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# EFFECT OF TOPICAL APPLICATION OF METHYLSULFONYLMETHANE (MSM), EDTA ON PITTING EDEMA AND OXIDATIVE STRESS IN A DOUBLE BLIND, PLACEBO-CONTROLLED STUDY

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**Abstract**

No pharmacological treatment exists for lower extremity pitting edema, characterized by inflammation, found in chronic venous insufficiency. Treatment with EDTA, an effective metal chelator, was explored because it can modulate free calcium and iron and prevent further free radical production. However, EDTA may not effectively penetrate the cell membrane, hence methylsulfonylmethane(MSM), reported to facilitate transmembrane transport, was added. The effect of topical application of a lotion containing MSM+EDTA was assessed in two phases of a double blind, placebo controlled clinical trial. In phase 1, patients having swelling in the lower extremities were randomly distributed to receive the MSM+EDTA lotion or a placebo (vehicle) alone. In the second phase, patients were given MSM as placebo followed by MSM+EDTA lotion for 2 weeks. The circumference of calf, ankle and foot for both legs were found to decline significantly after 2 weeks of application of the lotion/ but not placebo, and total antioxidant capacity (FRAP) and lipid peroxidation products (MDA), assayed in blood, showed decline in oxidative stress. Application of MSM alone increased the swelling. Thus EDTA+MSM offers an efficacious treatment for lower extremity pitting edema, through reduction in oxidative stress.

***Key words:*** Lower extremity pitting edema, EDTA, MSM (methylsulfonylmethane), Oxidative stress, topical chelation therapy.

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**Abbreviations: EDTA** : Ethylene diamine tetraacetic acid; **MSM**: methylsulfonylmethane; **FRAP** : ferric-reducing-ability-of-plasma; **MDA** : malondialdehyde; **ACD** : Acid-Citrate- Dextrose; **TPTZ** : 2, 4, 6-tripyridyl-s-triazine; **RBCs** : red blood cells; **TBA** : thiobarbituric acid.

## INTRODUCTION

Edema is a condition of abnormally large fluid volume in the circulatory system or in tissues between body cells. Its main cause is a disturbance in fluid homeostasis, resulting in increased interstitial fluid, due to increase in its secretion or impairment in its removal. Some factors which cause edema by disturbing this balance of fluid homeostasis are immobility of muscles, high intake of salty foods, heat, inflammation and heavy metals.

Chronic venous insufficiency is a major cause for lower extremity pitting edema which results from increased flow from veins to interstitial tissue, and by a decreased lymphatic flow from interstitial tissue to the lymph nodes. It is a common condition, especially among the elderly, and affects approximately 5 million people in the United States alone (1).

 

Chronic venous insufficiency is characterized by inflammatory conditions and increased oxidative stress (21). The surrounding tissue has excess iron and calcium¸ which leads to stress on the lymphatic system and reduces its capacity to drain fluids.

Ethylene diamine tetraacetic acid (EDTA) is a well known chelating agent and EDTA chelation therapy has been reported to be beneficial for treating edema by consistently improving blood flow (2, 9, 10). It is reported to function by reducing calcium deposits, removing heavy metals (10, 17, 18) and controlling lipid peroxidation (8), an effect attributed to its antioxidant functions (9, 11, 20). Once a chelator combines with metal ions in blood, the complexes are then excreted in the urine (3, 4).

However, its effectiveness may be variable and its efficacy has not been demonstrated conclusively (14, 15, 16). This may be attributed to the limited ability of EDTA to cross biological membranes (5, 14, 15, 17). It has been suggested that permeability enhancers should be explored to facilitate entry of EDTA through biological membranes (22). Methylsulfonylmethane (MSM) is a naturally occurring organosulfone which has been described as a permeability enhancer (13). It has recently been reported to enhance EDTA transport across biologic membranes and thus promote localized chelation (22). MSM is found widely in fruits, vegetables and grains in small amounts and is considered safe at recommended oral dosages for humans (12).

There is no pharmacological treatment for chronic venous insufficiency. So the question arises whether topical application of a lotion containing EDTA, with MSM as a permeability enhancer, can be used as a treatment for this condition.

Hence, the present study was conducted on patients having pitting edema in the lower extremities, in two double blind, placebo controlled clinical trials, differing in the placebo used. The effect of applying the active lotion for two weeks on girth and computed volume of both legs was studied, and oxidative stress, indexed by blood levels of total antioxidant capacity as ferric-reducing ability of plasma (FRAP) and lipid peroxidation products as malondialdehyde (MDA), were measured.

## MATERIALS AND METHODS

A randomized, double blind, placebo controlled study was conducted in phases 1 and 2. Patients visiting a local physician were screened for lower limb pitting edema. The exclusion criteria were: no ulceration, no wounds on swollen limb, no acute problems, no high risk of organ failure; and the inclusion criteria was lower extremities' pitting edema. Informed consent was sought and obtained from those patients who satisfied all inclusion and exclusion criteria.

In Phase 1 patients were randomly distributed to receive the active lotion containing MSM+EDTA in an aqueous vehicle containing aqueous sodium alginate or a placebo containing the vehicle alone. In Phase 2, a solution of MSM was used as placebo. 13 patients, aged 40-70 years, completed Phase 1. Of these, 8 received the active lotion while 5 received the placebo. In Phase 2, four patients satisfying the inclusion criteria were first administered the placebo containing MSM alone for one week, followed by one week during which no lotion was applied, after which they were given the active lotion containing MSM+EDTA for two weeks.

Composition of the active lotion and placebo:

Phase 1 and 2: Active lotion: 5.4 g MSM + 2.6 g EDTA per dL vehicle.

Vehicle: 0.9 g sodium alginate per dL distilled water.

Phase 1: Placebo: 0.9 g Sodium alginate per dL distilled water.

Phase 2 Placebo: 5.4 g MSM in 0.9 g sodium chloride per dL distilled water.

### *Measurement of swelling*

Circumference of edematous area was measured in centimeters thrice at points of greatest swelling at the dorsum of foot, ankle and mid-calf in both legs separately and the average was calculated.

Measurements were recorded on the day of enrollment (baseline), and a bottle containing about 85 g of the active lotion containing EDTA + MSM was given to patients for topical application. Patients were instructed to apply 10-15 drops of lotion on swollen area topically twice a day. Patient compliance was ensured by maintaining adequate telephonic contact with them and, on follow-up visits, amount of lotion used in the preceding period was assessed. Follow-up measurements were taken on completion of 2 weeks of application of active lotion and placebo.

Baseline and week 2 measurements were used to calculate changes in swelling in calf, ankle and foot of left and right leg respectively using the following two methods.

In the first method, change in swelling between baseline and week 2 after application of lotion was calculated for calf, ankle and foot respectively for each leg using the following formula:

Percent change in swelling = {[Final circumference (week 2) – Initial circumference (Baseline)] / [Initial circumference]} x 100

A negative value denotes reduction in swelling and a positive value denotes increase in swelling.

In the second method, change in average volume of leg was calculated as follows:

Circumference in centimeters was measured at the ankle and the calf as described above, and the distance between the two points of measurement was recorded.

Assuming that this corresponds to a trapezium,

 

Volume of a trapezium = h/2 ($A^2$+$B^2$)

Where h = distance between points of circumference measurement at calf and ankle,

A = circumference at calf
B = circumference at ankle.

The volumes of left and right leg were calculated separately at baseline and at end of week 2.

Per cent reduction in volume of the extremities was calculated using the formula:

Per cent reduction in volume= [1 – (Volume of leg at week 2/Volume of leg at baseline)] x 100.

A positive value was obtained to denote reduction in swelling and a negative value to denote increase in swelling. Values were presented for the average change in volume obtained for both extremities, to obtain a single composite value to index change in volume. This simplified comparisons among individual patients.

*Collection and processing of Blood Sample*

5 ml of venous blood was drawn into Acid-Citrate-Dextrose (ACD) vials and kept on ice for not more than 1 hour before processing. The samples were centrifuged at 3000 rpm for 15 min, plasma was collected and red blood cells (RBCs) were washed three times with normal saline. RBC were used to prepare 1:20 hemolysate. Packed RBCs obtained were suspended in approximately 1 volume of 0.154 M NaCl .To 0.2 ml of this suspension, 1.8 ml of β -merceptoethanol-EDTA stabilizing solution (0.05 ml of β-merceptoethanol and 10 ml of neutralized 10% EDTA in 1 litre distilled water) was added . Plasma and 1:20 hemolysate were transferred into separate Eppendorf tubes and stored at -70ºC, until analysis.

*Biochemical estimations*

To estimate FRAP (6), 40µl plasma was allowed to react with 2 ml of working FRAP solution containing acetate buffer, pH 3.6, 10mM 2, 4, 6-tripyridyl-s-triazine (TPTZ) in 40 mM HCl and 20 mM $FeCl_3.6H_2O$, in the ratio of 10:1:1, at $370^0$ C. $Fe_{+2}$-TPTZ complex was measured in a uv-vis double beam spectrophotometer at 593 nm, and time scanning was done at 30 second intervals for 4 minutes. The standard curve was linear between 40 - 400µl $FeSO_4$. Quantification was done by regression analysis.

*Lipid Peroxidation*

MDA was taken as the index for lipid peroxidation, and estimated separately in plasma as well as hemolysate, by the thiobarbituric acid (TBA) method (19). 0.3 ml of plasma / hemolysate was mixed with 0.7 ml of 0.1 M phosphate buffer pH 7.4, and 2ml of TBA-TCA-HCl reagent containing 15% (w/v) TCA, 0.375 % (w/v) TBA and 0.25N HCl in the ratio of 1:1:1, incubated in boiling water bath for 30 minutes and centrifuged to obtain clear supernatant. Its color was measured at 534nm in a uv-vis double beam spectrophotometer. MDA was expressed as mg per g of hemoglobin for hemolysate and mg per g of protein for plasma.

*Statistical analysis*

Mean and standard error were calculated for various groups and parameters. Statistical significance was obtained using Student's t- test and p-values were obtained.

## RESULTS

Table 1 presents changes in lower limb edema after local application of active lotion or placebo. Patients who applied the active lotion showed a consistent and statistically significant ($p<0.0005$ to 0.2) decline in swelling, ranging from 2.87 to 6.85 per cent, as indexed by average circumference of calf, ankle and foot of both legs, while those on placebo showed changes ranging from 2.67 per cent increase to 0.58 per cent decrease in swelling. A mean decline of 9.75 per cent in computed volume of the measured part of the leg was shown by patients on active lotion while those on placebo showed a 1.65 per cent increase in volume. The difference was statistically significant at $p<0.000$.

As shown in Table 2, of the 48 values (6 measurements of change in swelling of calf, ankle and foot of left and right legs for 8 patients) available for patients on active lotion, 47 showed a reduction in swelling, ranging from 0.91 to 18.18 per cent (Fig 1), and one value showed no change. Of the 24 values obtained for patients on placebo, 15 showed increase in swelling. Thus, 98 percent values on active lotion showed a decline in swelling, and 68 per cent values on placebo showed an increase in swelling.

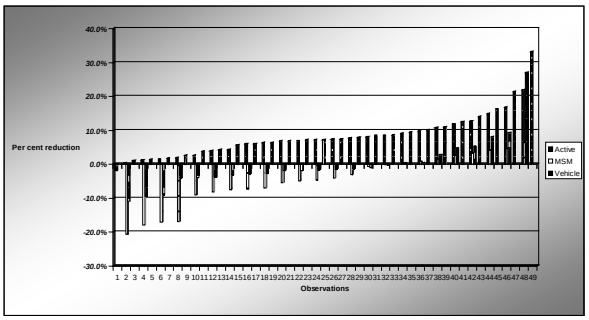


**Figure 1.** Percent reduction in calculated leg volume of individual patients on active lotion (EDTA+MSM) or placebo: Vehicle or MSM.

Table 3 presents effect of application of active lotion on oxidative stress as indexed by changes in Ferric Reducing Ability of Plasma (FRAP), MDA in plasma, and in hemolysate. There is a mean reduction of 3.364 per cent in swelling, a reduction of 2.18 per cent in FRAP,

 

**Table 1.** Changes in lower limb pitting edema after local application of active lotion or placebo

| | **Per cent change in swelling** | | | | | | **Volume reduction in swelling** |
|---|---|---|---|---|---|---|---|
| | **Right leg** | | | **Left leg** | | | |
| | **Calf** | **Ankle** | **Foot** | **Calf** | **Ankle** | **Foot** | |
| | | | **Phase 1** | | | | |
| MSM+ EDTA Lotion | -4.13 ±0.91 | -6.85 ±1.93 | -3.08 ±0.69 | -3.84 ±0.88 | -3.98 ±1.35 | -2.87 ±0.95 | 9.75 ±1.16 |
| Placebo (0.9 g Sodium alginate/100ml water) | 0.68 ±0.44 | 2.67 ±1.08 | -0.04 ±0.74 | -0.58 ±2.04 | 1.02 ±1.26 | 0.93 ±0.69 | -1.65 ±0.60 |
| P values | 0.0005 | 0.0005 | 0.0055 | 0.2 | 0.015 | 0.004 | 0.000 |
| | | | **Phase 2** | | | | |
| MSM+ EDTA Lotion | -2.47 ±0.182 | -1.10 ±1.35 | -1.57 ±0.82 | -0.45 ±0.30 | -0.75 ±0.55 | -1.13 ±0.52 | 2.56 ±0.71 |
| Placebo (0.9 g MSM/100ml water) | 2.32 ±2.77 | 0.62 ±1.30 | 0.49 ±1.63 | 4.68 ±1.18 | 3.85 ±2.49 | 2.75 ±2.01 | -7.42 ±2.93 |
| P values | 0.129 | 0.393 | 0.295 | 0.003 | 0.114 | 0.103 | 0.012 |

All values are Mean ± standard error

 

**Table 2.** Proportion of patients on active lotion and placebo showing reduction in swelling

| Per cent Proportion of measurements | Per cent showing decrease in leg volume | Per cent showing increase in leg volume | Per cent showing no change in leg volume |
|---|---|---|---|
| | **Phase 1** | | |
| On active lotion[a] | 97.9* | 0 | 2.1 |
| On Placebo[b] | 21 | 68** | 11 |
| | **Phase 2** | | |
| On active lotion[c] | 71 | 25 | 4 |
| On Placebo[d] | 33 | 67 | 0 |

[a] Based on 48 measurements, [b] Based on 24 measurements, [c] Based on 24 measurements, [d] Based on 24 measurements

* Includes 26.5 per cent who showed >10 % reduction in leg volume and 71.4 percent who showed >5 % reduction in leg volume.

**Table 3.** Changes in oxidative stress indicators after local application of active lotion in patients having lower extremity pitting edema

| **Per cent reduction in volume of leg** | **Percent change in FRAP (Δ FRAP)** | **Percent change in MDA in plasma (ΔMDA P)** | **Percent change in MDA in hemolysate (Δ MDA H)** |
|---|---|---|---|
| | | **Phase 1** | |
| 9.6±1.64 | -2.18±0.715 | -25.41±11.76 | -27.69±9.01 |
| | | **Phase 2** | |
| 2.56±0.7 | -1.8±0.5 | -28.6±6.6 | 20.9±4.8 |

All values are mean ± standard error

25.41 per cent in MDA of plasma and 27.692 per cent in MDA of hemolysate after two weeks of application of lotion. Table 3 shows that the application of MSM alone increases the swelling from 1.22 to 4.04 when MSM+EDTA was applied on same patients it decreases the swelling. Table 4 represents decrease in FRAP, MDA in plasma and hemolysate.

The results suggest that the active lotion is significantly effective in reducing lower extremity edema whereas both placebos are ineffective. There is a significant reduction in FRAP, MDA in plasma as well as hemolysate on application of lotion for 2 weeks.

## DISCUSSION

A remarkably consistent decrease in lower limb edema is demonstrated in all patients who applied the active lotion, containing EDTA + MSM in an aqueous vehicle of 0.9 g sodium alginate, for 2 weeks, while patients who applied a placebo containing the vehicle alone did not show a similar decrease. This indicates the

 

efficacy of EDTA, the active ingredient in the lotion, in reducing the swelling.

The main cause for lower extremity edema is the pooling of blood in lower limb, due to leakage of excess fluid into surrounding tissue, caused by inflammation. The existence of an interconnection between inflammation and iron metabolism is fairly well-documented (17). Unliganded ionized iron is typically absent in normal tissue, but its presence in inflamed tissue can be the trigger for production of very reactive and dangerous hydroxyl radical, which is very damaging and is the major cause for inflammation (16). EDTA contains four carboxylate groups which gives it the property of chelating metals, and its reactivity with various metals follows the activity series. Hence, it is reasonable to propose that EDTA from the active lotion preferentially binds to the free iron at the site of inflammation, since EDTA has a very high affinity for unbound iron and rapidly removes it from the body. This causes reduction of the oxidative stress, especially as indexed by lipid peroxidation products, observed in the present study, and the inflammation is resolved quickly, leading to reduction in swelling.

The biochemical data obtained suggests a consistent but small reduction in total antioxidant capacity of plasma, as indexed by its ferric reducing ability (FRAP) in all patients who used the active lotion. The effect of the lotion on MDA which is an index of lipid peroxidation was larger and more striking. MDA values showed an approximately 21-29 per cent decline in both plasma and hemolysate. Thus reduction in oxidative stress was observed as a result of application of the lotion containing EDTA+MSM, due to the calcium modulation achieved by the chelating property of EDTA

When MSM alone was applied as placebo, the swelling was found to increase. It is hypothesized that MSM increases ion permeability into the cell and disturbs the ion balance, which results in increased amount of fluid in the cell. This finding corroborates the role of MSM as a permeability enhancer (13, 22). Moreover, it is recognized that blood plasma thiols generally function as antioxidants but can have either pro-oxidant or antioxidant actions depending on local physiological circumstances. It can be surmised that in conditions of inflammation, as in the case of our patients, free radicals are high so MSM functions as an oxidant, thereby accounting for the present increase in swelling.

The limiting factor of this study is its small sample size. However, it must be emphasized that it was an intensive pilot study, of longitudinal design, requiring constant monitoring of patient compliance with regard to use of the lotion. Moreover, it was a double-blind study, so the reliability of results was high. Another limitation was that some patients who received the placebo could not be motivated to return for follow-up visits. Those on placebo, who did complete the two week trial declined to give their final blood samples for assaying the parameters of oxidative stress. Hence, biochemical studies could be completed on only a subset of 5 patients on active lotion in phase 1 and 4 in phase 2. It may be pointed out that biochemical assays involved two longitudinal blood collections, on the first and last visit of the patient, hence results were reliable and dependable.

In conclusion, the study suggests that the active lotion which contains the chelating agent EDTA, with MSM, functions as an effective therapeutic agent for lower extremity pitting edema, and its mode of action is through reduction of oxidative stress which can be attributed to its chelating properties. The presence of MSM in the solution seems to ensure the penetration of the EDTA into the skin and perhaps also into the erythrocyte. The findings are encouraging and call for more extensive studies to test the therapeutic efficacy of the MSM+EDTA lotion and explain its mode of action.

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Other articles in this theme issue include references (25-39).

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