3±0.06*	0.34±0.07*	1.96±0.14
C	0.17±0.06	0.24±0.03	3.07±0.68*
D	0.21±0.03	0.29±0.02	4.22±0.29*
E	0.1±0.04*	0.16±0.02*	0.59±0.12*
F	0.14±0.03	0.21±0.03	1.91±0.35
G	0.59±0.02*#&	0.47±0.02*#&	3.49±0.06*#&
H	0.16±0.02	0.16±0.02	3.49±0.06*#&
I	0.16±0.02	0.3±0.02#	1.44±0.06#

Values presented as Mean ± SEM, *p<0.05 versus A#p<0.05 vs. E, &p<0.05 versus F. Number of mice per treatment group (A-D) = 10, E=5, F=10, G=6, H=8, I=8. Group A- Normal control, B-D: Melatonin control at (5, 10 and 20 mg/kg respectively, E: Cyclophosphamide control, F: Erythropoietin control, G-I: cyclophosphamide+ melatonin at (5, 10 and 20 mg/kg).

Mid cells which include monocytes, basophils and eosinophils increased significantly ($p<0.001$) in groups B, G and decreased in group E compared to group A (control). Compared to group E (cyclophosphamide control) there was a significant increase in mid cells in groups G and I. While compared to standard drug erythropoietin (group F), mid cells increased significantly in group G.

Lymphocytes increased significantly ($p<0.001$) in groups C, D, G and H, and decreased in group E compared to group A (control). Compared to group E (cyclophosphamide control) there was a significant increase in lymphocytes in groups G-I. While compared to standard drug erythropoietin (group F), lymphocytes increased significantly in groups G and H.

Effect of melatonin on red cells in CYP-induced hematotoxicity

Figure 3 shows the effect of melatonin on red blood cell (RBC) count in cyclophosphamide-induced

hematotoxicity. There was a significant ($p<0.001$) increase in RBC in groups B and D and a significant decrease in group E compared to group A (control). Compared to group E (cyclophosphamide control) there was a significant increase in RBC in groups F to I. While compared to standard drug erythropoietin (group F), RBC increased significantly in group G.

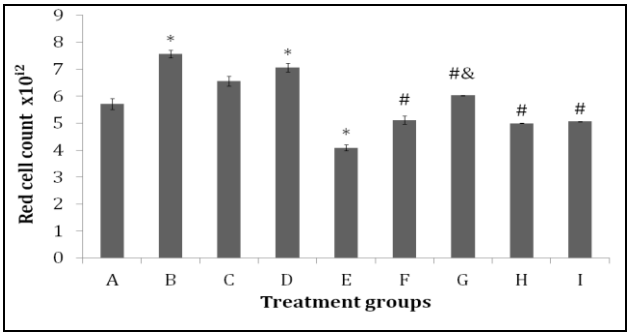

Figure 3: Effect of melatonin on red blood cell count.
Each bar represents mean±SEM, *p<0.05 versus A#p<0.05 versus E, &p<0.05 versus F. Number of mice per treatment group (A-D) = 10, E=5, F=10, G=6, H=8, I=8. Group A- normal control, B-D: MELATONIN control at (5, 10 and 20 mg/kg respectively, E: cyclophosphamide control, F: erythropoietin control, G-I: cyclophosphamide+ melatonin at (5, 10 and 20 mg/kg).

Effect of melatonin on platelets in CYP-induced hematotoxicity

Figure 4 shows the effect of melatonin on platelet count in cyclophosphamide-induced hematotoxicity. There was a significant ($p<0.001$) increase in platelet count in groups B, C, G, H and I compared to group A (control). Compared to group E (cyclophosphamide control) there was a significant increase in platelet count in groups G to I. While compared to standard drug erythropoietin (group F), platelet count also increased significantly in group G-I.

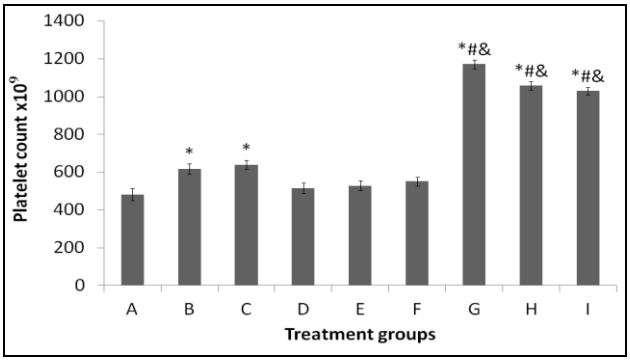

Figure 4: Effect of melatonin on platelet count.
Each bar represents mean±SEM, *p<0.05 versus A#p<0.05 versus E, &p<0.05 versus F. Number of mice per treatment group (A-D) = 10, E=5, F=10, G=6, H=8, I=8. Group A- normal control, B-D: melatonin control at (5, 10 and 20 mg/kg respectively, E: cyclophosphamide control, F: erythropoietin control, G-I: cyclophosphamide+ melatonin at (5, 10 and 20 mg/kg).

DISCUSSION

This study evaluated effects of melatonin on haematological indices in cyclophosphamide induced hematotoxicity in mice. In this study, in consonance with previous reports, cyclophosphamide was found to induce weight loss in mice.[18-20] This may be related to taste disturbance induced by cyclophosphamide with consequent reduced appetite and intake.[21,22] This study showed that melatonin ameliorated weight loss induced by cyclophosphamide. Compared with the group treated with cyclophosphamide alone, the administration of melatonin at increasing doses was associated with significant reduction in weight loss. This result is similar to that of a previous report.[23] This ameliorative effect of melatonin on the weight loss induced by cyclophosphamide may be related to melatonin's ability to increase food intake.[24]

It was observed that all the mice groups that had melatonin had increased total white cell count compared with the normal control group. The increment in the white blood count appears to be dose dependent in both healthy mice and cyclophosphamide treated mice; in the healthy mice, increased white blood count was observed with increasing doses of melatonin. However, in the cyclophosphamide treated mice groups, the increment in total white cell count is inversely related to the dose of melatonin (5 mg /kg>10 mg/kg/20 mg/kg). A previous study reported that mice that had melatonin alone in their study had increased white blood cell count but compared with the control group the increment was not significant statistically.[25] Similarly, though in rats, another study had reported that rats groups that had melatonin alone had increased white blood cell count compared with the control group.[26] In agreement with previous reports, this study observed that the mice group that had cyclophosphamide only had the lowest mean total white blood cell count which implied that cyclophosphamide induces reduced total white cell count.[27-29]

Red blood cell count increased in all the healthy mice groups when compared with normal control, though this was only significant in mice groups that had melatonin doses of 5 mg/kg and 20 mg/kg. In the groups that had cyclophosphamide and melatonin, there was no significant difference in their red blood counts when compared with the group that had standard drug erythropoietin and cyclophosphamide except the group that had melatonin at 5mg/kg that had increased red blood cell count. This suggests that melatonin probably stimulates red blood cell elevation particularly at low dose of 5 mg/kg. This is supported by an earlier study conducted in rats and had melatonin administered intraperitoneally.[30] As expected, the group who had cyclophosphamide alone, had reduced red blood cell count.[31,32]

This study showed that melatonin causes increased platelet count in all the mice groups that had melatonin. This is in consonance with previous works.[33,34] This increment was significant among the mice groups that had cyclophosphamide with melatonin. Compared to the control group, cyclophosphamide did not affect platelet count; the group that had cyclophosphamide alone had platelet count slightly higher than control but this was not significant statistically. A previous study had made similar observation; the increment in the platelet count compared to control was significant in their study.[32] However, cyclophosphamide has been reported to cause a reduction in platelet count in another study.[35]

This study showed that melatonin at the dose of 5 mg/kg body weight causes significant increase in granulocytes count in the group that had cyclophosphamide and melatonin. This suggests that low dose melatonin appears to induce/stimulate granulocytes increase.[36] In consonance with previous reports, this study showed that cyclophosphamide induces reduced granulocytes count.[27,33,37]

This study has some limitations. This study compared the effects of melatonin on cyclophosphamide induced hematotoxicity with only erythropoietin as standard due to the unavailability of granulocyte colony stimulating factors. Also, this study did not measure the serum level of melatonin and cyclophosphamide. Despite these limitations this study provides information on the ameliorative/ protective effects of melatonin on cyclophosphamide induced hematotoxicity.

CONCLUSION

In conclusion, this study observed that melatonin ameliorated weight loss induced by cyclophosphamide. Melatonin may also improve blood cell counts. Therefore, we recommend more research into the potential ameliorative effects of melatonin on cyclophosphamide induced hematotoxicity.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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