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Original research-Orijinal araştırma

The efficacy of micronized flavonoid fraction (450 mg diosmin plus 50 mg hesperidin) in the treatment of lymphedema after axillary dissection

Aksiller diseksiyon sonrası kolda gelişen lenf ödem profilkasisinde mikronize flavonoid fraksiyonunun etkinliği

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Abstract

Aim. Lymphedema is one of the most important complications that occurs secondary to modified radical mastectomy and breast conserving surgery in breast cancer treatment. micronized flavonoid fraction (MFF) (diosmin 90%, hesperidin 10%) is a well known chemical agent used for the acceleration of the flow of lymphatic and venous drainage. Our goal was to evaluate the efficacy of MFF in the treatment of lymphedema. **Method.** Fifty-four patients who underwent modified radical mastectomy or breast conserving surgery, because of breast cancer between July 2001 and July 2004 in our clinic were included in the trial. The patients who required post operative axillary radiotherapy were excluded. Patients were randomized into two groups. Groups were allocated as follows: Group I (30 patients): Placebo treatment for six months was performed. Group II (24 patients): Patients were treated with 2x1 .500 mg/day/p.o MFF for six months. The diameters and the volumes of the patients' arms were measured and recorded preoperatively and postoperatively at the 1st, 3rd and 6th months. The 10% increase of diameter and/or volume in the arm at the operation side was accepted as lymphedema. The results were evaluated by using Mann Whitney U test. **Results.** There were 30 patients in group 1 and 24 patients in group 2. No statistically significant difference was detected between the groups by means of preoperative diameter and volume of the arms. Post operative dissected numbers of the lymph nodes were also not different among groups. Postoperative lymphedema was detected in 5 (16.6%) and 4 (10.7%) patients in Group I and in Group II respectively. These results similarly showed no statistically significance. And also we detected no statistically difference between the two groups in the measurements of the arms at the1st, 3rd and 6th month control visits. **Conclusion.** As a result, the MFF in the treatment of lymphedema can be accepted as ineffective but further investigations with larger number of patients are required to confirm this conclusion.

Keywords: Postoperative lymphedema, axillary dissection, micronized flavonoid fraction

Özet

Amaç. Meme kanserinin cerrahi tedavisinde uygulanan yöntemlerden modifiye radikal mastektomi ve meme koruyucu cerrahi sonrasında görülen önemli komplikasyonlardan birisi lenfödemdir. Mikronize Flavanoid Fraksiyon (MFF) (diosmin %90, hesperidin %10) venöz akımı ve lenfatik akımı hızlandıran bir ajan olarak günümüzde kullanılmakta olan bir ilaçtır. Biz bu çalışmada MFF 500 mg'ın lenfödem üzerine etkisini araştırmayı amaçladık. **Yöntem.** Bu amaçla kliniğimizde Temmuz 2001-Temmuz 2004 tarihleri arasında meme kanseri nedeniyle modifiye radikal mastektomi veya meme koruyucu cerrahi uygulanan hastalar çalışmaya dâhil edildi. Operasyon sonrasında aksiller radyoterapi endikasyonu koyulan hastalar çalışma dışı bırakıldı. Hastalar 2 gruba randomize edildi. Grup 1: Kontrol: Bu hastalara operasyon sonrasında 6 ay plasebo verildi. Grup 2: MFF 500 mg: Bu hastalara operasyon sonrasında 6 ay MFF 500 mg 2x1

verildi. Hastaların tamamının preoperatif ve postoperatif 1. ay, 3. ay ve 6. aylarında kol çapları ve kol hacimleri ölçülerek kaydedildi. Operasyon tarafındaki % 10'luk hacim ve/veya çap artışı lenfödem olarak kabul edildi. Sonuçlar Mann Whitney U testi ile değerlendirildi. **Bulgular.** Grup 1'de 30 hasta grup 2'de ise 24 hasta vardı. Gruplar arasında preoperatif kol çapları ve kol hacimleri açısından istatistiksel olarak anlamlı fark yoktu. Diseke edilen lenf nodu sayıları her iki grupta istatistiksel olarak farksızdı. Postoperatif lenfödem gelişimine baktığımızda grup 1'de 5 hastada (%16,6), grup 2'de ise 4 hastada %10,7 oranında lenfödem geliştiği görüldü. Bu oranlar arasında istatistiksel olarak anlamlı fark yoktu. Gruplar arasında postoperatif 1. 3. ve 6. ay yapılan hacim ve çap ölçümleri değerlendirildiğinde çap değişimi ve hacim değişimi açısından anlamlı fark saptanmadı. **Sonuç.** Sonuç olarak aksiller diseksiyon sonrasında gelişen lenfödemin önlenmesinde MFF etkisinin olmadığı ancak daha kesin sonuca varılması için daha büyük grupları içeren çalışmaların gerektiği kanaatine varıldı.

Anahtar sözcükler: Post-operatif lenfödem, aksiller diseksiyon, mikronize flavonoid fraksiyonu

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Introduction

Breast cancer is still the most common form of cancer in women. Although chemotherapy, radiotherapy and hormonal treatment methods are used in the treatment of breast cancer, surgery is still the primary curative treatment option.

Lymphedema in the arm is one of the most common complications of surgery for breast cancer [1-4]. A review of the literature suggests that prevalence rates of 15% to 30% are reasonable [4, 5]. Lymphedema is a chronic, progressive complication that also disturbs the patient's comfort. It may not only cause arm pain, limitation of shoulder movement, burning sensation, skin temperature increase, but also may cause sociological and psychological problems [6]. Traditional treatment of this complication includes compression, manual lymphatic drainage and elevation of the arm [6, 7]. The effectiveness of these treatment methods has not been proved yet. MFF is an agent that is primarily used in the treatment of varicose veins in the lower extremities and hemorrhoids. MFF 1000 mg / day increases venous flow and can be effective in the treatment of varicose veins. Studies on the mechanism of action of the MFF demonstrated; facilitation in lymphatic drainage and acceleration in lymph flow [8, 9]. After being shown the positive effect on the lymphatic drainage, it is used for the treatment of patients with lymphedema due to axillary lymph node dissection and studies have shown a therapeutic effect in arm lymphedema [10].

In this study we evaluated prospectively, the efficacy of .MFF, in the treatment of lymphedema after axillary dissection (AD).

Material and methods

The study was designed as prospective, randomized and double-blind. The patients who were hospitalized for breast cancer surgery between July 2001 and July 2004 in our clinic were included in trial. The patients were consecutively randomized into 2 groups.

The criteria for inclusion in the study were as follows: 1- Established diagnosis of breast cancer, 2- No prior radiotherapy, chemotherapy and hormone therapy, 3- No prior MFF therapy, 4- Absence of preoperative lymphedema or lymphatic function disorder, 5- No prior antiplatelet drug use, 6- Preoperatively planned modified radical mastectomy or breast conserving surgery, 7-Clinically N0M0.

Diameters of the patients arm and arm volumes were recorded before the operation. The diameters of both arms were measured from10 cm proximal and 10 cm distal to the upper epicondyle and arm volumes were measured using the water overflow test just as had been done in previous similar studies [11, 12]. After surgery, some patients who were included in the study were excluded. The criteria for exclusion from the study were as follows: 1-Indication of postoperative radiotherapy, 2- Removal of 10 or less lymph nodes in AD. Groups were allocated as follows: Group I (30 patients): Placebo treatment for six months was performed. Group II (24 patients): Patients were treated with 2x1 500 mg/day/p.o MFF for six months. The diameters and the volumes of the arm of the patients were measured and recorded, preoperatively and postoperatively at the 1st 3rd and 6th months by the same surgeon, who was also unaware of the groups of patients. The 10% of increase of diameter and/or volume of the arm at the operation side was accepted as lymphedema. These techniques have previously been applied to assess lymphedema and have been shown to have good correlation [13, 14]. Both groups of patients underwent surgery; the differences between postoperative and preoperative measurements were calculated and compared statistically.

The study was approved by the hospital ethics committee. The information document about the study was read and signed by the patients. Chi-Square and Mann-Whitney test was used in the statistical evaluation of data. Categorical variables were summarized as number and percentage and variables were summarized as mean ± SD. Statistical analysis was made by using SPSS 10, 0 program. A value of $p<0.05$ was considered as statistically significant.

Results

The 80 patients who were hospitalized for breast cancer surgery between July 2001 and July 2004 in our clinic were included in trial. There were 40 patients in each group. Ten patients in group 1 and 16 patients in group 2 were excluded after the evaluation of the pathologic results.

The preoperative mean diameter of forearm was 21.07±069 (20-22) cm on the right, 21.0±0.83 (19-22) cm on the left, in group1; and; 21.29±2.29 (20-26) cm on the right, 21.29±2.21 (17-25) cm on the left, in group 2. The preoperative mean diameter of arm was 30.47±2.01 (28-34) cm on the right, 30.5±2.03 (26-34) cm on the left, in group1; and; 31.13±3.19 (26-35) cm on the right, 31.17±3.10 (23-35) cm on the left in group 2.

The preoperative volume measurements were; 1673.33±10.63 (1550-1900) cm^3 on the right side, 1681.67±98.68 (1500-1900) cm^3 on the left side, in group 1; and; 1668.75±211.01 (1550-1800) cm3 on the right, 1670.83±210.55 (900-2000) cm^3 on the left, in group 2. There was not any statistically significant difference between the two groups in terms of volume and diameter ($p>0.05$). Breast Conserving Surgery (BCS) in 16 (53.3%) patients and Modified Radical Mastectomy (MRM) in 14 (46.7%) patients were applied in group 1. On the other hand 12 (50%) patients underwent BCS and the rest 12 (50%) patients underwent MRM in group 2. There was no significant difference between the two groups in terms of the applied type of operation ($p>0.05$).

Values obtained by measurements carried out in the first month after surgery, considering the differences between the preoperative values, there was no statistically significant difference between groups 1 and group 2 in terms of arm diameters and volumes ($p>0.05$) (Table 1).The diameter and volume differences between preoperative and postoperative measurements in the 3rd month were compared and a significantly volume improving noticed on the left arm of the patients in group 2, when ($p<0.05$). There was no statistical difference in values of the other diameter and volume (Table 2).

Table 1. The difference between preoperative measurements and measurements of the first month postoperatively.

	Group 1	Gruop 2	P
Post-op first month right forearm-Pre-op right forearm (cm)	0.21±0.42	0.08±0.29	0.054
Postop first month right arm-Pre-op right arm (cm)	0.57±0.75	0.08±0.51	0.087
Posto-p first month right volume-Pre-op right volume (cm^3)	39.26 ±56.08	8.33±35.88	0.101
Post-op first month left forearm-Pre-op left forearm (cm)	0.56±1.03	0.17±0.38	0.326
Post-op first month left arm-Pre-op left arm (cm)	0.94±0.92	0.50±0.90	0.176
Post-op first month left volume-Pre-op left volume (cm^3)	34.37±90.77	54.16±126.95	0.523

Table 2. The differences of the measurements of the preoperative and the postoperative 3rd month

	Grup 1	Grup 2	P
Post-op 3rd month right forearm-Pre-op right forearm (cm)	0.21±0.42	0.25±0.45	0.833
Post-op 3rd month right arm-Pre-op right arm (cm)	1.57±1.60	1.50±1.67	0.894
Post-op 3rd month right volume-Pre-op right volume (cm^3)	57.14 ±54.97	66.67±53.65	0.749
Post-op 3rd month left forearm-Pre-op left forearm (cm)	0.69±1.01	0.25±0.45	0.248
Post-op 3rd month left arm-Pre-op left arm (cm)	1.50±1.32	1.42±1.44	0.829
Post-op 3rd month left volume-Pre-op left volume (cm^3)	28.13±98.26	83.33±121.23	0.039*

(* p ‹ 0.05)

Values obtained by measurements carried out in the 6th month after surgery, considering the differences between the preoperative values, between group 1 and group 2 had no statistically significant difference in terms of arm diameters and volumes($p>0.05$) (Table 3).

Table 3. The differences of the measurements of the preoperative and the postoperative 6th month.

	Grup 1	Grup 2	P
Post-op 6th month right forearm-Pre-op right forearm(cm)	0.29±0.46	0.33±0.89	0.441
Post-op 6th month right arm-Pre-op right arm (cm)	1.14±2.07	1.42±1.73	0.871
Post-op 6th month right volume-Pre-op right volume (cm^3)	35.71 ±92.88	66.67±57.74	0.409
Post-op 6th month left forearm-Pre-op left forearm (cm)	0.75±1.06	0.50±0.79	0.560
Post-op 6th month left arm-Pre-op left arm (cm)	1.88±1.09	1,92±1,37	0.962
Post-op 6th month left volume-Pre-op left volume (cm^3)	53.13±92.13	108.33±152.01	0.191

Lymphedema was detected in 5(16.6%) patients in group 1 and in 4(10.7%) patients in group 2 and there was no statistically significant difference between these two values ($p>0.05$).

Discussion

The arm lympedemais one of the most common problems at the beginning of the late postoperative period, in the patients who underwent AD due to breast cancer. Lymphedema impairs quality of life of patients leading to physiological problems in addition to the psychological and sociological problems [4, 5, 15,]. In one study, the data of 923 patients who underwent MRM 20 years ago, was evaluated, and the lymphedema developed in 49% of them. Lymphedema in 13% of them was found to be at a serious level. The infection and weight gain were identified as a reason of serious lymphedema in these patients [16]. In another study, quality of life of patients, whom developed lymphedema after MRM, was investigated. The incidence of lymphedema was 8.3% in this study. However, in these patients, general health and mental health, were also significantly impaired when compared with the non-lymphedema patients [17]. In our study, the development of lymphedema rates were; 16.6% and10.7%; in group 1 and in

group 2, and these data was inconcordance with the literature. Various methods have been tried in the treatment of postoperative patients with lymphedema. In a study of low dose laser treatment, 33% volume reduction and a little decrease in arm stiffness, has been achieved[A3]. In another study, vitamin E and pentoxifylline were used for therapeutic purposes and no benefit had been detected [18]. In another trial; Cluzan et al. [19] used CYCLO 3 FORT (Ruscus+Hesperidin methyl Chalcone) as a therapeutic agent and have been able to achieve, significant response within 3 months after administration especially in the forearm. In addition to these; external compression methods have been used to treat patients with lymphedema. Lympho-press was detected as an effective treatment and in that study Lympho-press was used successfully in the treatment of lymphedema[20]. MFF is an agent that is lately and primarily used in the treatment of varicose veins in the lower extremities and hemorrhoids. MFF 1000 mg / day increases venous flow and can be effective in the treatment of varicose veins. Pecking showed the efficacy of MFF 1000mg/day in the treatment of post AD lymphedema in 1995 in his study [21]. Same author used the same agent in another trial and also detected significant improvement in the treatment in 1997[10]. In another paper; MFF had been found effective not only in venous insufficiency but also in post mastectomy lymphedema[22]. However, in those studies the drug was used for treatment not for prophylaxis so by a prophylactic manner as we used, it is natural to not to reach the same results.

As far as we know; there is not any effective agent in the prophylaxis of lymphedema. In our study, MFF also showed no significant difference in the development of lymphedema between the groups.

Some studies suggest that, nursing care in the early postoperative period and performance of microsurgical methods (if necessary), could be effective in prevention of the formation of lymphedema [23, 24]. Arm lymphedema is one of the most serious complications that occurs secondary to AD due to modified radical mastectomy and breast conserving surgery. As a result ; MFF can be accepted as ineffective in the treatment of lymphedema but further investigations with larger number of patients are required to confirm this conclusion.

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