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The effect of an antioxidant complex and exercise on induced lymphedema in rats

Efectul unui complex de antioxidanți şi al efortului fizic asupra limfedemului indus la şobolani

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Abstract

Background. The incidence and complexity of breast cancer related lymphedema determined us to study the effect of an antioxidant complex and of physical activity on lymphedema in female rats.

Aims. Redox homeostasis in animals with induced lymphedema, the effect of physical exercise and of supplementation with an antioxidant complex with phyto-homeopathic properties were studied.

Methods. The research was conducted on female Wistar rats, assigned to 5 groups (n = 10 animals/group): group I - control group; groups II-IV were operated for right axillary lymph node excision; group III was subjected to physical exercise; group IV was supplemented with an antioxidant complex; group V was subjected to physical exercise and supplemented with an antioxidant complex. Forelimb volume was measured to assess lymphedema before surgery and on days 3, 7, 14, 21 post-surgery. Redox homeostasis was determined based on the values of malonaldehyde (MDA) and thiol groups (SH) on day 21 post-surgery.

Results. At 21 days, we found a reduction in the volume of the affected limb after the regular exercise program and supplementation with the antioxidant complex.

Conclusions. Supplementation with the antioxidant complex has a positive role in improving lymphedema.

Key words: lymphedema, antioxidant complex, exercise.

Rezumat

Premize. Incidența şi complexitatea diagnosticului de limfedem, secundar intervenției chirurgicale pentru tratamentul cancerului de sân, ne-au determinat să studiem efectul unui complex de antioxidanți şi al efortului fizic asupra limfedemului la şobolani femele.

Obiective. S-a studiat: homeostazia redox la animale cu limfedem indus şi influența efortului fizic şi al suplimentării cu un complex fitohomeopat cu proprietăți antioxidante, cu efecte asupra circulației limfatice şi venoase.

Metode. Cercetările au fost efectuate pe şobolani femele, rasa Wistar, grupate în 5 loturi (n=10 animale/lot): lotul I - lotul martor; loturile II-IV au fost operate pentru extirparea ganglionară axilară dreaptă; lotul III a fost supus şi efortului fizic; lotul IV a fost suplimentat cu un complex antioxidant; lotul V a fost supus efortului fizic şi suplimentării cu un complex antioxidant. S-a măsurat volumul membrelor anterioare pentru a evalua edemul limfatic înainte de operație, în ziua 3, 7, 14 şi 21 postoperator. Homeostazia redox s-a determinat pe baza valorilor MDA şi SH la 21 zile postoperator.

Rezultate. La 21 zile s-a constatat o reducere a volumului membrului afectat de limfedem după programul regulat de exercițiu fizic şi după administrarea de complex antioxidant.

Concluzii. Administrarea complexului de antioxidanți are un rol favorabil în ameliorarea limfedemului.

Cuvinte cheie: limfedem, complex antioxidant, efort fizic.

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Introduction

Breast cancer is the most common type of cancer in females (Fong et al., 2014). The standard treatment of breast cancer is aggressive and has many side effects. The most frequent side effects are lymphedema and decreased range of motion. Upper limb lymphedema occurs in 24-49% of cases after total mastectomy and in 2.4-49% after axillary lymph node dissection (Smykla et al., 2013).

Lymphedema is a chronic and progressive condition caused by the damage of the lymphatic system and insufficient regeneration of lymphatic vessels (Mendez et al., 2012). Lymphedema manifests itself by increasing extracellular fluid, fibrosis, chronic inflammation of the tissues and an increased number of stagnant proteins at the cellular level (Hayes et al., 2008; Erickson et al., 2001; Cormie et al., 2013), disfigurement of the affected limb, physical discomfort and impaired arm function. Lymphedema also affects patients psychically, causing anxiety, depression, it affects social relationships, alters body image and decreases self-esteem (Torres et al., 2010). Lymphedema predisposes to the occurrence of erysipelas, lymphangitis and lymphangiosarcoma (Liu, 2004; Masmoudi et al., 2004; Ocana & Delgaco, 2006).

To decrease the incidence of postoperative complications, many studies recommend to start the rehabilitation program after surgery as soon as possible (Petito et al., 2012), ideally from the first postoperative day (Cinar et al., 2008; Kilgour et al., 2008; Rezende et al., 2006; Springer et al., 2010; Pinto e Silva et al., 2004).

After the wound is healed, hydrotherapy is recommended because it has no side effects; adherence to it is estimated at almost 90% and has the effect of reducing muscle tension in the neck, wrists, shoulders and legs (Cantarero-Villanueva et al., 2013).

Hypothesis

An antioxidant complex and physical exercise may have positive effects on the treatment of induced lymphedema in rats.

Material and methods

Research protocol

The research was approved by the Ethics Committee of the ”Iuliu Hatieganu” University of Medicine and Pharmacy Cluj-Napoca.

a) Period and place of the research

The experiment took place in the Experimental Research Laboratory at the Physiology Department of the ”Iuliu Hatieganu” University of Medicine and Pharmacy Cluj-Napoca, in July 2016.

b) Subjects and groups

The subjects of this study were female Wistar rats aged between 6-7 months, with a weight of 280-300 g, from the biobase of the ”Iuliu Haţieganu” University of Medicine and Pharmacy Cluj-Napoca.

The subjects were assigned to 5 groups (n = 10 animals/group):

- Group I - control group
- Groups II-IV were operated for right axillary lymph node excision
- Group III was subjected to physical exercise
- Group IV was supplemented with an antioxidant complex
- Group V was subjected to physical exercise and supplemented with an antioxidant complex.

Surgery for axillary lymph node excision in order to induce lymphedema was performed using the method of Mendez & al. (2012).

Supplementation with the antioxidant complex (AO) was carried out by administration of the Circulation Blend SP-11B product, produced by Secom. The daily AO dose was 10 mg/day/animal, by oropharyngeal gavage.

c) Tests applied

- For aerobic exercise capacity, the method of Nayanatara et al. (2005) was used, consisting of swimming for 15 minutes, every day, in the swimming pool of the Physiology Department Laboratory of the University of Medicine and Pharmacy Cluj-Napoca.
- Lymphedema was assessed based on the volume of the forelegs, determined using a Ugo Basile 7140 Plethysmometer device before surgery and on days 3, 7, 14 and 21 post-surgery. Values are expressed as % of controls.
- The O/AO balance was assessed by measurement of malonaldehyde (MDA) – using the fluorescence method (Conti et al., 1991) and the carbonyl assay (CA) – according to the method of Hu (1994), from venous blood from the retrobulbar vein, on the 21st postoperative day. Values were expressed in μmol/ml for MDA and nmol/ml for CA. Determinations were performed in the Laboratory for the Study of Oxidative Stress of the Physiology Discipline at UMPh Cluj-Napoca.

d) Statistical analysis

- Statistical analysis was performed using the MedCalc 16.8 program. We conducted a comparative and correlation analysis.

Results

a) Comparative analysis of the studied indicators

Comparative analysis of MDA by groups (Table I)

The statistical analysis of MDA values, considering all control groups, revealed highly statistically significant differences between at least two groups ($p < 0.01$).

The statistical analysis of MDA values, considering all groups with surgical excision of axillary lymph nodes, revealed highly statistically significant differences between at least two groups ($p < 0.01$).

The statistical analysis of MDA values, considering all exercise groups, revealed no statistically significant differences between groups ($p > 0.05$).

The statistical analysis of MDA values, considering all groups with antioxidant supplementation, revealed no statistically significant differences between groups ($p > 0.05$).

The statistical analysis of MDA values for unpaired samples revealed:

- Highly statistically significant differences between groups I-IV I-V, II-IV ($p < 0.01$);
- Statistically significant differences between groups I-II, I-III ($p < 0.05$).

Comparative analysis of CA by groups (Table II)

The statistical analysis of CA values, considering all control groups, revealed highly statistically significant

Table I

Comparative analysis of malonaldehyde (expressed in nmol/ml) in the studied groups and statistical significance.

Group	Mean	SE	SD	Median	Min.	Max.	25 - 75 P
I	2.16	0.291	0.11	2.115	1.674	2.569	2.049 to 2.380
II	1.764	0.4254	0.1608	1.505	1.429	2.544	1.446 to 1.994
III	1.477	0.582	0.22	1.362	0.856	2.606	1.099 to 1.711
IV	1.262	0.2222	0.08399	1.346	0.828	1.502	1.174 to 1.389
V	1.342	0.3785	0.1431	1.423	0.843	1.794	0.960 to 1.644
p	I-II:0.0350	I-III:0.0350	I-IV:0.0017	I-V:0.0027	II-III:0.2248	II-IV:0.0060	II-V:0.1102
	III-IV:0.6547	III-V:0.9491	IV-V:0.4062				

Table II

Comparative analysis of the carbonyl assay (expressed in μmol/ml) in the studied groups and statistical significance.

Group	Mean	SE	SD	Median	Min.	Max.	25 - 75 P
I	0.261	0.01839	0.006951	0.263	0.237	0.284	0.243 to 0.275
II	0.24	0.08061	0.03047	0.226	0.157	0.373	0.171 to 0.293
III	0.18	0.05968	0.02256	0.18	0.0604	0.238	0.170 to 0.227
IV	0.213	0.07064	0.0267	0.242	0.123	0.304	0.139 to 0.259
V	0.227	0.07405	0.02799	0.198	0.17	0.388	0.192 to 0.229
p	I-II:0.6547	I-III:0.0027	I-IV:0.1797	I-V:0.0253	II-III:0.3379	II-IV:0.6547	II-V:0.9491
	III-IV:0.2502	III-V:0.3379	IV-V:0.9491				

differences between at least two groups ($p < 0.01$).

The statistical analysis of CA values, considering all groups with surgical excision of axillary lymph nodes, revealed highly statistically significant differences between at least two groups ($p < 0.01$).

The statistical analysis of CA values, considering all exercise groups, revealed no statistically significant differences between groups ($p > 0.05$).

The statistical analysis of CA values, considering all groups with antioxidant supplementation, revealed no statistically significant differences between groups ($p > 0.05$).

The statistical analysis of CA values for unpaired samples revealed:

- Highly statistically significant differences between groups I-III ($p < 0.01$);
- Statistically significant differences between groups I-V ($p < 0.05$).

Comparative analysis of lymphedema by groups (Table III)

The statistical analysis of the volumes of the right foreleg with lymphedema, considering all control groups, revealed highly statistically significant differences between all groups, at all time points ($p < 0.01$).

The statistical analysis of the right foreleg volumes, considering all control groups and the groups with surgical excision of axillary lymph nodes, revealed highly statistically significant differences between all groups, at all time points ($p < 0.01$).

The statistical analysis of the right foreleg volumes, considering all groups with surgical excision of axillary lymph nodes, revealed highly statistically significant differences between groups II-III on days 14 and 21; groups III-IV on days 7, 14 and 21; groups III-V on day 14; and groups IV-V on day 21 ($p < 0.01$).

The statistical analysis of the right foreleg volumes, considering all groups with surgical excision of axillary lymph nodes, revealed statistically significant differences between groups II-III on day 7; groups II-IV on day 21; groups II-V on day 14; and groups IV-V on day 14 ($p < 0.05$).

The comparative analysis of lymphedema in all groups at different time points revealed that on postoperative day 3, all animals had an increased right foreleg volume. Group II had an improvement in lymphedema starting with day 7, continuing with days 14 and 21. In groups III and V, a very significant improvement was observed on days 14 and 21 compared to day 3.

Comparative analysis of lymphedema by evaluation moments (Table III)

The statistical analysis of the right foreleg volumes, considering the control group (I) at the studied moments, showed no statistically significant differences ($p > 0.05$).

The statistical analysis of the right foreleg volumes, considering group II at the studied moments, showed highly statistically significant differences between days: 0-3, 0-7, 3-14, 3-21, 7-14, 7-21, 14-21 ($p < 0.01$).

The statistical analysis of the right foreleg volumes, considering group II at the studied moments, showed statistically significant differences between days: 0-14, 3-7 ($p < 0.05$).

The statistical analysis of the right foreleg volumes, considering group III at the studied moments, showed highly statistically significant differences between days: 3-14, 3-21, 7-14, 7-21, 14-21 ($p < 0.01$). The statistical analysis of the right foreleg volumes, considering group III at the studied moments, showed statistically significant differences between days: 0-3, 0-7, 0-14 ($p < 0.05$).

The statistical analysis of the right foreleg volumes, considering group IV at the studied moments, showed highly statistically significant differences between days: 0-14, 0-21, 3-14, 3-21, 7-14, 7-21, 14-21 ($p < 0.01$).

The statistical analysis of the right foreleg volumes, considering group IV at the studied moments, showed statistically significant differences between days: 3-7 ($p < 0.05$).

The statistical analysis of the right foreleg volumes, considering group V at the studied moments, showed

Table III

Comparative analysis of the foreleg volumes (expressed as % of controls) in the studied groups and statistical significance

Group	Moment	Mean	SE	SD	Median	Min.	Max.	25 - 75 P	p	
I	Day 0	100	0	0	100	100	100	100.000 – 100.000	D0-D3:1.0000	D3-D14:1.0000
	Day 3	100	0	0	100	100	100	100.000 – 100.000	D0-D7:1.0000	D3-D21:1.0000
	Day 7	100	0	0	100	100	100	100.000 – 100.000	D0-D14:1.0000	D7-D14:1.0000
	Day 14	100	0	0	100	100	100	100.000 – 100.000	D0-D21:1.0000	D7-D21:1.0000
	Day 21	100	0	0	100	100	100	100.000 – 100.000	D3-D7:1.0000	D14-D21:1.0000
II	Day 0	101.082	7.3809	2.3341	102.381	88.462	111.905	94.118 – 106.522	D0-D3:0.0057	D3-D14:0.0017
	Day 3	250.23	27.9477	8.8378	243.878	205.769	290.476	231.373 – 271.429	D0-D7:0.0011	D3-D21:0.0017
	Day 7	227.04	32.4631	10.2657	228.084	177.551	278.571	194.231 – 251.163	D0-D14:0.0108	D7-D14:0.0060
	Day 14	180.498	26.9371	8.5183	175.799	144.231	216.667	157.143 – 211.628	D0-D21:0.0708	D7-D21:0.0017
	Day 21	148.897	24.8855	7.8695	142.641	117.391	186.047	129.412 – 171.429	D3-D7:0.0476	D14-D21:0.0073
III	Day 0	101.744	13.5355	4.2803	103.204	82.692	119.048	85.714 – 114.286	D0-D3:0.0208	D3-D14:0.0073
	Day 3	270.19	35.6502	11.2736	269.218	225	330.233	240.816 – 300.000	D0-D7:0.0298	D3-D21:0.0017
	Day 7	271.098	34.3526	10.8633	268.367	226.923	323.256	245.098 – 297.619	D0-D14:0.0169	D7-D14:0.0060
	Day 14	235.73	30.1531	9.5353	244.728	190.385	278.571	209.615 – 258.140	D0-D21:0.0700	D7-D21:0.0017
	Day 21	184.241	28.5403	9.0252	186.735	134.615	223.81	167.308 – 200.000	D3-D7:0.8983	D14-D21:0.0017
IV	Day 0	108.926	10.8449	3.4295	106.322	96.154	126.19	100.000 – 118.605	D0-D3:0.0893	D3-D14:0.0017
	Day 3	262.206	17.186	5.4347	262.601	236.735	281.395	251.923 – 278.571	D0-D7:0.2656	D3-D21:0.0017
	Day 7	228.337	23.6483	7.4782	220.36	202.041	276.744	215.686 – 236.735	D0-D14:0.0044	D7-D14:0.0017
	Day 14	163.951	19.5799	6.1917	163.37	134.615	192.857	148.980 – 181.395	D0-D21:0.0019	D7-D21:0.0017
	Day 21	125.796	11.3972	3.6041	124.158	109.615	145.238	118.367 – 135.714	D3-D7:0.0181	D14-D21:0.0017
V	Day 0	111.447	10.1938	3.2236	109.583	98.077	126.19	104.082 – 118.605	D0-D3:0.0051	D3-D14:0.0017
	Day 3	259.875	25.3531	8.0173	257.934	228.846	311.905	244.231 – 271.429	D0-D7:0.0062	D3-D21:0.0017
	Day 7	250.03	29.4244	9.3048	247.877	211.538	307.143	226.531 – 262.745	D0-D14:0.0001	D7-D14:0.0017
	Day 14	196.45	26.5621	8.3997	187.223	167.308	235.714	173.077 – 220.930	D0-D21:0.0085	D7-D21:0.0017
	Dat 21	165.318	16.4758	5.2101	167.252	139.216	183.721	146.154 – 178.571	D3-D7:0.2774	D14-D21:0.0017
p	D0(I-II):0.0001		D3(I-II): 0.0001		D7(I-II):0.0001			D14(I-II): 0.0001		D21(I-II): 0.0001
	D0(I-III):0.0001		D3(I-III):0.0001		D7(I-III):0.0001			D14(I-III): 0.0001		D21(I-III): 0.0001
	D0(I-IV):0.0001		D3(I-IV):0.0001		D7(I-IV): 0.0001			D14(I-IV): 0.0001		D21(I-IV): 0.0001
	D0(I-V):0.0001		D3(I-V):0.0001		D7(I-V): 0.0001			D14(I-V): 0.0001		D21(I-V): 0.0001
	D0(II-III): 0.7913		D3(II-III):0.1988		D7(II-III): 0.0191			D14(II-III):0.0015		D21(II-III):0.0089
	D0(II-IV):0.1508		D3(II-IV):0.2899		D7(II-IV): 0.9698			D14(II-IV):0.1903		D21(II-IV):0.0355
	D0(II-V):0.0539		D3(II-V):0.5453		D7(II-V):0.1620			D14(II-V):0.0265		D21(II-V):0.1212
	D0(III-IV): 0.3445		D3(III-IV):0.5453		D7(III-IV):0.0041			D14(III-IV):0.0001		D21(III-IV):0.0001
	D0(III-V):0.1620		D3(III-V):0.5708		D7(III-V): 0.1509			D14(III-V):0.0089		D21(III-V):0.0696
	D0(IV-V): 0.6229		D3(IV-V):0.5708		D7(IV-V): 0.0539			D14(IV-V):0.0185		D21(IV-V):0.0002

Table IV

Correlation analysis of the studied indicators.

Items		Group I		Group II		Group III		Group IV		Group V	
MDA	CA	-0.071	*	0.75	****	0.143	*	0.25	*	0.714	****
	Lymphedema	-	-	0.607	***	-0.464	***	0	*	0.071	*
CA	Lymphedema	-	-	0.356	**	0.607	***	0.055	*	-0.357	**

highly statistically significant differences between days: 3-7, 14-21 ($p < 0.01$).

The statistical analysis of the right foreleg volumes, considering group V at the studied moments, showed statistically significant differences between days: 0-3, 0-7, 0-14, 0-21, 3-14, 3-21, 7-14, 7-21, 14-21 ($p < 0.05$).

b) Correlation analysis of the studied indicators (Table IV)

The correlation analysis of the studied indicators showed:

- for group II: a very good positive correlation between MDA-CA; a good positive correlation between MDA-lymphedema; an acceptable positive correlation between CA-lymphedema;
- for group III: a good positive correlation between MDA-lymphedema;
- for group IV: an acceptable positive correlation between MDA-lymphedema and CA-lymphedema;
- for group V: a very good positive correlation between MDA-CA; an acceptable positive correlation between CA-lymphedema.

Discussions

Circulation Blend SP-11B is a plant extract-based product with homeopathic nutrients which improves the blood and lymphatic flow (Secom). The complex contains a patented blend with natural homeopathic components including: pepper (Capsicum annuum - seeds), thorn (Ruscus aculeatus - root), kelp (Laminaria spp. – whole plant), Gentiana (Gentiana lutea - root), ginger (Zingiber officinale - root), verbina (Verbena officinalis – the aerial part) (Secom).

A number of studies have shown the antioxidant (AO) action of the bioactive compounds of the product:

- Chili seeds contain two fractions of phenolic flavonoids (quercetin and catechin) and capsaicinoids in pericarp (Materská & Perucka, 2005), whose AO activity increases with maturity; the mature seeds contain high quantities of antioxidant vitamins C and A (Ghazemnezhad et al., 2011; Marin et al., 2004);
- Thorn root contains phenolic compounds and ellagic phenolic acids and quercetin (Luis et al., 2011);

- Kelp, called "the gift of the sea", is a seaweed that contains three sulfate polysaccharide fractions (F1, F2, F3) with a powerful AO effect (Amin & Siew Hong, 2002; Wanga et al., 2008);

- Ginger root contains phenolic compounds such as α-zingiberene, gingerol and shogaol, with an AO effect (Stoilova et al., 2006; Zancana et al., 2002) stronger than that of quercetin (Stoilova et al., 2006);

- Verbena (aerial part), due to its total phenolic and flavonoid content, has AO effects (Rehechoa et al., 2011; Casanova et al., 2008).

Quercetin, present in most components of the AO blend, is a powerful protector for the cardiovascular system and reduces oxidative stress (***, 2015). Also, quercetin has the ability to modulate the signal transduction pathways associated with inflammatory and carcinogenic processes. Animal studies have demonstrated that administration of this flavonoid prevents chemically induced carcinogenesis, and epidemiological studies indicate a protective effect on lung cancer. For these reasons, quercetin is considered a positive agent in cancer prevention (Murakami et al., 2008).

Highly statistically significant differences were observed between groups I-II, I-III I-IV I-IV, which shows that after surgery for removal of axillary lymph nodes, the right forelimb volume increased significantly.

Highly statistically significant differences were also observed between groups II-III on days 14 and 21; groups III-IV on days 7, 14 and 21; groups III-V on day 14; groups IV-V on day 21, and statistically significant differences between groups II-III on day 7; groups II-IV on day 21; groups II-V on day 14; groups IV-V on day 14, which demonstrates the beneficial effect of the AO complex on lymphatic and circulatory system function through the development of remaining lymphatic vessels favoring extracellular fluid resorption and reduction of lymphedema.

The same positive effect is demonstrated by other experimental studies which used AOs; either a moderate effect (Ewertz & Jensen, 2011), or a significant improvement (Chang et al., 2013) on lymphedema and blood circulation (Kasseroller & Schrauzer, 2000) was obtained. Even fibrosis in the context of lymphedema was significantly reduced by AO intake (Delanian & Lefaix, 2004).

Active physical exercise stimulates skeletal muscle contraction, which acts as a major pumping mechanism of lymph and venous blood (Bicego et al., 2006), playing a key role in the development of the collateral lymphatic network (Lane et al., 2005), acting in favor of lymph angiogenesis (de Oliveira et al., 2014). Physical exercise associated with an AO complex decreases the positive AO effect on lymphedema. Moderate physical effort has AO effects, while intensive exercise has a pro-oxidant effect (Bulduş, 2012).

Our results show that the experimental model used for the induction of lymphedema is a valid model (Mendez et al., 2012).

Redox homeostasis in animals with or without exercise, with or without AO supplementation, is established under lymphedema conditions with the reduction of oxidative stress on account of MDA (G II-G V).

Moderate physical exercise has an AO effect in animals with lymphedema; this is also evidenced by other authors (Bulduş, 2012), in the absence of lymphedema.

Associating AO supplementation with physical exercise in animals with lymphedema (G V) determines at 21 days a decrease of oxidative stress and an AO effect simultaneously with the reduction of lymphedema, the effects being superior to those in animals with lymphedema, subjected to physical exercise (G III).

Conclusions

1. The AO complex determines at 21 days a decrease of oxidative stress in animals with lymphedema with or without physical exercise, compared to control values.

2. AO supplementation reduces lymphedema in animals with or without physical exercise at 21 days compared to day 3.

3. AO supplementation has significant favorable effects on lymphedema at 21 days, compared to the association of AO and physical exercise therapy.

4. Associated AO and physical exercise therapy has a significant favorable effect compared to physical exercise therapy in lymphedema at 21 days, and it could be recommended after radical mastectomy with lymph node dissection.

Conflicts of interests

There are no conflicts of interests.

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