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Abstract: Lymphoedema is a potentially debilitating condition with particularly high incidence among breast cancer patients following surgery. Horsechestnut complex has been used by herbalists to improve peripheral vascular circulation and lymphatic drainage. Nuclear medicine lymphoscintigraphy offers a tool to quantitate the effects of horsechestnut complex on lymphatic drainage rates. Methods: A prospective clinical trial in 15 "normal volunteers was undertaken using a repeat measures design. Bilateral upper limb lymphoscintigraphy was performed on each volunteer at baseline and following a 3 month course of horsechestnut complex. Lymphatic drainage rates were evaluated quantitatively. Results: A significant increase was noted in the percentage of activity that migrated away from the injection site with respect to baseline versus follow-up series. The baseline mean of 6.63% varied significantly from the follow-up mean of 8.19% ($p = 0.002$) over a 2 hour sampling window. The matched pairs t test indicated a statistically significant difference ($p = 0.017$) with a mean increase in percentage migration of 1.56% after herbal treatment (95% CI 0.30% - 2.82%). Conclusion: Horsechestnut complex has the potential to accelerate lymphatic drainage in the normal population. A multi-centre randomised controlled trial is required to evaluate the clinical benefits of horsechestnut complex in managing lymphoedema in breast cancer survivors.

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Improving lymphatic drainage with herbal preparations: a potentially novel approach to management of lymphoedema.

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Foot line: Herbal enhancement of lymphatic clearance

ABSTRACT

Lymphoedema is a potentially debilitating condition with particularly high incidence among breast cancer patients following surgery. Horsechestnut complex has been used by herbalists to improve peripheral vascular circulation and lymphatic drainage. Nuclear medicine lymphoscintigraphy offers a tool to quantitate the effects of horsechestnut complex on lymphatic drainage rates.

Methods: A prospective clinical trial in 15 'normal' volunteers was undertaken using a repeat measures design. Bilateral upper limb lymphoscintigraphy was performed on each volunteer at baseline and following a 3 month course of horsechestnut complex. Lymphatic drainage rates were evaluated quantitatively.

Results: A significant increase was noted in the percentage of activity that migrated away from the injection site with respect to baseline versus follow-up series. The baseline mean of 6.63% varied significantly from the follow-up mean of 8.19% ($p = 0.002$) over a 2 hour sampling window. The matched pairs t test indicated a statistically significant difference ($p = 0.017$) with a mean increase in percentage migration of 1.56% after herbal treatment (95% CI 0.30% - 2.82%).

Conclusion: Horsechestnut complex has the potential to accelerate lymphatic drainage in the normal population. A multi-centre randomised controlled trial is required to evaluate the clinical benefits of horsechestnut complex in managing lymphoedema in breast cancer survivors.

Key words: lymphoedema, lymphoscintigraphy, horsechestnut, herbal medicine, breast cancer

INTRODUCTION

Earlier diagnosis and improved treatment options have resulted in a substantial improvement in breast cancer survival over the last three decades (7). The mortality rate from breast cancer is decreasing by 2% per annum and the five year survival is increasing (6). Breast cancer survival is, however, often associated with significant morbidity. Secondary lymphoedema is a significant problem for breast cancer patients after treatment; manifesting as a localised, acquired, lymphatic microcirculatory disturbance (8,9). In breast cancer patients, the lymphatic flow abnormalities and fibrosis may arise following surgery and / or radiation therapy (9). In Australia, lymphoedema occurs in between 7% and 39% of breast cancer survivors (10-12) while internationally the incidence has been reported between 15% and 32% (13-16).

With as many as 39% of breast cancer survivors developing lymphoedema, it represents a significant contributor to post treatment morbidity. The associated functional, aesthetic and psychological problems have a significant impact on the QOL of breast cancer survivors. Breast cancer survivors in rural and remote Australia may be more prone to these QOL factors and to secondary complications due to geographic isolation and a sparsity of specialised care. With an absence of any standardised management plan for lymphoedema in breast cancer survivors, herbal medicine might offer relief and/or control for patients; a solution independent of geographic location. Conservative therapies such as diet, mechanical compression, and massage / physical therapies are the standard non-invasive approaches to this condition (8). Botanical agents may play a role in the treatment of lymphoedema as another non-invasive approach. Extracts such as *Aesculus hippocastanum* and *Ruscus aculeatus* can intervene in the pathogenesis of decreased vascular integrity.

Horse chestnut seed extract (HCSE) has reported venotonic, vascular protective, anti-inflammatory and free-radical scavenging properties (17). The active component is thought to be the aescin (18). The ability of HCSE to inhibit the activity of the enzymes elastase and hyaluronidase (18) is ideal for the treatment of lymphoedema.

The active component of Butcher's broom is thought to be the saponin glycoside ruscogenin (18). The anti-inflammatory and astringent properties of the extract make it effective in increasing venous tone (21). Cluzan et al. (22) used a double-blind, placebo controlled study to show that Butcher's broom had a significant, positive effect in patients with lymphoedema. It is thought that Butcher's broom extract inhibits macromolecular permeability *in vivo* (18,21,23).

While there is significant interest and research in a wide variety of complementary and alternative medicines (CAMs), there remains a paucity of evidence based literature supporting their role. Much of the published data draws heavily on qualitative evaluation, often in small populations and limited by bias. The qualitative approach is consistent with the non linear, holistic approach adopted by CAM practitioners that perhaps highlights the benefits individuals may experience rather than the diluted experiences of a larger group. None the less, evidence based practice demands greater rigour, randomised controlled trials and reproducible evidence across populations. Furthermore, evidence based approaches in CAMs to date have often relied on rudimentary tools that provide evidence by extrapolation rather than direct measurement.

AIMS AND OBJECTIVES

Nuclear medicine scintigraphy provides sensitive physiological imaging and quantitation using radiopharmaceuticals that model specific biological pathways. Herbal medicine offers therapeutic and preventative options for either disease or symptoms. For many herbal formulas, the proposed mechanism of action is to alter physiology in some fashion. This pilot investigation aimed to specifically measure physiological parameters using non invasive nuclear medicine 'gold standards' pre and post herbal medicine interventions.

The aim of this investigation was to evaluate the effect of a standardised herbal formulation of horse chestnut and Butcher's broom (horsechestnut complex) on lymphatic flow in a group of normal volunteers. More specifically, the investigation aimed to determine whether horsechestnut complex in normal volunteers provided sufficient evidence of improved lymphatic drainage to pursue a controlled trial of lymphatic flow rates and symptoms in breast cancer patients.

METHODOLOGY

This investigation was a prospective clinical trial in 15 'normal' volunteers using a repeat measures design. Normal volunteers recruited from the local community by advertisement were female, between 50 to 60 years of age with no history of breast cancer, lymphoedema, radiation therapy, chemotherapy or surgery to the chest, neck or upper limbs. The use of warfarin (or aspirin therapeutically) and planned surgery requiring general anaesthesia during the study period were exclusion criteria. These selection criteria ensured a 'normal' patient group was used that might demonstrate the greatest improvement in lymphatic flow (ie. lymphatic drainage requires little additional assistance in the young fit male).

Bilateral upper limb baseline lymphoscintigraphy was performed on each volunteer. Lymphatic drainage rates were evaluated quantitatively. After the baseline study was completed, volunteers were provided a standardised formulation of *Aesculus hippocastanum* and *Ruscus aculeatus* for oral (capsule) administration daily for three months. The standardised preparation of Horsechestnut Complex was produced and supplied by MediHerb Pty Ltd. Each tablet contains 1.2g dry seed equivalent of *Aesculus hippocastanum* extract (standardised to contain 40mg of escin), 800mg dry root and rhizome equivalent of *Ruscus aculeatus* extract (standardised to contain 20mg of ruscogenin) and 1.5g dry leaf equivalent of Ginkgo biloba. All patients undertook consultation with a certified herbalist to ensure the herbal formulation was not contraindicated. Each patient was prescribed one tablet, twice daily after a meal and this dosage represents the lower end of the dosage recommendations of the manufacturer (two to three tablets per day).

After the three month course, volunteers underwent follow-up bilateral upper limb lymphoscintigraphy. Three months was considered an adequate treatment period to elicit a measurable effect although the authors recognise the nature of the pathology of interest might see a greater improvement with more prolonged treatment. Quantitative evaluations were compared between the 30 matched pairs (right and left arms at baseline and follow-up).

The sample size was determined for a comparison of two proportions (e.g. baseline versus follow-up) to estimate the maximum study sample required. A total sample size was determined as 30 for 95% confidence and an 80% study power capable of determining a 10% difference between groups in a two sided test. Thus, a total of 15 patient data sets (30/2) were required since each patient provides data for each group. This study power was considered sufficient for the purposes of this initial pilot investigation.

Acquisition protocol

Each study (baseline and follow-up) was performed immediately following the subcutaneous administration of four doses of 99m technetium (99mTc) antimony sulphur colloid; one each in the web space between the first and second, and second and third digits of both the left and right hands. Each dose approximated 4.0 MBq of 99mTc antimony sulphur colloid in a volume of 0.1 ml. A 30 seconds per frame continuous dynamic acquisition was commenced for 90 frames in the palmar (including forearms) projection immediately upon administration of the radiopharmaceutical (128 matrix). At 45 minutes post radiopharmaceutical administration, a static planar image (256 matrix) was performed of the palmar hands (including forearms) and then of the anterior liver (the radiopharmaceutical is cleared rapidly from circulation by the liver) for 180 seconds each. The static palmar images was repeated at approximately three hours post injection.

Data Analysis

Regions of interest (ROIs) were placed over the injection sites of each hand on the dynamic data set. Background ROIs were placed immediately distal and medial to the injection sites. Time activity curves were generated for the background corrected data and half clearance times were determined for each limb. Decay correction was not employed for the dynamic data set.

Both hands had ROIs generated to incorporate the injection sites on the 45 minute and 3 hour post administration static images. The specific time difference between the 45 minute and the 3 hour series was determined and the 3 hour data set was decay corrected back to the 45 minute data set. The proportion of the injection site activity that had migrated from the injection site between the two sampling points was determined. Liver ROIs were employed to calculate the decay corrected percentage of the injected dose (both hands combined) in the liver at 3 hours post injection.

Statistical analysis

The statistical significance was calculated using Chi-Square analysis for nominal data and Student's *t* test for continuous data. The χ^2 Pearson Chi Square test was employed for categorical data with normal distribution and the G^2 Likelihood Ratio Chi-Square test for categorical data without normal distribution. The *F* test analysis of variances was used to determine statistically significant differences within grouped data. A *P* value less than 0.05 was considered significant.

The differences between independent means and proportions were calculated with a 95% confidence interval (CI). Confidence intervals without an overlap and / or those which did not include zero were considered to support a statistically significant difference while confidence intervals with an overlap and/or those that included zero represented differences for which chance could not be excluded as the cause. The matched pairs *t* test was used to assess agreement between pairs.

Approvals

This investigation was approved by institutional Ethics in Human Research and Radiation Safety Committees at Charles Sturt University.

RESULTS

No statistically significant difference was noted in the change in (delta) half clearance time over the initial 45 minutes between the baseline data and the follow-up data ($p = 0.832$). Furthermore, no statistically significant difference in delta half clearance times were noted isolated to the left hand ($p = 0.221$) and the right hand ($p = 0.989$). No statistically significant difference was noted between the mean half clearance time for the baseline studies (287.2 minutes) and the follow-up studies (296.9 minutes; $p = 0.832$).

The time difference between the 45 minute static image and the 3 hour static image demonstrated some variability. The mean time difference for the baseline studies was 2 hours and 21 minutes while the mean for the follow-up studies was 2 hours and 16 minutes ($p = 0.196$). The 95% confidence intervals for the means were 2 hours and 4 minutes to 2 hours and 42 minutes, and 1 hour and 57 minutes to 2 hours and 43 minutes respectively. The overlap of the 95% confidence intervals supports the absence of a statistically significant variation.

No statistically significant differences were noted in the percentage migration of activity away from the injection site between the 45 minute image and the 3 hour image with respect to hand side (Table 1). The baseline left mean of 6.52% did not differ from the right mean of 6.73% ($p = 0.750$). The follow-up left mean of 8.55% did not differ from the right mean of 7.82% ($p = 0.412$). There was, however, a statistically significant variation in the percentage migration away from the injection site between the baseline and the follow-up for the left hand with a mean increase of 2.02% ($p = 0.012$). Conversely, the right hand did not show a statistically significant improvement between baseline and follow-up with a mean increase in percentage migration of 1.09% ($p = 0.301$). This finding may simply reflect a decreased physiological effect on lymphatics in the dominant hand (right) where increased musculoskeletal activity associated with handedness reduces the margin for improvement. Alternatively, it may signify increased degeneration of normal lymphatic flow in the non-dominant hand leaving a greater margin for short term improvement.

There was a statistically significant increase in the percentage of activity that migrated away from the injection site between the 45 minute and 3 hour images with respect to baseline versus follow-up series (Table 1). The baseline mean of 6.63% varied significantly from the follow-up mean of 8.19% ($p = 0.002$). Despite a small overlap in 95% confidence intervals, the matched pairs *t* test indicated a statistically significant difference ($p = 0.017$) with a mean increase in percentage migration of 1.56% after herbal treatment. The absence of zero in the 95% confidence interval supports this finding.

While the mean percentage of the injected dose that localised in liver at 3 hours post injection was higher for the follow-up studies (0.42% with 95% CI 0.32% - 0.52%) than the baseline studies (0.40% with 95% CI 0.33% - 0.48%), no statistically significant variation was noted ($p = 0.686$). This result is likely to be confounded by *in vivo* degeneration of the radiopharmaceutical integrity resulting in variable organ distribution. This is supported by the observation of thyroid and stomach activity (free pertechnetate) and the discrepancy between liver percentage and migration percentage; although the latter could also indicate retention in lymph nodes.

Table 1: Summary of the results.

Parameter	Baseline	Follow-Up	p Value
Left Mean (n =15)	6.52	8.55	0.750
Left 95% CI	5.14 to 7.90	7.01 to 10.07	
Difference	2.02		0.012
95% CI of Difference	0.51 to 3.54		
Right Mean (n = 15)	6.73	7.82	0.412
Right 95% CI	5.38 to 8.08	5.98 to 9.66	
Difference	1.09		0.301
95% CI of Difference	-1.09 to 3.28		
Combined Mean (n = 30)	6.63	8.19	0.002
Combined 95% CI	5.72 to 7.53	7.06 to 9.31	
Difference	1.56		0.017
95% CI of Difference	0.30-2.82		

DISCUSSION / CONCLUSION

While this investigation is limited by the small sample size and the absence of a pathology group, the pilot investigation was designed to determine whether sufficient evidence exists to investigate the application of horsechestnut complex for the treatment of lymphoedema in breast cancer survivors. In that regard, this study has successfully demonstrated a 1.6% increase in lymphatic migration away from the injection site ($p = 0.02$) after herbal treatment. This improvement is manifest after 3 months of herbal treatment but in only a 2 hour sampling window. Not surprisingly then, the initial dynamic data showed no differences. Further evaluation in a breast cancer population, therefore, would benefit from a simplified protocol with minimal demands on patient time consisting of injection, static imaging at 5 minutes post injection and then further static imaging at 6 hours and 24 hours after injection.

The clinical significance of these pilot findings require some debate. While a 1.6% improvement in lymphatic flow might be argued as negligible (despite a statistical difference), this improvement was detected over a 2 hour period. If the 1.6% were to be sustained over 24 hours, 7 days, 3 months or more (for the duration herbal treatment), then the physical volume represented by the 1.6% could be quite substantial. Indeed, a large volume (greater than 500ml) of additional fluid clearance would be achievable in a short period. The key principle is that the horsechestnut complex is not an immediate solution to an acute problem but rather:

1. A gradual physiological reversal of a chronic manifestation.
2. A measure to prevent or slow onset of a chronic, progressive disorder.

The question does remain with regard to the mechanism of action and, thus, the clinical implications in pathology. HCSE has been reported to reduce abnormally increased capillary permeability (19) and to improve venous emptying (20). Butcher's broom has been reported to exhibit improved venous emptying (24) and decreased capillary filtration rate (25). Improved peripheral vascular circulation noted with horsechestnut complex, in theory atleast, results from improved venous return which decreases the pressure gradient across the capillary bed reducing interstitial leakage. If sustained, the clinical implications of horsechestnut complex therapy is lymphoedema patients are very promising because not only is lymphatic clearance increased but the oedema deposition rate is also decreased. Alternatively, if reported peripheral vascular improvements are the result of increased arterial flow, the increased pressure gradient across the capillary bed might be expected to exacerbate the symptoms of lymphoedema due to increases interstitial leakage; a differentiation not possible in a pilot study of normal volunteers. A randomised controlled trial in unilateral lymphoedema patients using both a placebo group and the non affected limb as controls will provide significant insight into both the mechanism of action and clinical benefits in a pathological population.

There has also been some suggestion that horsechestnut complex may encourage lymphangiogenesis. In this case, the 1.6% improvement noted in this pilot investigation might be expected to progressively increase over a period of several years as the lymphatics progressively build and repair.

Secondary lymphoedema is a significant problem for breast cancer patients after treatment; manifesting as a localised, acquired, lymphatic microcirculatory disturbance (8,9). In breast cancer patients, the lymphatic flow abnormalities and fibrosis may arise following surgery and / or radiation

therapy (26). The resulting morbidity includes pain, paresthesia, recurrent skin infections and functional limitations caused by the swelling, tightness and heaviness of the patients arm (8,13). The positive implications of the results of this pilot investigation support a potential role for horsechestnut complex in the lymphoedema patient to decrease morbidity and improve quality of life in a cost effective manner.

The authors conclude that a multi-centre randomised controlled trial is required to evaluate the clinical benefits of horsechestnut complex in managing lymphoedema in breast cancer survivors.

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