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RESEARCH ARTICLE

The Role of Using Micronized Purified Flavonoid Fraction After Rubber Band Ligation in Hemorrhoidal Disease: A Retrospective Analysis

Hemoroidal Hastalıkta Lastik Band Ligasyonu Sonrası Mikronize Purifiye Flavonoid Fraksiyonu Kullanımının Rolü: Retrospektif Bir Analiz

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ABSTRACT

Aim: To investigate the effect of the addition of micronized purified flavonoid fraction (MPFF) on occurrence and severity of symptoms in patients who underwent rubber band ligation (RBL) for hemorrhoidal disease (HD).

Method: Patients who underwent RBL for HD in a single clinic in 2020 were retrospectively assessed. Patients aged ≥ eighteen years treated by a single surgeon for stage II and III internal HD with RBL and MPFF or RBL alone were included. The patients were divided into those who received combined therapy (RBL+MPFF) and those who only had RBL. The presence of bleeding, pain, and/or itching and occurrence of prolapse were recorded at the time of admission and on visit 1 (seventh post-operative day) and visit 2 (28th post-operative day). Complications arising from RBL were also recorded. All patients were asked to evaluate general anal area comfort with a visual analog scale at admission and each visit.

Results: The rate of bleeding on the first visit was significantly lower in the RBL+MPFF group compared to RBL alone ($p<0.05$). The proportion of patients with persistent pain and itching and prolapse tended to be lower in the RBL+MPFF group but the difference was not significant. Anal region comfort scores were significantly higher in the RBL+MPFF group at both visit 1 and 2 ($p<0.05$). The complication rate was lower in the RBL+MPFF group compared to the RBL only group, but this did not reach statistical significance ($p>0.05$).

Conclusion: Giiving MPFF to patients undergoing RBL provides earlier control of bleeding, the most common symptom. Combined therapy results in an improvement in general anal area comfort compared to RBL alone.

Keywords: Hemorrhoidal disease, anal bleeding, flavonoid, rubber band ligation

ÖZ

Amaç: Hemoroid hastalığı (HH) nedeni ile lastik band ligasyonu (LBL) uygulanan hastalarda tedaviye mikronize purifiye flavonoid fraksiyonu (MPFF) eklenmesinin, semptomlardaki düzelme üzerine etkisini araştırmaktır.

Yöntem: Kliniğimizde 2020 yılında HH nedeniyle LBL uygulanan hastalar retrospektif olarak tarandı. On sekiz yaş ve üzerinde, aynı cerrah tarafından, evre II ve III internal HH nedeniyle LBL+MPFF veya sadece LBL ile tedavi edilen hastalar çalışmaya dahil edildi. Hastalarda başvuru anında, 1. vizitte (7. gün) ve 2. vizitte (28. gün) kanama, ağrı, kaşıntı ve prolapsus şikayetlerinin varlığı sorgulandı. Ayrıca LBL komplikasyonları kaydedildi. Tüm hastalardan başvuru esnasında, 1. ve 2. vizitlerde genel anal bölge konforlarını bir visual anolog skala ile değerlendirmeleri istendi. Hastalar kombine tedavi alan ve sadece LBL uygulanan hastalar olarak iki gruba ayrıldı.

Bulgular: Kanamanın 1. vizitte devam etme oranı MPFF verilen grupta verilmeyen gruba göre anlamlı düzeyde düşük bulundu ($p<0,05$). Ağrı, kaşıntı ve prolapsus şikayetlerinin 1. vizitte devam etme oranları MPFF kullanılan grupta kullanılmayan gruba göre daha düşük oranlarda olmasına karşın bu gerileme anlamlı değildi ($p>0,05$). Birinci ve 2. vizitlerde anal bölge konfor skoru MPFF kullanan grupta kullanmayan gruba göre anlamlı olarak yüksekti ($p<0,05$). Komplikasyon oranı MPFF kullanılan grupta, kullanılmayan gruba göre düşüktü. Ancak istatistiksel anlamlılık yoktu ($p>0,05$).

Sonuç: LBL uygulanan hastalara MPFF eklenmesi, en sık semptom olan kanamanın daha erken kontrol altına alınmasını sağlar. Kombine tedavi uygulanması sadece LBL uygulanmasına göre genel anal bölge konforunda iyileşmeye neden olmaktadır.

Anahtar Kelimeler: Hemoroidal hastalık, anal kanama, flavonoid,lastik band ligasyonu

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Introduction

Hemorrhoidal disease (HD) is a common disease that results in 45% of the population consulting a physician at some point in their lives, with bleeding as the most important symptom.[1] The treatment of HD ranges from simple lifestyle changes to surgery. According to the guideline for the treatment of HD published by the European Society of Coloproctology (ESCP) in 2020, basic treatment is recommended first for all patients.[2] This basic treatment consists of toilet training, high fiber diet, and topical and pharmacological treatment. Pharmacological treatment includes phlebotonics that have been shown to improve symptoms in patients with HD. Phlebotonics may be natural, especially some flavonoids or synthetic such as calcium dobesilate. In the ESCP guideline, rubber band ligation (RBL) is recommended as the first choice in patients in whom basic therapy has failed, especially in the treatment of Stage II HD.

Phlebotonic therapy consisting of flavonoid preparations control the symptoms of HD.[3,4,5] Flavonoids decrease venous tone and capillary permeability and increase lymphatic drainage. They also control the symptoms of HD through anti-inflammatory effects.[6,7] Micronized purified fractionated flavonoid (MPFF) preparations are widely used.

RBL is at the forefront of non-surgical treatment methods for HD and has been shown to have the lowest recurrence rate and also to be safer than other non-surgical treatments, such as injection sclerotherapy or infrared coagulation.[8] RBL is the most commonly used non-surgical treatment method for HD by surgeons.[9] In the ESCP-2020 HD treatment guideline, RBL is the first treatment recommendation for all Stage II and selected stage III patients who do not respond to basic therapy.[2]

In the literature, studies on the combined use of RBL and MPFF preparations are very limited. The aim of this study was to investigate the effect of adding MPFF to the treatment of patients who underwent RBL for HD, on occurrence and severity of symptoms, especially bleeding.

Materials and Methods

Study Design

Ethical approval for this study was obtained from the local ethics committee and the Declaration of Helsinki of the World Medical Association regarding human materials and data was observed at all times. Written informed consent was obtained from all participants. All patients who underwent RBL for HD in our clinic in 2020 were retrospectively assessed. There were no criteria for adding or not adding MPFF to patients who underwent RBL. Consecutive patients in the first half of 2020 had MPFF added into their treatment protocol and constituted the RBL+MPFF group, whilst consecutive patients in the second half of 2020 only underwent RBL and were included in the RBL only group.

Participants and Eligibility Criteria

Patients aged 18 years or over who were treated by the same surgeon for stage II and III internal HD with during 2020 were included in the study. Exclusion criteria included: patients using anticoagulants or anti-aggregants; being treated with any other phlebotonic agent; pregnant women; lactating patients; patients with chronic liver disease, inflammatory bowel disease or a diagnosis of colorectal cancer; those who did not attend follow-up; and those who lacked follow-up information.

Treatment Protocol

RBL was performed in the proctology unit of our clinic. The procedure was performed 10 minutes after the application of a topical lidocaine preparation to the anal canal. After examination by anoscope, the stage II-III internal hemorrhoid packs were banded with a band ligation device. Up to three packs were banded in the same session. Care was taken to leave intact mucosa between the banded packs.

MPFF (Daflon 500 mg film tablet, Les Laboratoires Servier, CITY, France) was administered at a dose of 3 g/day for the first five days and then at a dose of 1 g/day for a total of 21 days after RBL application in patients attending clinic in the first half of 2020.

A non-steroidal anti-inflammatory drug (Naproxen sodium, Apranax 550 mg, Abdi İbrahim İlaç San. ve Tic. A.Ş., Istanbul, Turkey), a laxative (lactulose suspension 4 scales/day, Duphalac, Abbott Biologicals BV Veerweg 12, 8121 AA Olst/ The Netherlands) and a hot water sitz bath were suggested for all patients.

Follow up and Evaluation

The age and gender of all patients was recorded at presentation. In addition, at visit 1 (post-operative day 7) and visit 2 (post-operative day 28) persistence of bleeding, pain and itching and any occurrence of prolapse was also recorded. All patients were asked to evaluate their general anal comfort, taking into account bleeding, pain, itching and sagging on a visual analog scale where 1 represented the worst possible symptom and 10 represented no problem at all at each attendance day. In addition, complications due to RBL were also recorded. The patients included in the study were divided into 2 groups according to the treatment applied:

Group 1. RBL+MPFF

Group 2. RBL only.

The groups were compared statistically in terms of the presence of symptoms, overall anal comfort, and occurrence of complications at each time point.

Statistical analysis

Statistical Package for Social Sciences (SPSS), version 22.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Shapiro-Wilk test was used to check whether continuous variables were distributed normally. Student's t-test was used for comparison between groups with continuous variables. The Mann-Whitney U test was used for the comparison between the groups with the variables in which the ordinal or normality assumption could not be achieved. For comparisons between groups with categorical variables, $\chi 2$ test or Fisher's exact test was used, as appropriate.

Results

One hundred and five patients presented to the unit during the study period. Of these, 36 were excluded because they did not meet the inclusion criteria and thus 69 patients were assessed. The mean age of the participants was 40.25±14.5 years and 42 (60.8%) were male while 27 (39.2%) were female. All participants had bleeding complaints. The next most common complaint was anal pain in 44.9% (n=31) (see Table 1).

Thirty-seven (53.6%) of the participants were treated with MPFF after RBL (RBL+MPFF group), while the remaining 32 (46.4%) constituted the RBL only group. The distribution of symptoms at admission was similar in the groups (p>0.05). The frequency of persistent bleeding at visit 1 was found to be significantly lower in the RBL+MPFF group compared to the RBL only group (p<0.05). Although the frequency of reporting pain and/or pruritus and occurrence of prolapse at visit 1 were lower in the RBL+MPFF group than in the RBL only group, this difference was not significant. On assessment of the groups at the 2nd visit, the incidence of all symptoms was similar and no significant difference was detected (Table 2).

There was no significant difference in patient-reported anal region comfort scores at the time of admission. However, at the first and second visits, the anal region comfort score was significantly better in the RBL+MPFF group than in the RBL only group (p<0.05) (Table 3).

In this cohort, the overall complication rate due to RBL was 17.3%. The complication rate was 10.8% in the RBL+MPFF group and 25% in the RBL only group. The only post-procedural complication reported in the group receiving MPFF was pain whereas the RBL only group reported both pain and urinary retention. No serious bleeding or infection

Table 1. Demographic characteristics of the patients included in the study and those identified in the application

	All patients (n=69)
Average age (SD)	40.25±14.5
Male/female	42/27
Bleeding on application	69 (100%)
Pain on application	31 (44.9%)
Itching on application	8 (11.6%)
Prolapse in application	20 (29%)
Anal comfort in application	2.58±0.9

SD: Standard deviation

Table 2. Detection rates of symptoms at admission and scheduled controls. Statistical comparison of regression and regression in symptoms at follow-up

		RBL+MPFF (n=37)	LBL (n=32)	p
Bleeding	**Application**	37 (100%)	32 (100%)	1
	1st visit	2 (5.4%)	7 (21.9%)	0.044
	2nd visit	1 (2.7%)	1 (3.1%)	0.918
Pain	**Application**	12 (32.4%)	11 (34.4%)	0.865
	1st visit	1 (2.7%)	3 (9.4%)	0.240
	2nd visit	1 (2.7%)	1 (3.1%)	0.918
Itching	**Application**	6 (16.2%)	5 (15.6%)	0.95
	1st visit	1 (2.7%)	2 (6.3%)	0.47
	2nd visit	0	1 (3.1%)	0.28
Prolapse	**Application**	13 (35.1%)	12 (37.5%)	0.84
	1st visit	1 (2.7%)	2 (6.3%)	0.47
	2nd visit	0	1 (3.1%)	0.28

RBL+MPFF: Rubber band ligation+micronized purified flavonoid fraction

was observed in any patient. Patients with prolonged severe pain were treated with analgesics and a hot water sitz bath. Urinary catheter was inserted in two patients (6.25%) in the RBL only group who developed urinary retention due to globe vesicale. Urinary catheter was *in situ* for <12 hours in both patients and no additional treatment was required. The complication rate in the RBL+MPFF group was proportionally lower than in the RBL only group but this was not significant (Table 4).

Discussion

RBL is a widely used, non-surgical technique in the treatment of HD. MPFF is a phlebotonic agent used in the treatment of HD and is recommended by the guidelines. In daily surgical practice, some clinicians combine these two methods. However, the number of studies examining the combined use of these two methods is limited. In the present study, patients who underwent RBL were divided into two groups according to whether they were given MPFF after the procedure or not.

The most common age at presentation for HD is between 45-65 years of age and there is no difference between genders.[1] The mean age of the 69 patients included in the study was 40.25±14.5, and the male/female ratio was 1.56. The most common cause of hematochezia is HD and the most common symptom in HD is hematochezia.[1,10] All participants (100%) in this study had hematochezia.

RBL is the most effective outpatient treatment for HD when compared to other methods, such as injection sclerotherapy and infrared coagulation. However, pain is more common with RBL than with other methods.[11] In the ESCP HD treatment guideline published in 2020, it was recommended as the first treatment method in stage I-II and some stage III patients who did not respond to basic therapy.[2] With the use of MPFF, there is a rapid reduction in bleeding due to internal HD.[12] In the case of MPFF combined with RBL, bleeding is stopped earlier.[13] In the RBL only group, bleeding persisted in 21.9% at the 1st visit, and 3.1% at the 2nd visit. In contrast, in the RBL+MPFF group the rate of persistent bleeding was only 5.4% at visit 1 and 2.7% at visit 2. This reduction in bleeding at first visit was significantly lower in the RBL+MPFF compared to the RBL only group while there was no difference in frwequencies of bleedin in the two groups at the second visit.

Oral flavonoids belong to the group of phlebotonics but the mechanism of action of these agents is not clear. However, they are used in the treatment of HD, especially in Asia and Europe. Oral flavonoids have been reported to change vascular permeability and reduce tissue edema.[14] In a Cochrane analysis, phlebotonics (flavonoids and calcium dobesilate) were superior to the control group with regard to bleeding, itching, and anal incontinence (or contamination) in the treatment of HD.[3] In a study comparing calcium dobesilate and flavonoids, flavonoids were found to be more effective in controlling the symptoms of HH.[15] Caetano et al.[13] showed that adding MPFF as an adjuvant therapy in patients undergoing RBL significantly reduced bleeding in the first month and itching in the first week. Although we found a significant reduction in bleeding at visit 1 in the RBL+MPFF group there was no difference in reports of itching between the groups

Caetano et al.[13] highlighted the decrease in global symptom score after RBL in patients who did and did not receive MPFF as adjuvant therapy but that this decrease was more pronounced in the MPFF group. The patient-reported anal region comfort scores at both visitis in our cohort are

Table 3. The distribution and statistical comparison of the mean scores and standard deviations of the patients in the study for anal area comfort according to the groups in the planned controls

	RBL+MPFF	RBL	p
Application	2.76±1.06	2.38±0.6	0.12
1st visit	8±1.31	5.97±0.82	0.001
2nd visit	8.97±0.95	7.44±1.54	0.001

RBL+MPFF: Rubber band ligation+micronized purified flavonoid fraction

Table 4. Statistical comparison of RBL-related complications detected in the study and their incidence in groups

	RBL+MPFF	RBL	p
Complication		8 (25%)	
Severe pain	4 (10.8%)	6	0.12
Urinary retention	4	2	

RBL+MPFF: Rubber band ligation+micronized purified flavonoid fraction

consistent with the report of Caetano et al.[13]

The complication rate following RBL is reported to be 3-18.8%, and the most common complications are pain and bleeding.[16] In our study, the overall complication rate was at the higher end of this range at 17.3%. Post-RBL pain is the most common complication. Some studies report moderate pain in 25-50% of patients within the first 48 hours after RBL.[17,18] Pain may sometimes be associated with dizziness, nausea, chills, and urinary retention.[18] Patients who experience pain and other pain-related symptoms, such as urinary retention, syncope, dizziness, and nausea, that require the use of analgesics are less satisfied with RBL.[16] To prevent pain, it is recommended to test the tissue by holding it during RBL. If there is pain immediately after the procedure, the band should be removed.[19] To the best of our knowledge, there is no published study investigating the effect of adjunct MPFF therapy on complications after RBL treatment. In our study, the addition of MPFF to RBL treatment caused a decrease in the rate of reporting post-procedure pain. However, this reduction was not significant which may be due to the relatively small sample size, or time scale for pain assessment. Urinary retention is a known early complication after RBL. Therefore, it is unlikely that MPFF will have an effect on urinary retention. Larger, prospective studies investigating the effects of MPFF on RBL complication rates are needed.

Study Limitations

The most important limitation of our study was that there was no group treated with MPFF alone. Thus future studies should also include an MPFF only group in their design.

Conclusion

Adding dietary MPFF as an adjunct therapy to patients undergoing RBL provided earlier control of hematochezia, the most common symptom in HD, in this study. Similarly, patiets reported a reduction in pain associated with RBL. Use of combined RBL and post-procedure MPFF therapy after RBL had a positive effect on patient-reported anal region comfort. There is a need for larger, prospective studies investigating the effect of the use of MPFF in patients undergoing RBL for HD. These studies should include not only RBL only and RBL+MPFF groups, but also MPFF only groups in their design.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the local ethics committee and the Declaration of Helsinki of the World Medical Association regarding human materials and data was observed at all times.

Informed Consent: Written informed consent was obtained from all participants.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: G.Ş., Concept: G.Ş., Design: G.Ş., A.Ş., Data Collection or Processing: G.Ş., A.Ş., Analysis or Interpretation: G.Ş., A.Ş., Literature Search: G.Ş., A.Ş., Writing: G.Ş., A.Ş.

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