Microcirculation and lymphedema: the role of aminaphthone

Abstract

Aims: The microcirculation, or the micro-vascular-tissue unit, represents the anatomical-functional unit where oxygen and nutrient absorption processes take place. The microcirculation plays a central role in the elimination and reabsorption of catabolites through the colloid-osmotic and hydrostatic pressure gradients equilibrium, which is modified in lymphedema. The latter is characterized by an interstitial edema of high protein concentration caused by inadequate lymphatic drainage. The effects of drug therapy with Aminaphtone in the pharmacological treatment of lymphedema have been evaluated. The management of lymphatic edema, in fact, involves the association of several treatments ranging from drug therapy, to manual and non-manual drainage techniques and compression therapy.

Materials and methods: A literature review was conducted in patients suffering from phlebo-lymphatic insufficiency and treated with aminaphthone. Three studies were analyzed and exactly: «Effects of Aminaphtone therapy on chronic venous and lymphatic stasis» (D. De Anna, F. Mari, S. Intini, V. Gasbarro, A. Sortini, E. Pozza, R. Marzola, U. Taddeo, F. Bresadola, I. Donini), “AMINAFTONE: A POSSIBLE ROLE IN SCLEROSIS SYSTEMIC” (Prof. Raffaela Scorzia, Dr. Giulia Solazar, Dr. Chiara Bellocci), - UOC Clinical Immunology, IRCCS Foundation Ca’ Granda Maggiore Policlinico Hospital - Milan, “Role of Amineftone in the treatment of lymphatic edema. Presentation of a series of cases and proposal for a randomized and controlled study. “(G Spezzigu, F Abritti, S Belletti, G Arpaia)1 (mettere per esteso il rif bibliografico – rivista ed anno di pubblicazione)

Results: After combined treatment of lymphedema, aminaphthone therapy was able to significantly reduced edema in patients with stages I and II lymphedema.

Conclusions: Although there were not many studies on this topic, it seems that aminaphthone treatment in combination therapy could have a role in the reduction of lymphedema in the early stages of pathology.

Keywords: aminaphthone, lymphedema, microcirculation, permeability, colloid-osmotic pressure, capillary filtrate, pathological condition, tissues, colloid-osmotic, hydrostatic pressure, equilibrium, chronic inflammation, fibrous tissue

Introduction

The microcirculation or micro-vascular-tissue unit consists of a dense network of capillaries, composed of endothelial cells and circulating cells, and regulates the blood supply, depending on the functional moments of the individual regions, through two different mechanisms: vasomotility control (nervous control) and permeability control (endothelial control). The Micro-circulatory unit consists of: arteriole, capillary venula, AVA, lymphatic capillary, nerve termination and connective matrix (Figure 1). Edema is the result of the modifications in the capillary exchange with accumulations of liquid within the tissues, generally circumscribed, which originate as a result of an alteration of the microvascular wall with abnormal increase of its permeability and modification of the gradients of hydrostatic pressure within the capillary bed. The microcirculation plays a central role in the elimination and reabsorption of catabolites through the colloid-osmotic and hydrostatic pressure equilibrium which is modified in cases of lymphedema which represents a pathological condition characterized by extravasal accumulation of lymph due to excess of lymphatic production. It happened when the lymphatic system is no longer able to regularly transport the lymph. This causes the deposition in tissues of liquids with a high protein concentration. The proteins thus deposited can cause a chronic inflammation in the tissues that can turn into fibrous tissue.

Lymphedema is classified as: primary (congenital or acquired), that is, a consequence of a congenital (spiegare meglio!!?) and secondary lymphatic dysplasia, that is due to a lesion of the lymphatic vessels and/or lymph nodes, in consequence of the obstruction, compression or removal, or an excessive lymphatic load (ex. anatomical obliteration following a trauma or a radical surgery, an advanced venous system diseases, etc.). The course of a lymphedema, both primary and secondary, is characterized by various stages with a different progression for each subject:

Stage I: It can start with a latency period (absence of clinical symptoms and the alteration of the lymphatic system can be ascertained only with instrumental examinations) and then it manifests as a mild soft edema that regresses totally or partially during the night or with the lower limbs elevations. The typical clinical signs are the edema on the back of the foot and the accentuation of the natural skin folds.
at the metatarsofalangee joints (Stemmer’s sign). Symptoms can be confused with other pathologies: occasional cramps, nocturnal tingling or pruritus.

**Stage II:** Lymphoedema occurs as a hard swelling, it has no tendency to regression and it is invasive. The symptoms become more and more persistent. The skin surface is dry, hyperkeratotic and grayish.

**Stage III:** Fibrolymphedema (Lymphoedema o lymphedema? Scriviamo sempruguale!!!) With hardened subcutaneous tissue and trophic disorders. The body reacts to the persistent stagnation of high-protein liquid producing fibromatosis. Resolution is unlikely at this stage. The most severe expression of this stage is called elephantiasis.$^{2-4}$

In physiological conditions the capillaries filter at the level of the arterial end (arterioles) and reabsorb into the venous (venula). 90% of the arterial filtrate is reabsorbed at the venous level and 10% (about 2 liters per day) of the interstitial fluid (with water, proteins, dead cells, viruses) is recovered by the lymphatic system, which prevents the formation of edemas by pouring it into the blood circulation. In pathological conditions, if the lymphatic system is damaged, for example due to radiotherapy or surgery with removal of the lymph nodes, the interstitial fluid cannot be completely reabsorbed by the capillaries, so it accumulates in the interstitial tissues and creates swelling. Lymphedema is therefore an edema due to an alteration of the lymphatic system. The lymphatic system consists of lymphatic capillaries. Lymphatic vessels originate between the cells of the interstitial connective tissues with very permeable capillaries covered. The lymphatic capillaries and the extracellular matrix, from which they originate, are endowed with negative pressure; this facilitates drainage of excess interstitial fluids (lymph), preventing edema and lymph nodes. The endothelium may be continuous or fenestrated, fusiform-like cells, with abluminal surface (interconnected with tissues by basal membrane, collagen, proteoglycans, heparansulphates, integrins) or luminal (interconnected with blood by Fazzy-Coat: mucopolisaccharides, glycoprotein, fibrinogen, fibrin) with elastic cytoskeleton that allows to saturate any continuous solutions. Among the endothelial functions we remember the function of selective barrier between blood and tissues. The formation of edema occurs at the microcirculation, that is in the area where the interchange of molecules takes place between the blood and the interstitial liquid and between this and the cells of all tissues (Figure 2).$^{5,6}$

![Figure 2](image)

**Figure 2** In pathological conditions, the district in which vascular-tissue exchanges occur is increased and extends also to arterioles and venules, as well as, of course, to capillaries.

In pathological conditions, the district in which vascular-tissue exchanges occur is increased and extends also to arterioles and venules, as well as, of course, to capillaries. The site in which the massive fluid outflow occurs, in pathological conditions, is represented by the collecting venules, and therefore not by the point of greatest filtration in physiological conditions (capillary-venular passage zone). From here, therefore, the inflammatory response and the changes in the microcirculation are activated. We assure:

I. Increased capillary permeability, with consequent accumulation of proteins in interstitial fluids (present in the extracellular space, ie between the capillary and the cell).

II. Decreased plasma-osmotic pressure.

III. Increased filtration at the level of the capillaries.

The increase in vascular permeability (detectable with fluorescence videocapillaroscopy) is due to: an increase in amplitude of the “small pores” system responsible for trans-capillary diffusion to mucopolisaccharide accumulation (on which the basal membrane thickening depends) which modifies the selectivity of the filtration process. It generates alteration between the colloid-osmotic pressure of the circulating blood that tends to retain the liquid inside the vessels and the hydrostatic pressure which, instead, favors the filtration. In physiological conditions the hydrostatic pressure tends to cause the liquids escape from the capillary lumen and that the colloidosmotic pressure tends to restrain them or make them fall, note that: In the proximal portion of the microcirculation the hydrostatic pressure (35 mmHg) prevails on colloidosmotic pressure (25 mmHg) for which a filtering pressure of 10 mmHg is present. The liquid is then filtered from the plasma in the gap.

In the intermediate portion of the microcirculation the hydrostatic pressure is equal to the colloidosmotic pressure (25 mmHg-25 mmHg) for which the filtering pressure is 0 mmHg, with the consequence that the amount of liquid that diffuses from the capillary lumen in the interstitium equals that that spreads from this to that. In the terminal portion of the microcirculation the colloid-osmotic pressure (25 mmHg) prevails on the hydrostatic pressure (15 mmHg) with the consequence that it exerts a resorption force that draws liquid from the interstitium. Briefly, within 24 hours, the excess of liquid that passes through the interstitium corresponds to about 5 L which re-enter the
blood through the lymphatic circulation. In pathological conditions, there is an increase in hydrostatic pressure, therefore a greater quantity of filtered liquid and a reduction in colloid-osmotic pressure, therefore a smaller quantity of retained liquid. (spiegare meglio!!!!). Therefore, an early diagnosis to reduce edema is essential to avoid the worst stages, especially in those who are familiar with lymphoedema (Figure 3).7

Suggestions and useful treatments are: Manual lymphatic drainage, Pressotherapy, Elastic brace (sock, bracelet or multi-layer bandage), Use of customized ergonomic insoles and postural rehabilitation, Nutrition and adequate physical activity and pharmacological therapy (phlebotonic, etc.).6

Figure 3 diagnosis to reduce edema is essential to avoid the worst stages, especially in those who are familiar with lymphoedema.

Materials and methods
Aminaphthone (2-hydroxy-3-methyl-1,4-naphthohydrochinone-2-paraminbenzoate) is a drug that has recently demonstrated to reduced the expression of VCAM and ELAM (E-Selectin), to reduced the endothelial expression of Endothelin 1 (ET-1) and to possess endothelial anti-flogistic activities by inhibits the expression of pro-inflammatory cytokine. Aminaphthone could represent a first drug that, in the presence of an endothelial activation (as in the cases of lymphedema), with the onset of an inflammatory state and increased production of endothelin-1 with consequent alteration of the vasal tone in the vasoconstrictive sense, Aminaftone administered at different concentrations and in different times, following in vitro experiments on human endothelial cell models stimulated with interleukin-1, effectively lowers endothelin production, in all treatment times considered. Furthermore, in vivo, the trial of 24 patients with systemic sclerosis (12 controls and 12 treated with aminaphasone 75mg for three months) showed that aminaphthone is able to decrease the adhesion molecules present in the serum. In the latest studies the overall effect of aminaphthone on the inflammatory status was evaluated. Through the use of kit-elisa and the multiplex system we researchers calculated the actual amount of protein produced for each cytokine whose gene expression was modulated by the drug. Aminaphthon down-regulates very effectively both gene transcription and protein product of almost all the most important molecules responsible for the inflammatory state. Down-regulates many cytokines among which for example IL-6 intervenes in the acute inflammatory phase. In the study (3) “Role of aminaphthone in the therapeutic lymphatic edema. Presentation of a series of cases and proposal for a randomized and controlled study. (“G.Spezzigu, F.Abritti, S. Belletti, G. Arpaia)” was pointed out the importance of a correctness of the diagnosis at the time of the first visit that was to understand the execution of a lymphoscintigraphy and an echography of soft tissue that shows lymphatic lakes (Figure 4).

Action mechanism
Phlebotonic action: > venous return (flowmeter)
Lymphagogue action: > lymphatic return (lymph collection)
> Lymphatic speed (lymphoscintigraphy)
Wall action (veins, capillaries, lymphatics): > resistance (endotoxin)
<permeability
Anti-sludge action: < erythrocyte aggregation
Oncotic action: > lymphatic oncotic pressure
(Spiegare meglio questi meccanismi d’azione ascrivibili al capillarema). The study (1) «Effects of Aminaftone therapy on chronic venous and lymphatic stasis» (De Anna, F. Mari, S. Intini, V. Gasbarro, A. Sortini, E. Pozza, R. Marzola, U. Taddeo, F. Bresadola, L. Donini) reports the therapeutic effects of the aminaphthone in the treatment of patients affected by IVC, intended as an attempt to resolve the multiple pathogenic mechanisms operating both on macroscopic venous structures and on the capillary microcosm lymphatic. It was carried out on 114 patients with IVC, divided into two randomized and controlled groups; the first group treated with the common phlebotonic, the second group with aminaphthone at a dose of 4-6 mg /kg/day, corresponding to 4/6 capsules of 75 mg/day. The effects of the therapy were evaluated by comparing the symptomatology before and after 90 days of therapy, both with subjective methods (symptom evaluation by score) and with objective methods (eco-Doppler and measurements).10

The study (2) “AMINAFTONE: A POSSIBLE ROLE IN SCLEROSIS SISTEMICA?” (Prof. Raffaella Scorza, Dr. Giulia Solazar, Dr. Chiara Bellochci - UOC Clinical Immunology, IRCCS Ca ‘Granda Foundation Maggiore Policlinico Hospital - Milan ) shows that, since the expression of an endothelial activation (as in the cases of lymphedema), with the onset of an inflammatory state and increased production of endothelin-1 with consequent alteration of the vasal tone in the vasoconstrictive sense, Aminaftone administered at different concentrations and in different times, following in vitro experiments on human endothelial cell models stimulated with interleukin-1, effectively lowers endothelin production, in all treatment times considered. Furthermore, in vivo, the trial of 24 patients with systemic sclerosis (12 controls and 12 treated with aminaphasone 75mg for three months) showed that aminaphthone is able to decrease the adhesion molecules present in the serum. In the latest studies the overall effect of aminaphthone on the inflammatory status was evaluated. Through the use of kit-elisa and the multiplex system we researchers calculated the actual amount of protein produced for each cytokine whose gene expression was modulated by the drug. Aminaphthon down-regulates very effectively both gene transcription and protein product of almost all the most important molecules responsible for the inflammatory state. Down-regulates many cytokines among which for example IL-6 intervenes in the acute inflammatory phase. In the study (3) “Role of aminaphthone in the therapeutic lymphatic edema. Presentation of a series of cases and proposal for a randomized and controlled study. (“G.Spezzigu, F.Abritti, S. Belletti, G. Arpaia)” was pointed out the importance of a correctness of the diagnosis at the time of the first visit that was to understand the execution of a lymphoscintigraphy and an echography of soft tissue that shows lymphatic lakes (Figure 4).
Results

In study (1) the differences were statistically significant for subjective and objective signs and symptoms of Lymphoedema in the group of patients who had taken aminaphthone. The authors have obtained excellent results also in the pathology concerning the lymphatic district having available a polyvalent drug able to acts on 3 different pathogenic fronts of the I.V.C. (venous, capillary and lymphatic). The lymphoglobin and lymphocinetic action of aminaphthone, has allowed a general and lasting improvement of the treated patients, postponing the therapy over time. The study (2) demonstrates, among the many results obtained, that in the cases of an endothelial activation, as in lymphedema, Aminaphtone effectively lowers the production of endothelin. In the study (3) A retrospective analysis seems to demonstrate that aminaphthone treatment was more effective in patients in the I or I / II stage of lymphedema, while in the more advanced stages (III) the influence of the treatment it was less remarkable.12

Conclusion

The superiority of the effectiveness of aminaphthone on several pathogenetic fronts has been demonstrated in more than 100 patients affected by Lymphoedema. The innovative and updated mechanism of action of aminaphthone together with its role in “endothelial-protection” seems to confirm its usefulness in patients affected by Lymphoedema. Obviously, there is a need of further controlled, randomized and double-blind clinical trials to confirm its effectiveness in patients affected by Lymphoedema also if it seems that its peculiar and specific mechanism of action could completely fit with the etiopathogenesis of this pathology.

Acknowledgements

None.

Conflict of interest

The author declares there is no conflict of interest.

References

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