

Effect of Ozone Therapy on Anemic Cancer Patients Undergoing Chemotherapy

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Abstract: The aim of this study was to evaluate effect of ozone therapy on anemic cancer patients undergoing chemotherapy. A randomized controlled study was carried out, thirty cancer patients of both sexes who have mild to moderate anemia which induced by chemotherapy were participated in this study. Their ages were between 35-55 years. The participants were selected from the out-patient clinic at national cancer institute and randomly distributed into two equal groups. Group A (Study group): includes 15 patients who received 40 minutes of ozone therapy and aerobic exercise in addition to conventional medical care, for three months. Group B (Control group): includes 15 patients who received 40 minutes of aerobic exercise in addition to conventional medical care, for three months. Red blood cells (RBCs) counts, Hemoglobin concentration (HB) and mean corpuscular volume (MCV) were assessment. Patients in both groups were assessed before treatment and after 8 weeks of treatment. The results of this study showed that there was a significant increase in Hb, RBCs and MCV post treatment in the study and control groups compared with that pre treatment ($p > 0.001$). It was concluded that both ozone therapy and aerobic exercise were effective for treatment of anemia in cancer patients undergoing chemotherapy.

Key words: Anemia • Cancer • Chemotherapy • Ozone Therapy • Aerobic Exercise

INTRODUCTION

Anemia derived from the Greek word “anaimia” meaning lack of blood, refers to a decreased oxygen-carrying capacity in the blood and is commonly associated with cancer [1]. Anemia is defined as a low number of red blood cells, In blood test it reported as a low hemoglobin or hematocrit [2]. It is considered frequent finding in cancer patients, occurring in >40% of cases, In patients treated with chemotherapy, the incidence of anemia may rise to 90% [1, 3]. Hemoglobin (Hb) concentration is the most reliable indicator of anemia at the population level. Measuring Hb concentration is relatively easy and inexpensive and this measurement is frequently used as a proxy indicator of iron deficiency [4]. Causes of anemia in patients with cancer are often multifactorial, adding to the complexity of the problem in evaluation. Anemia may be attributed to underlying comorbidities, such as bleeding, hemolysis, hereditary disease, renal

insufficiency, nutritional deficiencies, anemia of chronic disease, or a combination. The malignancy itself can lead to or exacerbate anemia in several ways [5]. The treatment of chemotherapy-induced anemia depends on the grade and on the symptoms of anemia. Transfusion remains an option for patients who need immediate correction of anemia [6]. Ozone therapy acts as a form of oxygen therapy that stimulates mitochondria and gives them bath of fresh air. Oxygen is the most vital element required for human life and it is the key to good health. The best way to optimize health is to oxygenate every cell in our body [7]. Ozone therapy has a wide field of application more than any other drug applied safely to anyone. Since it has no side effects, it does not interact with any other medicine. For this reason, ozone therapy is being administered successfully as a quite practical and useful natural treatment method [8]. Exercise could be an appropriate non pharmacologic intervention to counteract the decline in Hb observed in many cancer patients undergoing chemotherapy. Aerobic exercise

training is associated with improved hemorheology and can increase blood volume through an increase in plasma volume and RBC mass [9]. Moderate intensity aerobic exercise has been shown to prevent the decline in Hb in cancer patients undergoing chemotherapy therapy and to improve Hb in cancer patients with severe anemia [10].

The aim of this study was to evaluate effect of ozone therapy on anemic cancer patients undergoing chemotherapy.

MATERIALS AND METHODS

Thirty cancer patients of both sexes who have mild to moderate anemia which induced by chemotherapy referred to our outpatient clinic from the National Institution of Oncology in Cairo, Egypt, were eligible for the study if they fulfilled the following requirements:

- Patient with mild to moderate anemia.
- Patients diagnosed with cancer with malignant solid tumors confirmed by histology or cytology.
- The hemoglobin (HB) levels of the patients was >8.5 and <13.5 g/dl
- All patients were clinically and medically stable.
- All patients enrolled to the study have signed their informed consent.

The study excluded primary hematologic disease, seizure disorder, uncontrolled hypertension, recent history of thromboembolic disease (within 1 year), other clinically significant systemic disease, an active infectious process, pregnancy, ongoing blood loss, scheduled autologous blood donation or blood transfusion within the previous 30 days.

Procedures of the Study

Measurement Procedures: Automated hematology analyzer (Mindray- BC 2800 plus) was used to analyze the following measures:

- RBCs count.
- Hemoglobin concentration.
- MCV (mean corpuscular volume).

Therapeutic Equipment

Ozone Generator: Ozoned (portable) Kastner Praxisbedarf- D-76437 Rastatt.

Electronic Bicycle Ergometer: (UNIVERSAL, made in New York, USA) Equipped with pedals, display screen and foot straps also provided with programmable control unit.

Pulse Oximeter: (Tunturt TPN-400, made in Japan) it was used to detect pulse rate during the exercise.

Treatment Procedures: The intervention periods of both groups were identical, eight consecutive weeks, three sessions per week and duration of the session was about 30 to 40 minutes according the ability of each patient.

Procedures of Ozone Therapy for Group A: Each patient received ozone therapy in form of rectal insufflations with ozone concentration of 20 $\mu\text{g/ml}$, increased gradually up to 40 $\mu\text{g/ml}$ and the volume ranged from 150-300ml.

Three syringes of 50 ml were filled with ozone from the generator (total ozone dose of 150 ml) with the appropriate concentration was delivered the ozone into the rectum via the catheter in the first session, then the dose and the concentration of the ozone were increased gradually in the subsequent sessions to reach the maximum range (ozone dose of 300 ml, concentration of 40 $\mu\text{g/ml}$ by using 6 syringes).

Before starting the first treatment session, each patient was instructed carefully about the ozone therapy procedure as well as, its safety, values and effects to gain his/her confidence and cooperation during the treatment sessions.

Also, each patient was advised and instructed to evacuate his/her bladder and rectum before starting ozone therapy session.

Each patient was assumed a relaxed modified side lying position, then the catheter was held and lubricated with a neutral lubricant (KY gel) and closed by the clamp before inserting it into the rectum through the anus. After that, the syringe was introduced into the free end of the catheter and then the clamp was removed and the ozone was injected into the catheter (Figure 8), after that, the catheter was closed with the clamp again, to change the syringe. This procedure was repeated from 3 to 6 times according to the ozone dose which was used. Finally the catheter was removed from the patient's rectum, when all the syringes used. Then each patient was instructed to clean his/her anus by using sterile dressing and instructed to rest for 5 minutes.

Frequency: The procedure was repeated two times weekly.

Duration: Total duration time was three months [11].

Procedures of Aerobic Exercise for Group A, B: During the three months intervention period, an aerobic training on electronic bicycle ergometer program included

a 40 minute session three times a week (120 min/week)
 Aerobic exercise was consisted of three phases:
 Warm-up, training and cool down;

First Phase (Warming Up): Consisted of 5 minutes warming up in the form of pedaling at speed of 60 revolutions per min. without load.

Second Phase (Active Stage): Consisted of:

- Duration: 30 minutes.
- Mode: pedaling at speed of 60 revolution per min. with;
- Load: adjusted load to achieve 60% of the predictive age maximal heart rate which was calculated by the following equation:

Maximal heart rate=220-age in years

Moderate work load=60% of maximal heart rate

The heart rate was measured through pulse oximeter attached to the patient's ear.

Third Phase (Cooling Down): Consisted of 5 minutes cooling down in the form of pedaling at speed of 60 revolutions per min. without load.

Duration and Frequency: 3 sessions per week for 3 months [12].

Statistical Analysis: Descriptive statistics and unpaired t-test were conducted for comparison of subject characteristics between both groups. Chi-squared test was used for comparison of sex distribution between groups Normal distribution of data was checked using the Shapiro-Wilk test. Levene's test for homogeneity of variances was conducted to ensure the homogeneity between groups. Unpaired t-test was conducted to compare the mean values of Hb, RBCs and MCV between the study and control groups. Paired t-test was conducted for comparison between pre and post treatment in each group. The level of significance for all statistical tests was set at $p < 0.05$. All statistical analysis was

conducted through the statistical package for social studies (SPSS) version 22 for windows (IBM SPSS, Chicago, IL, USA) [13].

RESULTS

Subject Characteristics: Table 1 showed the mean±SD subjects' age of the study and control groups. There was no significant difference between both groups in the mean age ($p < 0.05$). Also, there was no significant difference in the distribution of sex between both groups ($p < 0.05$).

Effect of treatment on Hb, RBCs and MCV

Within Group Comparison: There was a significant increase in Hb, RBCs and MCV post treatment in the study and control groups compared with that pre-treatment ($p > 0.001$). The percent of increase in Hb, RBCs and MCV in the study group were 54.69, 59.86 and 14.1% respectively; and that in control group were 24.26, 30.84 and 8.72% respectively (Table 2).

Between Groups Comparison: There was no significant difference in Hb, RBCs and MCV between both groups pre-treatment ($p > 0.05$). Comparison between the study and control groups post treatment revealed a significant increase in Hb, RBCs and MCV of the study group compared with that of the control group ($p > 0.001$) (Table 2).

DISCUSSION

Anemia is defined as a low number of red blood cells, in blood test it reported as a low hemoglobin or hematocrit [2]. It is considered frequent finding in cancer patients, occurring in >40% of cases, in patients treated with chemotherapy, the incidence of anemia may rise to 90% [3]. Ozone therapy has a wide field of application more than any other drug applied safely to anyone. Since it has no side effects, it does not interact with any other medicine. For this reason, ozone therapy is being administered successfully as a quite practical and useful natural treatment method [8].

Table 1: Basic characteristics of participants

	Group A x̄±SD	Group B x̄±SD	p-value
Age (years)	46.33±6.37	45.86±7.23	0.85
Sex			
Male	5 (33%)	6 (40%)	0.7
Female	10 (67%)	9 (60%)	

x̄, Mean; SD, Standard deviation; p value, Probability value

Table 2: Mean Hb, RBCs and MCV pre and post treatment of the study and control groups

	Study group	Control group			
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Hb (g/dl)	̄±SD	̄±SD	MD	t- value	p value
Pre treatment	8.43±0.72	8.45±0.58	-0.02	-0.08	0.93
Post treatment	13.04±0.91	10.5±0.98	2.54	7.33	0.001
MD	-4.61	-2.05			
Percentage of change	54.69%	24.26%			
t- value	-22.61	-15.3			
	<i>p = 0.001</i>	<i>p = 0.001</i>			
RBCs (10 ⁶ /ul)					
Pre treatment	2.89±0.35	3.08±0.36	-0.19	-1.42	0.16
Post treatment	4.62±0.48	4.03±0.5	0.59	3.27	0.003
MD	-1.73	-0.95			
Percentage of change	59.86%	30.84%			
t- value	-18.86	-12.95			
	<i>p = 0.001</i>	<i>p = 0.001</i>			
MCV (fl)					
Pre treatment	80.02±5.12	77.88±4.08	2.14	1.26	0.21
Post treatment	91.3±1.72	84.67±2.93	6.63	7.53	0.001
MD	-11.28	-6.79			
Percentage of change	14.1%	8.72%			
t- value	-10.63	-9.06			
	<i>p = 0.001</i>	<i>p = 0.001</i>			

̄, Mean; SD, Standard deviation; p value, Probability value

Moderate intensity aerobic exercise has been shown to prevent the decline in Hb in cancer patients undergoing chemotherapy therapy and to improve Hb in cancer patients with severe anemia [10].

From the obtained results, the pre-treatment results revealed no significant difference between the mean values of Hb, RBCs and MCV between both groups pre-treatment ($p > 0.05$).

The post treatment results of this study showed a significant increase in Hb, RBCs and MCV post treatment in the study and control groups compared with that pre- treatment ($p > 0.001$). The percent of increase in Hb, RBCs and MCV in the study group were 54.69, 59.86 and 14.1% respectively; and that in control group were 24.26, 30.84 and 8.72% respectively.

Therefore; the Results of the Current Study Showed That There Was a Significant Improvement in Ozone Group and this Confirms the Effectiveness of Ozone Therapy as a Therapeutic Modality That Improve Anemia in Cancer Patients Receiving Chemotherapy: The results of our study supported by Bocci and Martinez *et al.* [14, 15] who found that ozone therapy increase the oxygen level in blood, oxygenates the tissues in the whole body and can activate biochemical pathways in leukocytes, erythrocytes and platelets without acute or chronic toxicity.

Also Gerard [7] showed that ozone therapy increases red blood cell membrane distend ability, making it more flexible. This is one way it is used in the treatment of heart disease. The administration of ozone changes the blood formation and helps the blood flow more effectively.

Also the results of our study supported by the works reported by Drouin *et al.* [10] assessed the effects of 7 weeks of aerobic exercise training on erythrocyte levels during radiation therapy for breast cancer. After training, erythrocyte levels increased significantly in the training subjects in contrast to the non-training ones.

Dimeo *et al.* [16] found that aerobic exercises at an intensity of 80% of the maximal heart rate enhances the process of hematopoiesis as a result of increased production of growth hormone in anemic patients. They have found that intense or prolonged exercise has been shown to affect the concentration of several cytokines and hormones that regulate the self-renewal, proliferation and maturation of blood stem cells.

Wang *et al.* [17] found on their study that aerobic exercise improves cardiovascular conditioning, decrease risk of heart disease, lowers blood pressure, increase high density lipoprotein (HDL), improves lung function and enhance RBCs and Hb productions.

Khalighfard *et al.* [12] documented that aerobic exercise can induce correction of anemia in cancer patients after myelotoxic chemotherapy, decrease fatigue

and enhance emotional and mood state in these patients and thus physical rehabilitation is strongly recommended.

Lianne *et al.* [18] stated that enhancement of oxygen transport and tissue oxidative capacity after low to moderate-intensity aerobic exercise caused by increased blood volume through an increase in plasma volume and (RBCs) mass, improved red cell deformability and decreased blood viscosity that may have allowed patients to maintain their aerobic capacity during chemotherapy.

Courneya *et al.* [19] stated that aerobic exercise improve cardiorespiratory fitness, fatigue and some aspects of QOL in anemic cancer patients.

Heba *et al.* [20] found that women who performed moderate intensity aerobic exercise during chemotherapy of breast cancer. There were significant declines of both Hb ($t = 16.30$; $P < 0.001$) and RBCs ($t = 10.38$; $P < 0.001$) in group B relative to group A. Regarding group A, Hb increased from 11.52 ± 0.62 to 12.10 ± 0.59 g/dL with a 5.03% change, while RBCs increased from 4.24 ± 0.37 to 4.49 ± 0.42 million cells/ μ l with a 5.89% change. Between-group differences were noteworthy regarding Hb ($t = -5.34$; $P < 0.001$) and RBCs ($t = -5.314$; $P < 0.001$). The results indicate that regular participation in moderate intensity aerobic exercise can enhance chemotherapy-induced anemia.

Finally; from the previous discussion of these results and according to reports of other investigators in similar studies, It can explained that ozone therapy and aerobic exercise improve anemia in cancer patients receiving chemotherapy.

This study was limited by the psychological conditions of the subjects that may affect the performance and the ability of the patients to apply the treatment procedures.

CONCLUSION

Finally, from the Previous Discussion of These Results and According to Reports of Other Investigators in Similar Studies: It can be explained that ozone therapy has a significant effect in improvement of anemia in cancer patients undergoing chemotherapy as evidenced by the highly significant increase in Hb, MCV and RBCs. The results of the current study would introduce a scientific applicable protocol to help physical therapists, physicians of dealing with anemia in cancer patients, organize a plan of care to overcome this problem and prevent the progression of it and the development of associated morbidities.

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