

Comparison of Flavonoids and Centella asiatica for the treatment of chronic anal fissure. A randomized clinical trial



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AIMS: We aim to test and compare the effects of Flavonoids (Fs) and Centella asiatica (Ca), and the traditional treatment to find out which best deals with healing time, bleeding and pain in the treatment of chronic Anal Fissure (AF).

Materials of Study: 98 outpatients were divided randomly into treated (either Fs or Ca) and control group. The control group (Group C, n=32) received the traditional treatment along with the other two subgroups which were treated, additionally, with Fs (Group A, n=30) or Ca (Group B, n=36). Patients were observed once weekly over 8 consecutive weeks.

RESULTS: The median time to stop bleeding in the group A was 1 week, in the Group B was 3 weeks and in the group C was 4 weeks. There were significant differences between Groups in terms of time to end bleeding (A vs B: p-value=0.022; A vs C: p-value<0.001; B vs C: p-value=0.070). As for pain score from baseline to the 2nd week were statistically different between Groups A and B on the one hand and Group C on the other hand (A vs C: p-value=0.004; B vs C: p-value 0.035). All patients healed within 8th week.

DISCUSSION: Either patients treated with Fs or Ca experienced early pain disappearance. Fs and Ca did not show side effects

CONCLUSIONS: The treatment with Fs is the most effective for bleeding. Patients additionally treated with either Fs or Ca experienced an earlier healing and disappearance of pain in comparison with patients underwent to the traditional treatment.

KEY WORDS: Anal bleeding, Anal fissure, Defecation pain

Introduction

Primary AF is a benign ulceration of the anal mucosa of elliptical shape and a few millimeters in length, usually located between the dentate line (pectinate line) and

the anal verge of the rectal canal back wall, which is more fragile due to the decussation of the sphincter fibers. Primary fissures are likely to be related to repetitive injury by hard stools, prolonged diarrhoea, or penetration. Secondary fissures could be found in patients with previous anal surgical procedures, inflammatory bowel disease (e.g. Crohn's disease), granulomatous diseases (e.g. tuberculosis, sarcoidosis), infections (e.g. HIV/AIDS, syphilis) or malignancy and require further investigation and multidisciplinary management. An acute lesion of the mucosa that fails to heal progresses into a chronic AF in 6-8 weeks². There are numerous therapies available for the treatment of chronic AF, both

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surgical ¹⁻⁶ and conservative ²⁻⁹. Among surgical options the lateral sphincterotomy showed a high success rate and a incontinence incidence up to 30% ². Aimed to reducing the resting sphincter hyper tone and improving the vascularity of mucosal layer, dilators ¹ and many preparations such as glyceryl trinitrate (GTN) ^{3,5}, nifedipine ^{2,3}, botulinum toxin ^{2,3}, diltiazem hydrochloride (DTZ) ^{2,4} were tested to obtain a temporary chemical sphincterotomy, antibiotics ²⁷. The properties and clinical use for both Fs and Ca (*over-the-counter* semi-essential nutrients *supplements*) were studied even if at the moment there is neither study on Fs nor on Ca in the AF medical therapy. Moreover there is not a direct comparison between Fs and Ca. The better known Fs are Diosmi ^{10,11,13}, Quercetin ¹², Rutin ¹⁴, and Troxerutin ¹⁵. Fs act on vascular resistance inhibiting formation of prostaglandins and thromboxanes, and endothelial adhesion molecules activation ¹¹ and strengthening capillaries wall reducing bleeding and hematomas ^{14,15}. Ca ¹⁶⁻²⁰ triterpenes act on microcirculation and on collagen type 1 synthesis accelerating the healing of many types of wounds by stimulation of reticuloendothelial system and production of fibronectin ¹⁹⁻²⁰. In this study, a comparative evaluation of both Fs and Ca was done to examine their efficacy in the management of chronic AF.

Materials and Methods

This prospective, randomized clinical trial was conducted on outpatients of Department "Paride Stefanini", University Hospital Umberto I, from June 2016 to March 2018. The study protocol was authorized by Sapienza University Ethics Committee and carried out according to the principles of the Helsinki Declaration and published online <http://clinicaltrials.gov/ct2/show/NCT03355846> Clinicaltrials.gov. *Inclusion criteria* were males and females 18 and older with chronic AF (a lesion of the anal mucosa that fails to heal in 6-8 weeks ²) having at least two of the following three criteria: (1) pain during and after defecation of more than 6 weeks duration, (2) the presence of a sentinel anal tag, and (3) visibility of the horizontal fibers of the internal anal sphincter in the base of lesion. *Exclusion criteria*: (1) acute AF, (2) specific local pathological conditions (Cohn's disease, anal cancer, tuberculosis), (3) presumed or confirmed pregnancy or lactation, (4) psychiatric and / or toxic employees, (5) allergy to Flavonoids or *Centella asiatica*, (6) cardiovascular and / or metabolic problems (decompensated diabetes, hypercholesterolemia), (7) thrombocytopenic patients or in treatment with oral anti-coagulants, (8) previous coloproctological surgery, anal stenosis; associated complications (abscess, fistula), (9) treatment (topical and / or systemic) with metronidazole ⁷⁻⁹, thyroid hormones, anticonvulsants, antidepressants, anticholinergics, antihistamines, statins ¹⁵⁻²⁰ and oral hypoglycemic agents ⁷⁻¹⁴, diuretics, steroidal anti-inflammato-

ry drugs, NSAIDs, antipyretics, antibiotics or antivirals for other reasons, (10) if the patient's personal clinical record does not have at least two controls. Characteristics of the population and subgroups by type of treatment are summarized in Table I. The first ninety-eight consecutive patients who satisfied at least two of the inclusion criteria and, having been informed regarding the treatment protocol, granted their informed consent were enrolled by the Principal Investigator MC) and then allocated according to a computer-generated randomization list either into in Group C (control group, n=32) or in the experimental group. The latter consists of two subgroups which received both the traditional treatment, and additionally, either Fs (Group A, n=30) or Ca (Group B, n=36). After the initial visit (and data collection) outpatients were checked once a week over 8 consecutive weeks. Data were collected by a questionnaire designed in the context of colorectal diseases prevention. Symptoms checked for at the beginning (D0) and over the following 8 weeks were: bleeding (Yes/No), anal pain during and after defecation, anal feeling of weight (Yes/No) and tenesmus (Yes/No) at every medical check point. Patients were interviewed about pain relief, healing of fissure and treatment side effects. Patients were given daily diary cards on which they were asked to report the worst pain experienced each day a on linear analog chart with a scale of 1 to 10 (Visual Analog Scale). Moreover they were asked about side effects (headache, blood pressure changes, anal irritation, allergic reactions), if any. Healing was defined as complete mucosa closure over the fissure, confirmed by anoscopy, and cessation of bleeding and pain. Patients who did not report any improvement of symptoms within 8 weeks, and patients who did not experience healing within 12 weeks (such as those intolerant to the conservative treatment) were offered surgical lateral sphincterotomy. The control patients in Group C received the traditional treatment (*e.g.* dilators, diet and hygienic care procedure) ^{1,6,9,25}. Patients in Group A were treated with both the traditional treatment and oral administration of Fs (300 mg Fs tablets twice per day before lunch and dinner for 15 consecutive days), and topical administration of 3 gr of Fs ointment inside the anus (once per day after hygienic procedure). Finally, patients in Group B received together with the tradi-

TABLE I - Baseline characteristics of the population and groups by type of treatment

	Total	Group A(Fs)	Group B(Ca)	Group C(Control)
N	98	30 (30.6%)	36 (36.7%)	32 (32.7%)
Sex (Male)	58 (59.8%)	13 (43.3%)	26 (72.2%)	19 (59.4%)
Age (18-85)	48.0 (14.9)	47.9 (15.4)	49.2 (14.4)	46.6 (15.5)
BMI	25.6 (4.4)	24.4 (3.5)	26.3 (4.8)	26.1 (4.6)

tional treatment oral administration of Ca (i.e. 60 mg tablets twice per day before lunch and dinner for 15 consecutive days) and topical administration of 3 gr of Ca ointment inside the anus (once per day after hygienic procedure). As for dilators^{1,7,8} treatment was limited to the first four weeks. As for *diet* and *hygienic procedure* continued over the full 8 week period. The *diet regimen* aims to obtain soft stools and a permanent modification of patients eating habits²⁵. The recommended regimen (rich in water and boiled vegetables^{22,23,25} free of seasonings, spice²¹, alcohol and chocolate was spread over 5 meals each day, according to the principles of Recommended Daily Allowance²⁵ enlightens the relationship between constipation and anorectal disorders such as acute, chronic AF and recurrence. We asked patients to record daily food intake and when stools change in the consistency to be recorded diary and show at the medical check. For their *Hygienic procedure* patients were advised to avoid to use toilet paper, and wash the anal region with lukewarm water and a medicated soap instead. After washing, the anal area should be pat-dried with a soft cotton towel by dabbing gently, avoiding any rubbing of the area⁷. *Statistical method* the allocations were performed by a computer-generated randomization table. The questionnaire data, collected verbally from the outpatients (by the PI MC), were later digitalized (by GAC, AIC and GC). Independent statistician (DAF) carried out statistical elaborations with the R software, version 3.3.3²⁴. The primary endpoint to be measured in

this trial was the time to healing within the 8 weeks of the study. The probability of achieving healing (bleeding) in the three groups was estimated using the Kaplan-Meier method. Log-rank test with post-hoc analysis performed by Bonferroni method was used to compare the curves. The proportional hazards assumption was verified using scaled Schoenfeld residuals. The disappearance of pain was set as a secondary endpoint. The Kruskal-Wallis test was used to evaluate changes in VAS scores (pain) after 2 weeks by treatment assignment and multiple comparisons between paired subgroups were assessed with the Nemenyi test. The statistical level of significance was set at 0.05. *Efficacy* evaluation, in terms of absence of bleeding and pain were also studied⁷⁻⁹. We evaluated the therapeutic effects of Flavonoids (*Fs*) and Centella asiatic (*Ca*) extracts in comparison with each other and with the control group as for pain and bleeding.

Results

COMPARISON OF FS, CA, AND CONTROLS ON CLINICAL EFFECTS

All the 98 patients affected by chronic AF were also affected by chronically constipation and 85 (86.7%) of them presented bleeding at baseline (29 in Group A, 28 in Group B and 28 in Group C). The Kaplan-Meier curves for time to bleeding healing are shown in Fig. 1. All patients stopped bleeding within 7 weeks after start

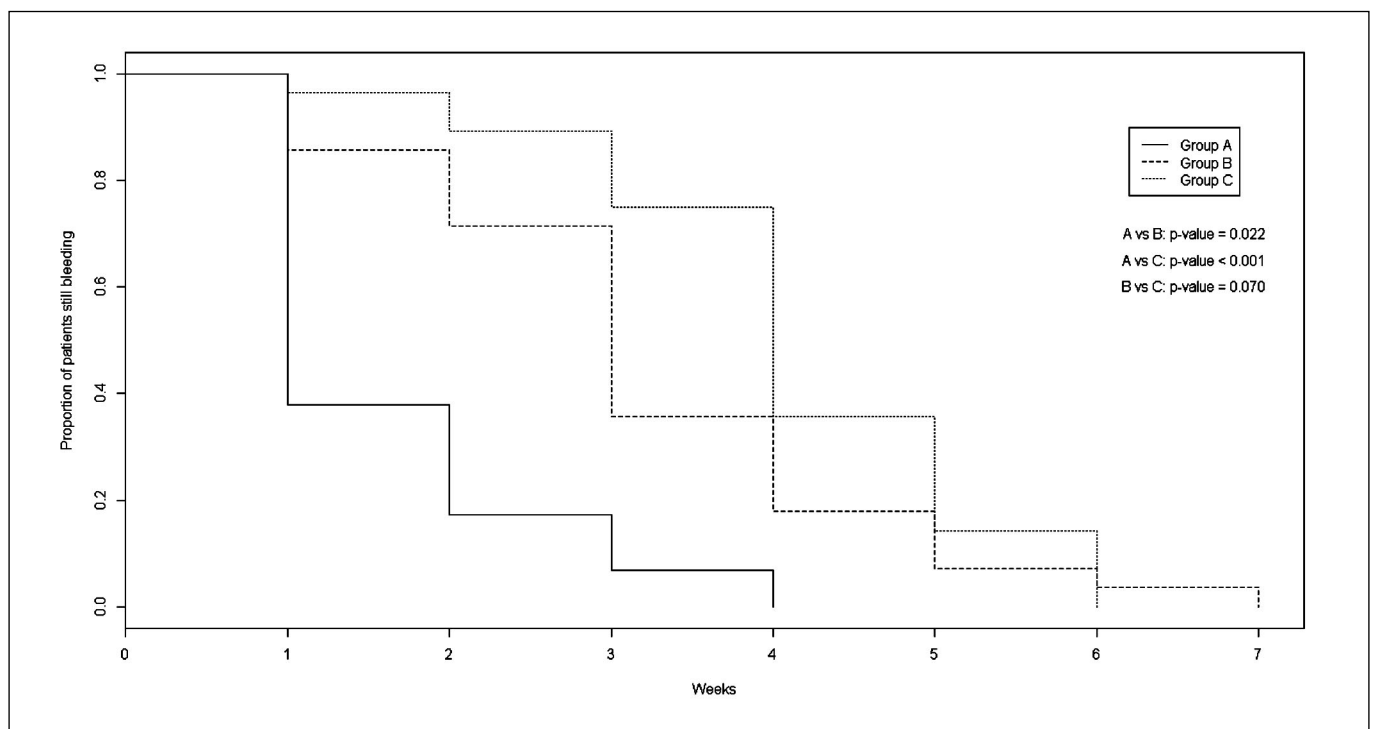


Fig. 1: The Kaplan-Meier curves for time to bleeding stop. At the baseline 96.7% in Group A, 77.8% in Group B and 87.8% in Group C presented bleeding respectively. The median time to stop bleeding in the Group A was 1 week, Group B was 3 weeks and Group C 4 weeks (p-value<0.001).

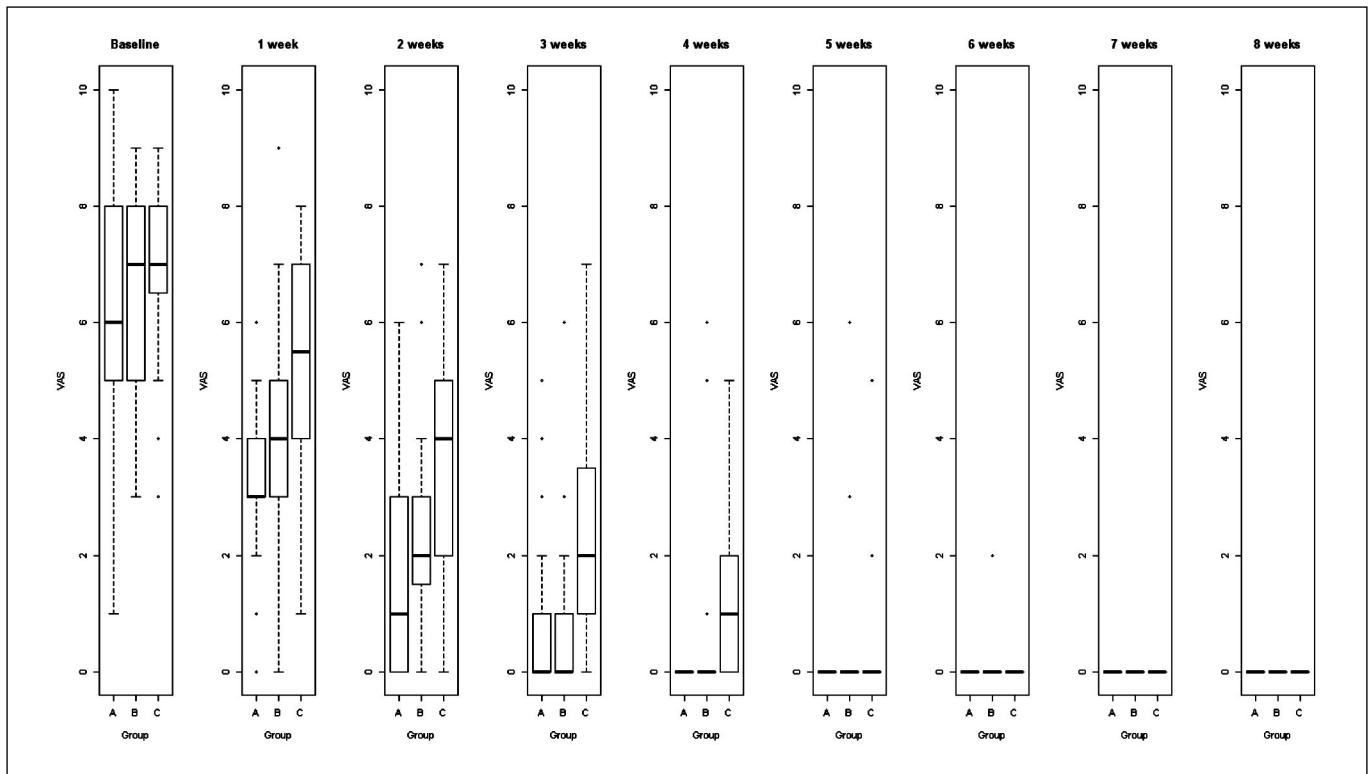


Fig. 2: Summary of the VAS scores (for pain evaluation) for each check point. Evaluating the change of VAS score from baseline to the 2nd week, the Nemenyi test showed differences between Group A and B with the control group (A vs C: p -value=0.004; B vs C: p -value 0.035), while between Group A and Group B p -value=0.665.

of treatment. The median time to stop bleeding in the Group A was 1 week (95% CI 1-4 weeks), in the Group B was 3 weeks (95% CI 2-3 weeks) and in the Group C was 4 weeks (95% CI 4-5 weeks). As for the bleeding the long rank test detected a statistical difference between the curves (p -value<0.001). Post-hoc analysis showed that there were significant differences between Group A and the other two groups, while there was no significant difference between Group B and Group C. (A vs B: p -value=0.022; A vs C: p -value<0.001; B vs C: p -value=0.070). As for pain the summary of the VAS scores for each time point and subgroup was showed in Fig. 2. Evaluating the change of VAS score from baseline to the 2nd week, the Nemenyi test showed statistically differences between the two treated groups with the control group (A vs C: p -value=0.004; B vs C: p -value 0.035), while there was no significant difference between Group A and Group B (p -value=0.665). As for weight sensation and tenesmus no statistical differences were found. *Healing* all patients obtained complete mucosal closure over the fissure, no patients required sphincterotomy^{1,2,6}.

Discussion

Sanei et al. referred that in their randomized clinical trial in the comparison of GTN with DTZ, 33.3% and

45.1% of their patients respectively, underwent sphincterotomy². Brady et al. evaluated the characteristics and outcomes of patients who received either Botulinum toxin, (BT) or lateral internal sphincterotomy (LIS)²⁶ comparing anal fissure treated with temporary chemical denervation (BT) instead of sphincterotomy (LIS) due to concerns for long-term incontinence as measured with Cleveland Clinic Fecal Incontinence (CCFI) score. Fissure recurrence was significantly higher for BT than LIS patients. Both LIS and BT patients had some durable changes in continence raising the question of whether there is a safe technique. In our own randomized clinical trial complete mucosal closure over the fissure, the stop of bleeding, and disappearance of defecation pain in all patients were obtained, earlier in Groups A and B compared to Group C. No patients required sphincterotomy^{1,2,6,26} and incontinence was not. Bhardwaj showed GTN³ to be as effective as diltiazem hydrochloride in producing a temporary chemical sphincterotomy with healing rates that Sajid indicates as ranging from 30-46%⁵ to 83-86%^{2,4}. On the other hand 80% of patients treated with GTN experienced headache during the treatment and DTZ showed fewer side effects². Similarly to our own preliminary research⁷, Fs and Ca did not show side effects in this clinical trial. DTZ²⁻⁶, GTN²⁻⁶ and botulinum toxin showed temporary incontinence of flatus of 18% and temporary incontinence of stools of

5% respectively ^{2-6,26,28}. Adverse reactions neither at Fs nor at Ca in the present trial were observed. Treatment limited to hygienic care routine was demonstrated not to be effective by itself. Constipation plays a significant role in AF management ^{22,23,25,29}. The treatment of AF requires first of all overcoming constipation or diarrhea with a specific diet, that gives the patients an appropriate provision of fibers and cellulose ^{7,9,22,23,25}, without contents irritating the mucosa ²³, aimed to obtain stable modification of the patient's eating behavior ^{3,6,8,9,22,23,25}. Our advice to patients is to avoid capsaicin alkaloid (8-metil-N-vanillil-6 nonenamide or C₁₈H₂₇NO₃) contained in hot and red pepper. Altomare and other Authors state the contrary, hence debate on this particular issue is still open ^{17,23}. In cases of patients affected by diverticulosis, soluble vegetable fibers (SVF) could be administrated in the early treatment for their viscous or gelling agents in liquid foods supplementation. SVF modulate feeling of satiety acting on enteric hormones ^{22,25}. The total calories intake per day ²²⁻²⁷ were according to RDA (Recommended Daily Allowance, intake levels of energy and nutrients for the Italian population) ²⁵. This dietary regimen resolves the constipation among 3rd and 8th week and could encourage a permanent modification of dietary habits as well as anal trauma reduction ²⁶⁻²⁸. These recommendations are based on moderate quality evidence 1B ²⁹. A favorable synergistic effect of all protocol components (*e.g.* dilators, dietary regimen, and hygienic procedure) reduces by itself bleeding and pain (Group C). The precocious healing of pain and bleeding together with the overcoming of stubborn constipation may prevent more invasive treatment ^{1,3-6,8,9,26}. As for *bleeding*, treatment with Fs ⁷⁻¹⁴ leads to its early disappearance with a remarkably rapid improvement in patient's quality of life. The median time to bleeding cessation in the Group A was 1 week. Fs seemed to be the most effective treatment on AF bleeding ⁷⁻¹⁴. As for *pain*, we observed statistical differences between Group A and Group B (from baseline to the 2nd week) on one hand, and the Group C on the other hand in terms of changes of VAS score. These results highlight that both Fs and Ca are effective on pain treatment. Group A ⁷⁻¹⁴ shows a nearly complete disappearance of bleeding already by the end of 1st week. Group B ¹⁵⁻²⁰ showed a significant difference in comparison with traditional treatment but lower than Group A. Fs and Ca seem to reduce bleeding and pain healing times compared to traditional treatment. We did not detect significant differences on weight sensation and tenesmus sensation with either Fs or Ca. Our results confirm that the hypertonus of the anal sphincter is a consequence of anal pain and irritation-infection ^{1,2,27}. Boyle ¹⁴ attributes to *Rutin* the property of strengthening the wall of capillaries as well as observed, reducing bleeding and lymphedema and inflammation ¹⁰⁻¹⁴. As for *effectiveness* in terms of *healing* and safety, on one hand all patients healed, within the end of 1st week (Group A), 3rd week (Group B) and 4th

week (Group C), an improved result compared to other Authors ^{2-5,26-28}. On the other hand no adverse reactions were observed in patients treated with Fs ¹⁰⁻¹⁵ nor in patients treated with Ca ¹⁶⁻²⁰, probably thanks to the great attention paid to exclusion criteria. Cho deposition ¹² documented that Fs ⁷⁻¹⁵ and Ca ¹⁶⁻²⁰ stimulate the synthesis of collagen type 1, the production and accumulation of new extracellular matrix improving vascular-connective tissue deposition, accelerating the repair processes of the tissue damage, reducing vascular ectasia and lymphedema. Last but not least both Fs and Ca are effective on microbial and leucocytes enzymatic hydrolysis inhibition that occurs during infection and inflammation respectively, shielding the collagen ^{7-20,27}. There are a number of *limitations* to our study. The majority of patients affected by AF recovered within the 4th week. Clinical data from 5th to 8th week were also considered. All cases were closed within 7th week. A telephone survey has not yet been carried out to evaluate the incidence of long-term recurrence and patients' satisfaction at 1 and 2 years. We hope to be able to report on these items in a forthcoming study

Conclusions

The purpose of the study is identify the most effective treatment, in terms of shorter time for disappearance of pain at evacuation and cessation of bleeding in patients affected by chronic anal fissure (AF). As for *bleeding* patients treated with Fs stop bleeding after the 1st week of treatment. A combined therapy with dilators, diet and hygienic protocol showed useful on bleeding and pain, especially with the adjunctive either Fs or Ca. As for VAS score and *pain*, from baseline to the 2nd week, statistical differences between Groups A and B compared to the Control group were detect. Fs and Ca resulted equally effective on pain. As for weight sensation and tenesmus no significant difference were found. In our opinion, avoiding capsaicin alkaloids, as well as alcoholic drinks is advisable. In the case of a suspected secondary AF, invasive therapies should be postponed or avoided in relation to the findings of second level investigations with a multidisciplinary management.

Riassunto

OBIETTIVO: Il presente studio longitudinale randomizzato si è proposto di valutare comparativamente l'efficacia dell'impiego di Flavonoidi (Fs) e di estratti di Centella asiatica (Ca) studiando il tempo di scomparsa del sanguinamento, dolore, sensazione di peso e tenesmo, in pazienti affetti da ragade anale cronica (RA).

MATERIALE DELLO STUDIO: 98 pazienti ambulatoriali sono stati divisi in 2 bracci: trattati (Gruppo A e Gruppo B) e controlli (Gruppo C). Tutti i pazienti ambulatoriali

partecipanti hanno ricevuto lo stesso trattamento tradizionale consistente in dieta specifica, dilatatori anali, e cure igieniche. Utilizzando una tavola di randomizzazione parte dei pazienti è stata collocata nel Gruppo C (n = 32). I pazienti assegnati al Gruppo A (n = 30) hanno ricevuto aggiuntivamente anche Fs e quelli allocati nel Gruppo B (n = 36) hanno ricevuto aggiuntivamente Ca. Tutti i pazienti ambulatoriali hanno eseguito il trattamento con dilatatori per le prime 4 settimane e sono stati ricontrollati settimanalmente per 8 settimane consecutive, tutti sono guariti entro la settima settimana. La dieta consigliata è ricca di fibra alimentare cotta per bollitura (fino a 500 grammi al giorno e 4 frutti), acqua non gassata (fino a 2000 cc al giorno) e priva di sale da cucina, spezie, piccanti, alcolici e cioccolato. La procedura igienica consiste nell'uso di un sapone medicato, asciugatura del perineo per tamponamento, senza stropicciare, evitando l'uso della carta igienica.

RISULTATI: Il tempo medio di scomparsa del sanguinamento durante defecazione nel Gruppo A è stato di 1 settimana (IC 95% 1-4 settimane), nel gruppo B è stato di 3 settimane (IC 95% 2-3 settimane) e nel gruppo C è stato di 4 settimane (IC 95% 4-5 settimane). Il comportamento della VAS è stato studiato per la valutazione del dolore defecatorio dalla rilevazione basale e alla 2^a settimana, risultando differenze statisticamente significative nei tre sottogruppi (A vs C: valore p-value = 0,004; B vs C: valore p-value = 0,035, ma non A vs B p-value=0.665 perché entrabi ugualmente efficaci). Per quanto riguarda la sensazione di peso e il tenesmo non sono emerse differenze significative tra i sottogruppi.

DISCUSSIONE: Questo studio evidenzia che il trattamento tradizionale per la RA (Gruppo C) non è efficace quanto il trattamento sinergico combinato con Fs (Gruppo A) oppure Ca (Gruppo B). I pazienti ambulatoriali dei sottogruppi Fs e Ca hanno avuto, infatti, una precoce scomparsa del sanguinamento e del dolore defecatorio ottenendo un rapido e notevole miglioramento della loro qualità di vita.

CONCLUSIONI: Nel trattamento della RA cronica è importante il superamento della costipazione. Il protocollo tradizionale con regime dietetico, dilatatori, e procedura igienica è efficace nel ridurre il sanguinamento e il dolore (Gruppo C) ma nei pazienti che hanno ricevuto la supplementazione con Fs (Gruppo A) oppure Ca (Gruppo B) abbiamo osservato una efficace azione sul dolore con la scomparsa in tempi significativamente più brevi ed un rapido recupero della qualità della vita. I Fs sono risultati più efficaci nel trattamento del sanguinamento.

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