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Micronised and purified flavonoid fraction prevents oedema formation and regulates peripheral circulation after conservatively treated distal radius fractures

Mikronize pürifiye flavonoid fraksiyonu konservatif tedavi edilen distal radius kırıklarında ödem oluşumunu önler ve periferik dolaşımı düzenler

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Objective

Therapeutic efficacy of micronised and purified flavonoid fraction (MPFF) on oedema formation was assessed in patients with distal radial fractures treated with closed reduction and short-arm circular casting.

Patients and methods

Hundred patients (28 males and 72 females) were evaluated in a prospective randomized controlled clinical trial. Patients were allocated into two groups. In Group I, the patients received non-steroidal anti-inflammatory medicine. In Group II, the patients received MPFF. Saturation of oxyhaemoglobin (SpO_2) was measured with pulse oximetry from the first and fourth fingers of both hands.

Results

SpO_2 in fractured extremities decreased after casting. SpO_2 in the fractured extremities increased earlier and this was significant in Group II. SpO_2 difference between the fractured and normal extremities was significant in Group II for the first three days. This difference consisted until the end of three weeks in Group I. Decrease in SpO_2 values and oedema formation was significantly better in patients treated with MPFF.

Discussion

Oedema formation contributes to the insufficiency in peripheral capillary circulation and decreases SpO_2 values after closed reduction and circular casting of distal radius fractures. Measurement of SpO_2 with pulse oximetry is a simple and inexpensive method to monitor peripheral capillary circulation after circular casting. Administration of MPFF is beneficial in preventing oedema formation and regulating peripheral SpO_2 after distal radial fractures.

Key words: Casting, fracture, micronised purified flavonoid fraction, oedema, radius

Amaç

Prospektif, randomize kontrollü klinik çalışmanın amacı kapalı redüksiyon ve sirküler alçı ile tedavi edilen radius alt uç kırıklarında mikronize pürifiye flavonoid fraksiyonunun (MPFF) periferik dolaşım üzerine etkilerini araştırmaktır.

Hastalar ve yöntem

Radius alt uç kırığı olan 100 hasta (28 kadın ve 72 erkek) tedavi edildi. Hastalar iki gruba ayrıldı. Grup I'deki hastalar steroid içermeyen anti-inflamatuar ilaç alırken Grup II'deki hasatalara MPFF verildi. Oksi-hemoglobin doygunluğu (SpO_2) oksimetre ile her iki elden ölçüldü.

Bulgular

Kırık tarafta alçılama sonrası SpO_2'düştü. SpO_2'de yükselme Grup II'de daha hızlı ve belirgin oldu. Kırık tarafla sağlam taraf arasında SpO_2 düzeyleri arasında Grup II'de üçüncü güne kadar anlamlı fark varken Grup I'de 21. güne kadar anlamlı fark saptandı. Grup II'deki hastalarda SpO_2'de düşme ve ödem oluşumu anlamlı olarak daha az görüldü.

Çıkarımlar

Ödem oluşumu kapalı redüksiyon ve sirküler alçılama sonrasında periferik dolaşım yetmezliğini arttırmakta ve SpO_2'de düşmeye neden olmaktadır. Alçılama sonrasında SpO_2'düzeyinin oksimetre ile ölçümü periferik dolaşımın kontrolü için basit ve etkili bir yöntemdir. MPFF uygulanması kapalı redüksiyon ve sirküler alçı ile tedavi edilen radius alt uç kırıkları sonrasında ödem oluşumunun önlenmesinde ve buna bağlı oluşabilecek komplikasyonların önüne geçilmesinde etkili bir tedavidir.

Anahtar sözcükler: Alçılama, kırık, mikronize pürifiye flavonoid fraksiyonu, ödem, radius

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Soft tissue swelling is a common problem after distal radius fractures. Closed reduction and circular casting contributes to oedema formation. This in-turn leads to decrease in tissue SpO_2 values necessitating re-casting.

S5682 is a purified flavonoid fraction consisting of 90% diosmin (450 mg, flavone derivate) and 10% hesperidin (50 mg, flavone derivate).[1,2] Micronized purified flavonoid fraction (MPFF) increases venous tone by increasing the tonus of smooth muscle fibers on the venous wall, improves lymphatic drainage and inhibits the activation, migration and adhesion of leukocytes.[1,2-5] By these mechanisms, MPFF inhibits oedema formation during the early phase of the inflammatory reaction.[5] Effects of MPFF after closed reduction and short-arm circular casting of the distal radius fractures was not assessed. It is assumed that MPFF will decrease oedema and regulate peripheral circulation in these patients.

The aim of the present study was to test the therapeutic efficacy of MPFF on oedema formation in patients with distal radial fractures treated with closed reduction and short-arm circular casting in a prospective randomized controlled clinical trial.

PATIENTS AND METHODS

One hundred displaced distal radius fractured patients were enrolled to this prospective randomized controlled clinical study. All patients were treated with closed reduction and short-arm circular casting in the emergency room between May 2002 and September 2006 in a single centre. Low- but not high-energy trauma patients with haematocrite values between 35-45% were included. Surgically treated patients after failure of conservative treatment during the follow-up period, patients admitted more than 24 hours after initial trauma (in order to eliminate possible bias of fracture oedema formation by delaying of treatment) and patients in whom re-reduction and casting was necessary after displacement during follow-up period were excluded from the study. Additionally, patients receiving venothropic treatment, patients with peripheral vascular diseases, patients with non-displaced distal radius fractures, patients with open fractures and smoking patients were excluded. The study was approved by the Local Ethics Committee of the institution and informed consent was obtained from all patients.

Patients were randomized according to their admittance order and assigned into two study groups having 50 patients in each group. Group I and Group II patients received non-steroidal anti-inflammatory drug (NSAID) and MPFF treatment, respectively. There were 28 (28%) males and 72 (72%) females. The mean age was 50 (range 18-65) years. In Group I [13] males, 37 females; mean age; 52 years (range 18-64); 24 fractures of type 2.3.A, 11 of type 2.3.B and 15 of type 2.3.C according to AO/ASIF Classification] the patients received NSAID (naproxen sodium 550 mg) twice a day for seven days to reduce inflammatory response and pain. In Group II [15 males, 35 females; a mean age; 49 years (range 21-65); 25 fractures of type 2.3.A, 8 of type 2.3.B and 17 of type 2.3.C according to AO/ASIF Classification] the patients received MPFF (Daflon 500 mg) twice a day for 30 days. The groups were homogenous and Group I was considered as the control group.

All of the closed reduction and short-arm circular castings were performed by the same two authors (MA and BÖ). Reduction with maximum of 10° dorsal angulation, 5 mm of radial shortening and 2 mm stepping at the articular surface was accepted as alignment. Fractures were immobilized with a circular cast for six weeks. Late collapse or los of reduction was not observed in any of the patients in both groups. Time to union and follow-up periods was similar in both groups.

Peripheral circulation was evaluated by a) measuring SpO_2 values and by b) capillary filling time as good, moderate or fair. SpO_2 measurements were carried-out with a pulse oximeter (PETAŞ KMA 275, Turkey) from the thumb and the fourth finger simultaneously in the fractured and normal hands, at hour 1, and at days 1, 3, 7, 21 and 45 of casting. All measurements were carried out by the same investigator, in a quiet, temperature-controlled room (22-24°C) after at least 30 minutes of rest in the supine position while the upper arm rests on the chest of the patient. Measurements were repeated for three times and mean values were calculated. Capillary filling time was assessed by applying pressure for five seconds to the finger pulp. Ordinarily the blood should return in two seconds or less; more time implies perfusion problems of the effected limb. 2-5 seconds of capillary filling time was considered as moderate disturbance while more than 5 seconds was considered as fair disturbance.

Severity of oedema was evaluated by measuring the circumference of all five fingers in both hands after one hour of casting and at control visits. Circumferential measurements were carried-out at the mid-level of the proximal phalanges with a steel tape to the nearest millimetre.[6] The two hands circumferential measurements were compared at a particular time and progressions were recorded. An increase of 0 to 15% in circumference of fingers was considered as mild, 16 to 30% as moderate, and more than 31% as severe oedema formation.

Groups were compared statistically by parametric and nonparametric tests. Mean, maximum and minimum values are presented. Differences between

groups and between the fractured and normal extremity were analyzed by the independent samples t test, Student's t test" and "Paired samples t test. SpO_2 change by time was evaluated with the "Independent samples t test. To evaluate the relations among the parameters, Pearson coefficients of correlation were calculated. Statistical calculations were performed with SPSS 13.0 (SPSS Inc., Chicago, IL., USA). A p value of <0.05 was considered significant.

RESULTS

Groups I and II were homogeneous with regard to age, gender, mechanism of injury, fracture type, fracture side, post reduction radiographs, union period and the follow-up period (p>0.05). Patient's demographic data are presented in Table I.

Table 1. Descriptive Data of the Patients.

Patients Characteristics		**GROUP I**	**GROUP II**
Age		*52 years (range, 18-64)*	*49 years (range, 21-65)*
Sex	Male	13	15
	Female	37	35
Fractured Side	Right	21	24
	Left	29	26
AO Classification	2.3.A	24	25
	2.3.B	11	8
	2.3.C	15	17

There was a decrease in SPO_2 values in the fractured extremity after injury and casting when compared to the normal extremity (p<0.01). The mean SpO_2 values were 94.3% and 97.1% in Group I and 94.1% and 97.2% in Group II, consecutively, in the fractured and normal extremities, respectively. Measured SpO_2 values of the patients are shown in Table II.

SpO_2 values increased with time in both groups. Increase in SpO_2 in Group II was earlier and more significant than in Group I (p<0.01). In Group II the mean SpO_2 was 97.3% on day 3, whereas the mean SpO_2 was 97.1% at day 21 in Group I (p<0.01). There was a significant difference in the SpO_2 values between the fractured and normal extremities until day 3 in Group II (p<0.05) whereas SpO_2 values remained significantly lower until day 21 in Group I (p<0.01). SpO_2 values of the fractured extremity between Group I and Group II remained significantly different on days 3 and 7 (p<0.01 and p<0.05).

Oedema occurred in six patients in week one (five in Group I and one in Group II). It was severe in two patients (one each in each groups) and mild in four patients (three in Group I and one in Group II). In five of these patients capillary circulation was poor until day 3.

Five patients (three in Group I and two in Group II) whose initial SpO_2 values were between 90% and 92% were followed up carefully. In the two patients of Group I who had SpO_2 values of 90% and 91%, short-arm casts were changed at days 7 and 8. These two patients had severe pain and oedema. Capillary circulation was initially poor in these patients. The circular cast was not changed in patients of Group II due to oedema.

Patients with oedema had lower (less than 95%) SpO_2 values in both groups. SpO_2 values decreased only without oedema formation. Thus, the SpO_2 decrease was parallel with the severity of oedema. Six patients with oedema had significantly lower SpO_2 values (p<0.01). SpO_2 values increased when oedema subsided.

In the MPFF group SpO_2 decrease and oedema formation was significantly (p<0.01) lower than that of the control group. There was no statistically significant correlation between SpO_2 values and age, gender or fracture side. Alteration in the SpO_2 values of both groups is presented in Figure 1.

Table 2. SpO_2 Values of the Patients.

Time of Measurement	NSAID Administered Control Group (Group I)		Micronised Purified Flavonoid Fraction Administered Group (Group II)	
	Fractured Extremity (%)	Normal Extremity (%)	Fractured Extremity (%)	Normal Extremity (%)
Hour One After Casting	94.3 (92-97) **	97.1 (94-99)	94.1 (92-98) **	97.2 (94-99)
Day 1	95.4 (90-98) **	97.3 (94-99)	96 (94-99) *	97.1 (95-98)
Day 3	96 (91-98) **	97.3 (95-99)	97.3 (94-98)	97.2 (95-99)
Day 7	96.7 (94-99) **	97.2 (95-99)	97.2 (94-98)	97.2 (95-99)
Day 21 (in short arm cast)	97.1 (94-99)	97.2 (94-99)	97.3 (95-99)	97.3 (95-99)
Day 45 (Without casting)	97.2 (95-99)	97.3 (95-99)	97.3 (95-99)	97.4 (95-99)

Statistical significance between the SpO_2 values of the fractured and unaffected arms. * P<0.05, ** P<0.01

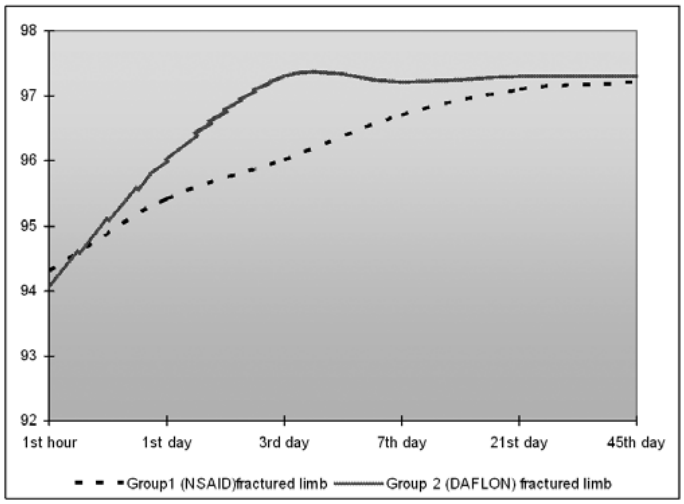

Figure 1. SpO_2 Values of the Patients.

MPFF was well tolerated by the patients. No allergic side effects were observed due to MPFF. Clinical acceptability was assessed as satisfactory by the patients and the investigators.

DISCUSSION

There are several reports on the effectiveness of MPFF in patients with haemorrhoids and venous insufficiency. Best to our knowledge, there is no report on the role of MPFF in oedema prevention and peripheral circulation restoration after extremity fractures. This is the first clinical report on the tolerability and efficacy of MPFF in peripheral capillary circulation insufficiency occurring after extremity fractures and circular casting.

In this study, MPFF reduced oedema after extremity fractures and circular casting. Micronised purified flavonoid fraction is beneficial in preventing oedema and circulatory problems.

Venous stasis and oedema interrupts the peripheral capillary circulation and increase morbidity after fractures and circular casting. By decreasing venous stasis and increasing capillary resistance, these complications may be prevented.

Flavonoids are known as having a large range of pharmacological applications, particularly in the field of microvascular disorders, where their involvement in capillary resistance and permeability has been well documented.[1] Flavonoids increase capillary resistance and inhibit oedema formation. MPFF prolongs the activity of noradrenalin on the venous wall and decreases venous capacitance, venous distensibility, venous emptying time, venostasis and oedema. Venous stasis reduces by increasing venous tone that leads to the improvement of venous return and a reduction in peripheral oedema after MPFF administration. In this study, in line with previous studies, oedema formation was lesser in the MPFF administered group.

MPFF is an oral phlebotropic and vascular protective agent consisting of 90% (450 mg) micronised diosmin and 10% (50 mg) flavonoid that improves venous tone and lymphatic drainage, reduces capillary hyper-permeability and oedema by protecting the microcirculation from inflammatory process and proptosis. Several studies demonstrated the favourable effects of MPFF on microcirculation.[2,8,1214]

This should result in the reduction of oedema in the fracture site and by this mechanism, circulatory complications of closed reduction and circular casting should be prevented. Our outcomes supported this

pretension. We had no need to change the casts in our patients treated by MPFF. In these patients oedema formation and SpO_2 decrease was significantly lower. Furthermore, patients who received MPFF increased their SpO_2 on the fractured extremity more rapidly when compare to the control.

Recent studies suggest MPFF has anti-inflammatory effects. Flavonoids counteract the biochemical mediators of inflammation such as PGE_2, PGF_2 and TXB_2. These lead to anti-oedema activity during the acute phase of inflammation.[5] Oedema formation was observed in six patients in this study; five in Group I and one in Group II. SpO_2 decrease was parallel to the oedema severity. These six patients with oedema had significantly lower SpO_2 values. In the present study, SpO_2 decrease was observed in the patients with oedema. SpO_2 decrease was not observed in the patient without oedema during follow-up. We did not change the circular cast in any patients in Group II due to oedema and SpO_2 decrease. The present study presented that MPFF reduced oedema and prevented SpO_2 decrease after distal radial fractures. Furthermore, MPFF increased SpO_2 values by reduction of capillary permeability and oedema.

MPFF also increases lymphatic flow and drainage which leads to a reduction in oedema. The lymphatic vessels play a physiological role in interstitial stasis in venous disease and fracture sites. The reduction in oedema occurs through an increase in lymphatic drainage and emptying of interstitial spaces. Increase of lymphatic flow and drainage may be beneficial in the prevention of oedema formation and in the prevention of SpO_2 decrease after fracture of distal radius. Parallel to this pretension in our study, increase in SpO_2 values in Group II was earlier and more significant than that in Group I.

Several indices of inflammation in microcirculation are reduced by MPFF. Daily administration of 1-4 tablets of MPFF 500 mg for 1-3 months had been efficient on venous oxymeter measurements in patients suffering from chronic venous insufficiency, venous ulcers and haemorrhoids (e.g. increases from baseline in O_2 pressure, O_2 saturation or pH and decreases from baseline in $C0_2$ pressure).[2] In the current study oral administration of MPFF increased oxygen pressure and saturation after distal radial fractures in cases treated by closed reduction and circular casting.

A number of events occur in the microcirculation involving extravasations of macromolecules and trapping of white blood cells, which initiate an inflammatory response releasing free radicals and other cytotoxic substances. These may eventually lead to interstitial oedema and morbidity after fractures. As previously reported, MPFF increases venous tone, improves lymphatic drainage, reduces capillary hyper-permeability and inhibits the activation of the leukocytes, extravasations of macromolecules, and releasing of free radicals and also certain pathways of the inflammatory response. With these properties, it could be suggested that this agent can also contribute to peripheral capillary circulation after extremity fractures and circular casting by reduction oedema formation, by improving capillary hyper-permeability and by protecting the microcirculation from inflammation. Better clinical results and SpO_2 values of our patients who received MPFF supported this affectation. The optimal dose of MPFF 500 mg per day was administrated to the patients in this study.

Oedema formation and the effect of oedema on peripheral circulation were evaluated with SpO2 values, finger diameter measurement and capillary filling time. Volumometric or impedanty measurements were not performed during this study. Measuring SpO_2 values, finger diameter and capillary filling time were simple, inexpensive and non-invasive.

In conclusion we believe that oedema formation disturbs peripheral capillary circulation and decreased SpO2 values after closed reduction and short-arm circular casting. Measurement of SpO_2 with pulse oximetry is simple and inexpensive to follow-up peripheral capillary circulation after circular casting. Furthermore, administration of MPFF is beneficial in preventing oedema formation after distal radial fractures.

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