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Treatment of Post-mastectomy Lymphedema with Herbal Medicine: An Innovative Pilot Study

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Background: Lymphedema of the arms or legs is a difficult clinical problem yet devoid of effective treatment. Lymphedema is the result of obstructed lymphatic flow secondary to chronic infection, parasitic infestation, or postsurgical obstruction (eg, after axillary dissections). We arranged this clinical trial to investigate whether patients with limb lymphedema can benefit from a standard dose of *Astragalus* plus *Paeoniae rubra* to improve the symptomatology, functional capacity, and quality of life (QOL).

Method: The pilot study was designed as a self-control clinical trial. Patients with post-mastectomy lymphedema were recruited. A double-herb formulation (*Astragalus, Paeoniae rubra*) with standard dosage was administered orally in a powdered form, 6 times per week for 6 months. Outcome measurements included standard limb volume changes measured by water displacement method; handgrip strength; and QOL for limb lymphedema questionnaire (LYMQOL).

Results: There were no reported adverse effects or complications; there were no episodes of infection during the period of study. There was a tendency of limb volume reduction by 6 months, which, however, did not reach statistical significance. There was a significant improvement in appearance and symptom scores as was assessed with the LYMQOL questionnaire.

Conclusions: The oral herbal formula improved the symptomatology and QOL among the pilot group of patients with post-mastectomy lymphedema. Side effects were absent, and there was a trend of lymphedema reduction. *(Plast Reconstr Surg Glob Open 2020;8:e2915; doi: 10.1097/GOX.0000000000002915; Published online 24 June 2020.)*

INTRODUCTION

With the exception of babies born with congenital lympho-obstruction, lymphedema of the extremities occurs as a result of repeated infection, parasitic infestations, and, in recent decades, after extensive axillary or groin dissections.[1] As the survival for breast cancer improves, the number of those at risk of lifelong chronic lymphedema also increased[2]; thus the need for effective diagnosis and treatment becomes crucial.[3] The proportion of women developing lymphedema following surgical treatment ranges from 3% to 15% after sentinel lymph node biopsy[4,5] and 49% after axillary lymph node dissection,[6] during mastectomy.

Treatment options have never been satisfactory. The early stage of lymphatic obstruction is not readily detectable clinically or via instrumentation.[7] In the severe late situations, surgical interventions are often disappointing.[8] Lymphatic reconnections/bypass or lymph node transfers are uncertain of long-term benefit, and tissue reductions are reserved as late palliative measures.[9]

Currently, standard treatment consists of physiotherapy, pressure therapy, exercises, and prevention of infection.[9] Discovery of an effective agent to help reduce the symptomatology of post-mastectomy lymphedema is therefore of vital importance.

A Phase II Clinical Trial Exploring the Efficacy of a Biologic

Ubenimex is a well-characterized, oral, small-molecule, dual inhibitor of aminopeptidase and leukotriene A4 hydrolase, the enzyme responsible for the formation of the proinflammatory mediator LTB4. Ubenimex has been

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approved for the adjunct treatment of nonlymphocytic leukemia in Japan and for pulmonary arterial hypertension in the United States.[10]

In 2016, Ubenimex was approved by US Food and Drug Administration for a phase II clinical trial in adult patients with lymphedema of the lower limb. The trial lasted for 24 weeks when the treatment group of 45 would be matched by controls.[11]

The logical explanation to Ubenimex's efficacy on preliminary arterial hypertension or nonlymphocytic leukemia is that it facilitates circulation via powerful anti-inflammatory and antifibrotic effects, and the molecular pathway of action is through LTB4.

A Herbal Form of the Biologic

A biologic agent Ubenimex is undergoing proper phase II clinical trial for lymphedema. Ubenimex has been used for anti-inflammatory and antifibrotic purposes; hence, it is assumed to be good for promoting lymphatic flow.[11]

In 2015, a group of bioscientists in Hong Kong found that when chemical derivatives from 2 medicinal plants, viz. calycosin and gallic acid, were mixed together, they attenuated the effects of LTB4 through the induction of LTB4 dehydrogenase. Calycosin was found in good quantities in the medicinal plant *Astragalus Radix* and gallic acid in *Paeoniae* species.[12,13] The 2 medicinal herbs, when mixed together, therefore could be crudely considered an agent with Ubenimex-like effects.

Ubenimex is available in Japan but not elsewhere, and in the United States, it still awaits proper approval. However, with a long history and popularity of herbal medicine in Hong Kong, we consider it appropriate to start a pilot study on the treatment of upper limb lymphedema after breast resection using the 2 medicinal herbs containing gallic acid and calycosin to mimic Ubenimex. In clinical trials conducted at our institution using medicinal herbs, we have followed an evidence-based approach to ensure the reliability of an efficacious outcome.[14]

Rationale and Aim

Molecular studies have indicated that when gallic acid and calycosin are mixed together, Ubenimex-like bioactivities result. *Astragalus* and *Paeoniae*, both being commonly used edible medicinal herbs, are rich sources of calycosin and gallic acid, respectively; thus the combined extracts would produce effects similar to those of Ubenimex, that is, anti-inflammatory and antifibrotic effects, promoting lymphatic flow. The aim of this pilot trial was to check the efficacy and safety of the 2 herbs in the treatment of lymphedema after mastectomy for breast cancer.

METHODS

This study is a self-control pilot study conducted between May 2018 and August 2019. A total of 9 subjects were recruited, and they received the herbal formulation for 6 months. All subjects were tested every 1 month for 6 months, beginning with the baseline measurement, producing a total of 6 measurements. The study compared the results of pre- and posttreatment. Subjects were included in the study if they were post-mastectomy patients with chronic lymphedema of the affected side for 2–19 years.

The herbal formula contained 2 herbs, viz. *Astragalus* and *Paeoniae rubra*, which have been reported to display antifibrotic effects in in vitro and in vivo experimental platforms. *Astragalus* and *Paeoniae* were bought from a reputable registered herbal supplier and properly authenticated by our research team. Dosage was determined according to the maximal doses recommended in the Chinese pharmacopeia, and the herbal formulation in granule form was orally ingested. The powdered form with a carefully calculated dosage was administrated to the subjects 6 days a week for 6 months.

Assessments

Subjects were monitored monthly by a surgeon, a Chinese Medicine practitioner, and a research staff. The role of the Chinese Medicine practitioner was to give explanations and instructions relevant to the medicinal herbs to ensure patient safety and to abide by the regulations set by the Ethical Regulatory Committee of the Chinese Medicine Council in Hong Kong.

Lymphedema volume was assessed by water displacement and circumferential measurements.[15,16] Water displacement was the result of immersing the affected arms to a standard marked level (Fig. 1).

Water displacement has been reported to be reliable, with an intraclass correlation coefficient of 0.99.[17,18] Volumetric measurements have been considered to be the "gold standard" for measuring limb volume.[19,20] Therefore, we reported the results using volumetric measurements, although we had taken circumferential measurements.

Edema volume was obtained by calculating the difference in volume between the pretreatment and the posttreatment of arm lymphedema. The changes in lymphedema volume were calculated.

For the circumferential measurements, a flexible measuring tape was used. Circumferences of the limb were taken in 6 predetermined points (mid-hand, wrist, and every 10 cm from the wrist up to 40 cm). Volume was calculated from circumference using the truncated cone method.[17] This method highly correlated with the water displacement method.[17,18,21,22]

Outcome Measures

Outcome measures included measurement of the displaced water volume for the affected limb, quality of life (QOL) for limb lymphedema questionnaire (LYMQOL), handgrip strength test, and tonometer for tissue indentation. Data collection also included age, gender, chronicity, symptoms (including infection episodes), body weight, and associated medical conditions at baseline and on monthly intervals.

Outcome assessments included (1) volume measurement using a special water displacement tank, which ensured a uniform dipping of the affected arm to a standard level (Fig. 1);[23] (2) circumferential measurements; (3) handgrip strength using a simple dynamometer; (4) tissue tension of affected arm using a tonometer; and (5) QOL evaluation using the special lymphedema QOL questionnaire (LYMQOL).[24]

Fig. 1. Standard water displacement tank.

Statistical Analysis

Continuous variables were compared using the one-way analysis of variance (ANOVA) or paired *t* test where appropriate (to compare pre- and posttreatment or changes at each visit) and were described as mean (SD). General linear models (for repeated measures) and one-way ANOVA (for continuous outcome variables) were used to examine the change of displaced water volume and LYMQOL. "Overall QOL," total score of LYMQOL, and differences between baseline and each visit measurements in 4 domains were compared via the one-way ANOVA test or paired *t* test.

A *P* value of less than 0.05 was considered to be statistically significant. Data were analyzed using the Statistical Package for the Social Sciences 25 (Statistical Package for the Social Sciences Inc, Chicago, Ill.).

RESULTS

A total of 10 patients satisfied the inclusion criteria. One patient chose not to continue the trial after 1 month. Nine patients completed the 6 months' treatment. Body weight of 7 patients was unchanged[3] or slightly decreased,[4] while insignificant increase was observed in 2 patients.

Volume changes in lymphedema limbs are represented in Table 1. Four patients had decreased lymphedema volume; in 2, the volume remained the same, while 2 had increases in lymphedema volume. The overall volume change in displaced water after 6 month's treatment was reduced by 94 ml (Table 1).

Hand Grip

No significant changes in handgrip strength were detected among the patients before and after treatment.

Tonometer

No significant tissue tension changes were detectable before and after treatment.

LYMQOL

This questionnaire offers independent scales of function, symptoms, appearance, mood and emotion, and so on. Each item was scored individually; all of those scores are subsequently added together to be divided later by the number of questions in that section to derive a summated score. A lower score denotes a better QOL.

Figure 2 gives the progress of 4 major QOL domains, viz. functional, appearance, symptomatic, and emotional. All these domains show a solid trend of improvement, of which the appearance and symptom domains reached statistical significance ($P = 0.013$ and 0.022).

DISCUSSION

In the pilot study, there were no reported adverse effects or complications; there were no episodes of soft-tissue infection during the period of study. There were no abnormalities in the blood tests with regard to renal and liver function or complete blood test picture after

Table 1. Upper Limb Displaced Water Volume (ml) of Individual Cases

	Basic Information			Visit							
Subject	Age	Affected Limb	Lymph Start	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Overall Volume Change
LYM-P-001	68	Right	2006	2975	2300	2750	2850	2750	2750	2650	–325
LYM-P-007	53	Left	2012	1050	950	950	950	1050	1000	950	–100
LYM-P-005	49	Right	2017	1350	1450	1350	1350	1350	1300	1300	–50
LYM-P-008	56	Right	2015	1150	1100	1200	1150	1150	1150	1145	–5
LYM-P-011	66	Left	2017	1350	—	1450	1450	1400	1450	1450	Same
LYM-P-013	60	Left	2009	1750	—	1750	1800	1700	1800	1750	Same
LYM-P-010	61	Left	2000	1400	1500	1350	1250	1550	—	1450	+50
LYM-P-003b	66	Left	2004	1450	1450	1400	1400	1500	1550	1550	+100
LYM-P-009	56	Left	2014	1150	1150	1250	1150	1150	—	—	—
Mean (SD)				1706 (585.4)	1537 (443.2)	1612 (517.5)	1637 (589.2)	1662 (545.4)	1650 (582.9)	1612 (529.7)	–94

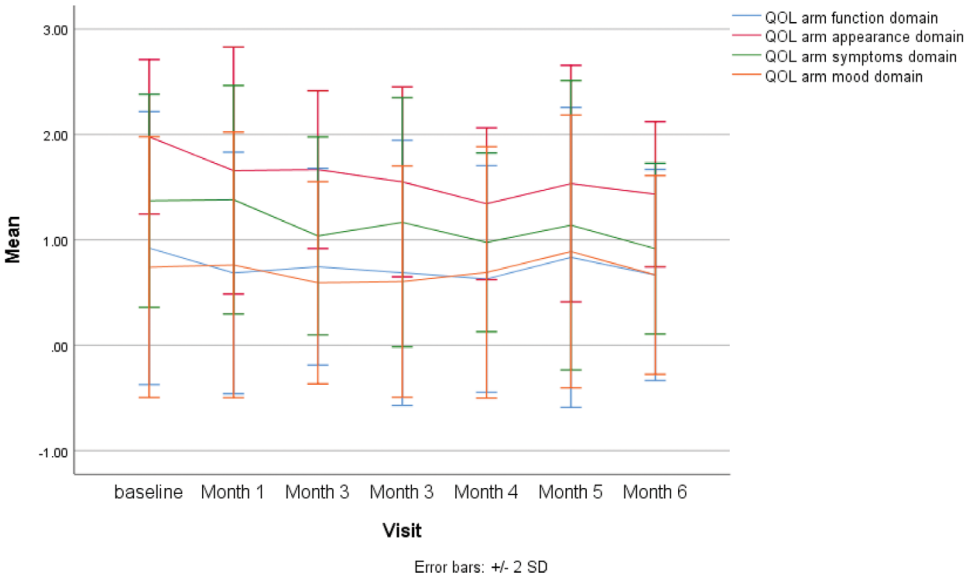

Fig. 2. Changes in LYMQOL domains at each visit (arm, n = 9).

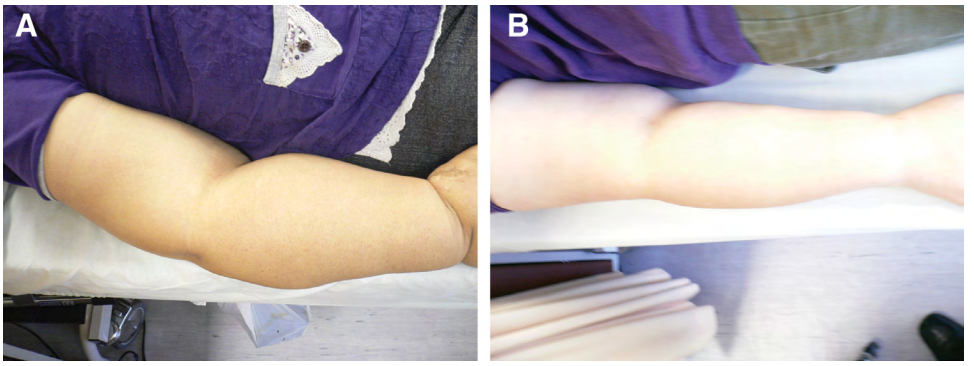

Fig. 3. Affected arm volume comparison. Appearance of lymphedematous arm before (A) and 4 months after (B) treatment (Case LYM-P-001, the best example of observable change in volume).

6 months of treatment. There was a clear tendency of decreasing edema for most patients as was measured by water displacement by 6 months. However, due to the small number, data did not reach statistical significance. While tissue tension and grip strength have been accepted as practical methods of assessment[17,25] used as indication of response to treatment for lymphedema, they were not found helpful in our pilot study.[26] There was a significant improvement in QOL scores, particular parameters related to comfort, which were more evident by the second and fourth month. The most encouraging improvements were "reduced heaviness," "less congestion," "more comfort," and "reduced tingling sensation." There was no objective change in function, but some patients reported that the affected limb appeared lighter and "less clumsy". Patient satisfaction was very high (Figs. 2 and 3).

There was a decreasing trend in the LYMQOL scores of which "improved appearance" and "symptom scores" were statistically significant after 6 months of treatment, suggesting that the double-herb formula may have changed the internal state of the lymphedema. A randomized clinical trial with larger numbers is indicated to consolidate the results of this study.

CONCLUSIONS

The oral double-herb formula has been observed to improve the symptomatology and QOL of patients with established lymphedema of the upper limb without adverse effects. Studies with a larger number of patients will improve statistical rigor and allow for a more detailed analysis. If Ubenimex or the herbal formula works via anti-inflammation, antifibrosis, and flow facilitation, early cases of lymphatic obstruction should be better candidates for treatment. We look forward to more sophisticated measurements for the early detection.[27] In addition, basic research into the molecular mechanisms would also be needed.

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