COMPARATIVE STUDY OF THE CLINICAL EFFICACY OF TWO DIFFERENT COUMARIN DOSAGES IN THE MANAGEMENT OF ARM LYMPHEDEMA AFTER TREATMENT FOR BREAST CANCER


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ABSTRACT

In a randomized, double-blind, parallel group study, we compared the clinical efficacy of coumarin 90 mg/day (Group A) with 135 mg/day (Group B) in 77 women (age 35-65 years) with lymphedema of the upper limb secondary to surgery and irradiation for treatment of breast cancer. During 12 months of coumarin therapy, the arm volume of lymphedema and a clinical score (degree of arm edema, heaviness, hardness, and neuralgia/dysesthesia) were determined. In both groups, the volume of arm lymphedema decreased (14.9% in Group A and 13.2% in Group B) (N.S.), the overall clinical score improved (12.9 ± 4.3 to 5.7 ± 3.5 in Group A and from 11.7 ± 3.7 to 4.7 ± 3.9 in Group B) (N.S.), and the overall efficacy of coumarin was similarly good or excellent (71.9% in Group A and 68.6% in Group B) (N.S.). Only mild to moderate side effects of drug therapy were recorded.

Coumarin prevents a spontaneous trend toward an increase in arm lymphedema after treatment of breast cancer, decreases the severity of local symptoms, and overall improves the quality of life. No difference was found between the apparent benefits of coumarin at 90 mg/day compared with 135 mg/day.

Lymphedema of the arm is a common sequela of radiosurgical treatment of breast cancer affecting about 17 to 38% of patients depending on therapeutic aggressiveness (1,2). Typically, after a clinical latency interval of 4 to 54 months after cancer therapy, arm lymphedema occurs spontaneously or is triggered by infection, trauma, strenuous exercise or sun exposure (3). Nonoperative management of lymphedema usually aims to reduce lymph formation and/or accelerate lymph return by physical measures including manual manipulation, remedial exercises and extensive compression therapy (4).

Coumarin (5,6-benz-α-pyrene or 1,2-benzopyrone) is a pharmacologic agent recommended for treatment of peripheral lymphedema. Coumarin presumably enhances the proteolytic activity of macrophages (5-8) and seemingly exerts a positive myotropic, chronotropic and bathmotropic effect on the lymphangion (the anatomical-functional contractile unit of the lymphatic system) (9). Because coumarin, in contrast to coumaadin, lacks a hydroxyl group in carbon 4 of its chemical structure, it has no anticoagulant activity (10).

The doses of coumarin recommended for treatment of patients with lymphedema has ranged from 30 mg/day (11,12) to 400 mg/day (13-15). The doses most frequently used in
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Overall</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>77</td>
<td>38</td>
<td>39</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.2 ± 7.49</td>
<td>52.0 ± 8.0</td>
<td>52.8 ± 7.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.5 ± 10.6</td>
<td>71.0 ± 8.9</td>
<td>72.1 ± 12.1</td>
</tr>
<tr>
<td>Heart rate</td>
<td>74.7 ± 11.3</td>
<td>74.0 ± 10.4</td>
<td>75.4 ± 12.1</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>129.7 ± 18.6</td>
<td>131.4 ± 19.4</td>
<td>128.0 ± 17.9</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>79.2 ± 11.7</td>
<td>80.7 ± 11.0</td>
<td>77.8 ± 12.4</td>
</tr>
<tr>
<td>Volume of the healthy extremity (ml)</td>
<td>2018 ± 489.0</td>
<td>2016.9 ± 530.5</td>
<td>2019.6 ± 451.8</td>
</tr>
<tr>
<td>Volume of the involved extremity</td>
<td>2508.6 ± 440.3</td>
<td>2541.2 ± 688.2</td>
<td>2476.8 ± 537.2</td>
</tr>
</tbody>
</table>

Differences between Groups A and B are not significant

Europe are 90 and 135 mg/day. Accordingly, we compared the efficacy of these two doses of coumarin over a 12 month period in female patients with arm lymphedema after radiosurgery for breast cancer. In this study, the commercial formulation of coumarin (Lysedem®) was used which contains 15 mg of coumarin and 90 mg of troxerutin. This sustained-release formulation improves bioavailability of coumarin from 2-6% to 35% (16). The safety of coumarin was also assessed.

**CLINICAL MATERIAL**

A multicenter, comparative, randomized, double-blind, parallel-group study was performed in which 6 centers from Spain participated: Hospital Valle de Hebrón in Barcelona (Breast Unit), Hospital Ramón y Cajal in Madrid (Rehabilitation Department), Clinical University Hospital in Zaragoza (Vascular Surgery Department), Hospital Duques del Infantado in Sevilla (Medical Oncology Department), Instituto Oncológico in San Sebastián (Vascular Surgery Department) and Hospital La Fe in Valencia (Rehabilitation Department). Seventy-seven women aged from 35 to 65 years (mean age 52 years) diagnosed as having unilateral arm lymphedema secondary to treatment of breast cancer participated in the study. All the patients initially had grade II lymphedema, according to the classification of the International Society of Lymphology (17), with an excess volume of at least 100 ml of less than 10 years duration. Patients on drug therapy with “venotonics” or physical therapy (manual lymphatic drainage) for lymphedema, patients with lymphedema secondary to reactivation of the cancer or where an arteriovenous component existed as evidenced by Doppler ultrasonography, or those with concomitant debilitating systemic diseases were excluded.

The 77 patients fulfilling the inclusion/exclusion criteria were randomized into one of the two arms of the study. Thirty-eight women were treated with coumarin 90 mg/day (Group A) and the other 39 with
coumarin 135 mg/day (Group B). The demographic data and other clinical parameters are shown in Table 1. The duration of treatment was 12 months, with follow-up visits at the end of months 1, 2, 4, 6, 9, and 12 of treatment. Before starting therapy and at each follow-up visit, the volume of lymphedema was calculated as the difference between the volume of the affected and that of contralateral non-edematous arm as measured using an opto-electronic device (Volumeter®, Bösl Medizintechnik GMBH, Germany). This device calculates arm volume after 190 determinations of the horizontal and vertical diameters of the arm at different levels, calculating the corresponding ellipses separately, and estimating the volume by computer integration using these measurements (18). The severity of clinical symptoms was also established: degree of hardness of the edema, heaviness, neurological signs (pain, cramps...), subjective sensation of edema at the wrist, forearm and arm, which was rated by the investigator as: 0=none; 1=mild; 2=moderate; 3=severe; 4=very severe. The sum of the scores obtained for the 6 symptoms was used as a marker of evolution of lymphedema as suggested by Pecking and Cluzan (19). At 6 and 12 months of treatment, the global impression of investigator and patient on the efficacy of treatment was rated as: none, mild, moderate, good or excellent. “Safety laboratory tests” were performed at the start of the study and at months 6 and 12 of treatment.

Statistical analysis

The results of the quantitative variables are given as mean ± standard deviation, and those of the categorical variables as absolute frequency and percentage. The variables tested, global clinical score and volume of lymphedema, were analyzed by an ANOVA for repeated measurements using the treatment group as between-subject factor. Each symptom making up the global clinical score was analyzed by a non-parametric test (Friedman test). A comparison of percentages was used to compare efficacy in the two treatment groups at 6 and 12 months. A two-tailed test was used in each instance with a p value of <0.05 considered as statistically significant.

For the efficacy analysis, the intention-to-treat sample was used as defined as follows: all patients included in the study had at least one valid efficacy measurement within the first six months of treatment. If no valid measurement was available at month 12, the last valid measurement available was used. The population for the safety analysis consisted of all patients included in the study taking at least one basic unit of the study drug.

RESULTS

Clinical Efficacy

Of the 77 patients starting the study, 53 completed the 12 months of treatment (23 patients in Group A and 30 patients in Group B), with 24 drop-outs during the study (15 in Group A and 9 in Group B) for the following reasons: 7 voluntary drop-outs (6 in Group A and 1 in B), 11 due to adverse events (6 in Group A and 5 in B), 4 patients lost to follow-up (3 in Group A and 1 in B), 1 drop-out due to protocol violation (Group A) and another drop-out for other causes (Group B). Three additional minor protocol violations occurred (two in Group A and one in B).

Seventy patients (35 in each group) were considered for the intention-to-treat analysis. Seven patients were excluded from the analysis for the following reasons: 4 drop-outs due to adverse events during the first days of treatment, which prevented obtaining any efficacy result, and 3 patients due to protocol violations, which prevented obtaining any valid efficacy result.

The mean volume of the healthy non-edematous arm in the 70 patients evaluable for efficacy increased slightly from 2037.7 ± 491.0 ml at the start of the study to 2047.0 ± 490.1 ml at the end of it, whereas mean
### TABLE 2
Changes (Mean ± S.D.) in the Clinical Score

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>n</th>
<th>Arm Hardness</th>
<th>Heaviness</th>
<th>Neurological signs</th>
<th>Wrist edema</th>
<th>Forearm edema</th>
<th>Arm edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>70</td>
<td></td>
<td>2.2 ± 1.0</td>
<td>2.1 ± 1.0</td>
<td>1.0 ± 1.0</td>
<td>2.7 ± 1.2</td>
<td>2.3 ± 1.1</td>
<td>2.1 ± 1.1</td>
</tr>
<tr>
<td>Month 1</td>
<td>70</td>
<td></td>
<td>1.7 ± 0.8</td>
<td>1.4 ± 0.9</td>
<td>0.6 ± 0.9</td>
<td>1.3 ± 1.0</td>
<td>1.9 ± 1.0</td>
<td>1.6 ± 0.9</td>
</tr>
<tr>
<td>Month 2</td>
<td>70</td>
<td></td>
<td>1.5 ± 0.9</td>
<td>1.3 ± 1.0</td>
<td>0.6 ± 0.9</td>
<td>1.3 ± 1.0</td>
<td>1.7 ± 0.9</td>
<td>1.4 ± 1.0</td>
</tr>
<tr>
<td>Month 4</td>
<td>70</td>
<td></td>
<td>1.3 ± 0.8</td>
<td>1.0 ± 0.9</td>
<td>0.5 ± 0.9</td>
<td>1.1 ± 0.9</td>
<td>1.5 ± 0.9</td>
<td>1.2 ± 1.0</td>
</tr>
<tr>
<td>Month 6</td>
<td>70</td>
<td></td>
<td>1.1 ± 0.8</td>
<td>0.8 ± 0.9</td>
<td>0.4 ± 0.8</td>
<td>0.9 ± 0.8</td>
<td>1.2 ± 0.9</td>
<td>0.9 ± 0.9</td>
</tr>
<tr>
<td>Month 9</td>
<td>70</td>
<td></td>
<td>0.9 ± 0.8</td>
<td>0.7 ± 0.9</td>
<td>0.3 ± 0.7</td>
<td>0.8 ± 0.9</td>
<td>1.2 ± 0.9</td>
<td>0.8 ± 1.0</td>
</tr>
<tr>
<td>Month 12</td>
<td>70</td>
<td></td>
<td>0.8 ± 0.8</td>
<td>0.6 ± 0.8</td>
<td>0.3 ± 0.7</td>
<td>0.7 ± 0.9</td>
<td>1.0 ± 0.9</td>
<td>0.8 ± 0.9</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.0005</td>
<td></td>
<td>&lt;0.0005</td>
<td>&lt;0.0005</td>
<td>&lt;0.0005</td>
<td>&lt;0.0005</td>
<td>&lt;0.0005</td>
<td>&lt;0.0005</td>
</tr>
</tbody>
</table>

0: None; 1: mild; 2: moderate; 3: severe; 4: very severe

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The volume of the lymphedematous arm decreased from 2536.8 ± 705.3 ml to 2475.8 ± 694.0 ml over 12 months. The mean volume of lymphedema, calculated as the difference in volume between the non-edematous and the edematous arm was 499.1 ± 449.6 ml at the start of the study to 428.9 ± 497.0 ml at the end. By treatment groups, the volume of lymphedema decreased from 520.3 ± 309.0 ml to 442.9 ± 346.8 ml (a 14.9% reduction) in Group A, and from 477.9 ± 560.2 ml to 414.9 ± 617.0 ml (a 13.2% reduction) in Group B. The ANOVA for repeated measurements did not detect significant differences between the mean volumes of lymphedema during the study (p=0.122). No differences were found between the two treatment groups throughout the 12 months of the study (p=0.524).

The clinical score also showed a progressive decrease in both groups during therapy with coumarin. The mean score decreased from 12.3 ± 4.1 at baseline to 5.2 ± 3.6 at the end of the study (p<0.0005). By treatment groups, global clinical score decreased from 12.9 ± 4.3 to 5.7 ± 3.5 in Group A, and from 11.7 ± 3.7 to 4.7 ± 3.9 in Group B. No significant differences were seen between the two groups in changes in clinical scores (p=0.910).

Assessment by Friedman test of the individual symptoms making up the clinical score (hardness, heaviness, subjective sensation of edema in the wrist, forearm and arm and neurological signs) (Table 2) showed a significant decrease in the severity of all symptoms in the overall sample (p<0.0005).

Efficacy of treatment after 6 months of administration was classified by the investigators as good or excellent in 45.5% (Group A) and 45.7% of the patients (Group B); moderate in 36.4% (Group A) and 28.6% (Group B) and mild or none in 18.1% (Group A) and 25.7% (Group B). At month 12 of treatment, the investigators classified the efficacy of coumarin as good or excellent in 71.9% (Group A) and 68.6% (Group B); as moderate in 12.5% (Group A) and 14.3% (Group B); and as mild or none in 15.6%
(Group A) and 14.3% (Group B). The consensus opinion of the patients was similar to the investigators. Uniformly, the differences between the two treatment groups were not statistically significant.

Side-Effects

Data obtained from all patients starting active treatment were considered for the toxicity, regardless of whether the three laboratory measurements (baseline, month 6 and month 12) planned in the protocol were completely available.

No notable changes were seen in erythrocytes, leukocytes, platelets, or differential white cell counts. A slight change was noted in creatinine serum levels (baseline: 0.89 ± 0.11 mg/ml; month 6: 0.90 ± 0.14 mg/dl; month 12: 0.86 ± 0.13 mg/dl, p<.01). No clinical changes in renal function were otherwise noted. A slight rise was also detected in the serum alkaline phosphatase level (baseline: 129 ± 61 U/l; month 6: 152 ± 60 U/l; month 12: 150 ± 66 U/l, p<.05). These levels, however, remained within the normal range except for one patient in each treatment group who had an absolute rise.

No significant changes were seen in other liver enzymes during the study: SGOT: baseline: 21.9 ± 9.0 U/l; month 6: 22.4 ± 10.2 U/l; month 12: 20.0 ± 7.6 U/l; SGPT: baseline: 22.3 ± 13.7 U/l; month 6: 25.5 ± 18.9 U/l; month 12: 22.1 ± 14.3 U/l. One patient in treatment Group B with a baseline SGPT plasma levels of 106 U/l showed a decrease during the study (88 U/l at 6 months of treatment and 68 U/l at 12 months). Two other patients (one patient in Group B and one in Group A) with baseline SGPT serum levels of 47 and 15 U/l, respectively, had abnormally elevated values after 6 months of treatment (82 and 107 U/l, respectively). These values decreased to 56 U/l and 43 U/l, respectively, after 12 months of treatment. The Group B patient had received concomitantly ranitidine, metomizole and ciniapride at different times of the study; however, the patient of Group A did not report taking other drugs.

During the study, 36 patients (18 in each treatment group) reported 57 adverse events, most of them seemingly unrelated to coumarin. In 16 adverse events reported by 12 patients, the causal relationship with the study drug was rated as possible, probable or definite. Twelve events reported by 7 patients (10% of the sample) included gastrointestinal complaints (primarily epigastric pain or heaviness). Although the severity of symptoms was considered to be mild or moderate in each patient, 2 patients with epigastric pain and headache in Group A and one patient in Group B with nausea and vomiting discontinued participation. The causal relationship was considered as definitely related to coumarin in the patient with headache from Group A and in the patient with nausea and vomiting from Group B. Epigastric pain was considered as probably related to coumarin. Finally in Group A, one patient report metrorrhagia and another patient reported an increase in vaginal bleeding during the menses.

DISCUSSION

Radiosurgical therapy in treatment of breast cancer obliterates a significant portion of axillary lymph collectors which together with fibrosis impairs lymph return in the arm. Dilatation of obstructed lymph vessels stimulates the pumping capacity of lymphangions which with increased lymph sequestration raises intralymphatic pressure. When intraluminal lymphatic pressure is sufficiently high, lymphatic valves become incompetent and plasma proteins become sequestered in the interstitial space. This phenomenon further increases interstitial colloid osmotic pressure thereby aggravating trapping of capillary filtrate within the tissue space. Accumulation of plasma and perhaps cellular elements with reduced trafficking in the interstitium stimulates fibroblasts with increased interstitial fibrosis. Together with
The natural course of arm lymphedema after treatment for breast cancer is one of a gradual increase in edema volume as shown in control groups (i.e., without drug treatment or with placebo) in several clinical trials. Clodius and Piller (12), in a parallel-group study in which one group included patients who received no drug therapy, found that the parameter of post-mastectomy lymphedema increased on the average of 1 cm each year, during the first 6 years in the untreated group, whereas it decreased on the average of 0.5 cm for every 10 months of treatment in patients receiving coumarin 30 mg/day. Desprez-Curely et al (21) performed a parallel-group, placebo-controlled study to assess the efficacy of coumarin, administered at doses of 135 mg/day, in the treatment of patients with post-mastectomy lymphedema. The study included a 6-month double-blind phase followed by a 12-month open study. The volume of arm lymphedema increased significantly in the placebo group during the double-blind phase, then decreased during the open phase. On the other hand, in the group treated with coumarin from the outset of the study, the volume of arm lymphedema decreased significantly after 18 months of treatment. The differences between placebo and coumarin treatment groups were significant at the end of the double-blind period, but gradually disappeared during the open phase of the study. Pecking and Cluzan (19) in a 9-month double-blind, parallel, placebo-controlled study, found that in the group treated with placebo, arm lymphedema volume increased at an average of 8.1%, whereas in the group treated with coumarin (90 mg/day), arm lymphedema volume decreased by 14.5%. Finally, in a 6-month, cross-over study performed by Casley-Smith et al (22), the gradual increase in arm lymphedema volume secondary to mastectomy during treatment with placebo was confirmed, whereas arm volume decreased significantly by 20% during treatment with coumarin (400 mg/day).

The inclusion of a group treated with placebo was deemed unethical even though the effect of coumarin against the spontaneous increase in the volume of arm lymphedema would be clearer than by studying the longitudinal evolution of a group on active treatment due to different evolution trends. In our 12-month study, volume reductions of 14.9% and 13.2% were found with the 90 mg/day and 135 mg/day doses of coumarin, respectively. These results are similar to those found by Pecking and Cluzan, with a 14.5% reduction with the 90 mg/day dose during 9 months (19), and lower than those reported by Casley-Smith et al, who found a 20% reduction with the dose of 400 mg/day for 6 months (21). Some authors have reported a reduction in volume of lymphedema greater than 15%. The fact that Casley-Smith et al (22) found a 20% reduction with the administration of 400 mg/day of coumarin for 6 months suggests a dose-dependent effect. The 21.1% reduction in volume after 12 months of treatment with 135 mg/day of coumarin found by Lafontan et al (23) in a series of 591 patients with post-
mastectomy lymphedema may relate to the fact that 407 patients had combined drug with physical therapy in that study. In our study, the severity of clinical symptoms, hardness, heaviness, neurological symptoms and subjective sensation of edema at the arm, forearm and wrist, decreased significantly throughout the study. These results are in agreement with those of others (12,19,21-23). Reduction in fibrosis and edema probably account for symptomatic improvement seen in these patients, which would probably further be aided by compression therapy.

Instances of hepatotoxicity associated with coumarin administration at doses of 400 mg/day have been recently reported (13-15). In our study, doses of 90 and 135 mg/day were used, and only two patients had increased SGPT detected at 6 months of treatment, which returned to normal levels without requiring drug discontinuation. Changes in transaminase serum levels in our study suggest a low hepatotoxicity potential, an observation consistent with that made by Cox (24), who in a study with 2,173 patients established an incidence of liver damage of 0.37% of patients related to coumarin administration. Cox reported that liver function abnormalities could be due to an idiosyncratic reaction.

In our study, coumarin was generally well tolerated, although 10% of patients had gastrointestinal disorders of mild to moderate severity, and 3 dropped out due to side-effects of coumarin.

CONCLUSIONS

In patients with arm lymphedema after radiosurgical treatment for breast cancer, coumarin therapy was associated with a progressive reduction in severity of symptoms during 12 months of treatment, along with a 14% reduction in the volume of arm edema. These findings suggest that coumarin can prevent the spontaneous trend to an increase in arm lymphedema over time. The beneficial effects of coumarin complement the application of physical therapy, compression bandages or other drainage maneuvers used to improve the quality of life in these patients. In this study, 90 mg/day of coumarin was equally effective to that of 135 mg/day.

REFERENCES

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