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EFFECTIVENESS OF PROCTEN® CREAM IN THE TREATMENT OF ANAL FISSURES

Introduction

Anal fissures are linear or oval ulcerations located below the dentate line and extending to the anal margin (as described by Lockhart and Mummery in 1934), involving the posterior anal commissure in 80% of cases, the anterior one in 10% of cases and other sites in the remaining 10% of patients. The anal fissures incidence, in according with the literature, is variable between the 11% and the 19% of the population.

The physiopathogenesis of primitive anal fissures is considerable multifactorial. According to the recent and accredited studies, the main cause, in the determinism of anal fissures, it would appear to be related to the basal tone of the internal sphincter muscle. The NO has been proven to be the main transmitter of the internal sphincter (Bhardwaj, Vezy-Gut 2000).

Lund JN showed that the nitric oxide synthetase deficiency in the internal sphincter muscle fibres associates to a higher incidence of anal fissures (Nitric Oxide deficiency in the internal anal sphincter of patients with chronic anal fissure, Colorectal Dis. 2006)

Until a few years ago, the only therapeutic option for anal fissures was surgery. In the last few years, the efforts of the pharmaceuticals industry allowed to enrich its own therapeutic paraphernalia to colon proctologist surgeon, towards anal fissures, of topical products, which with a different action mechanism, lead to healing of little more of 80% of primitive anal fissures (Canero et all. International Surgery Journal, 2018). Nowadays, it does not exist guidelines universally recognized as the "Gold Standard" in the treatment of anal fissures.

Aim of the study

The aim of our study is to check the effectiveness of PROCTEN® CREAM with Ozoile® in the treatment of primitive chronic anal fissures.

We undertook a first study 18 months ago to evaluate the effectiveness of PROCTEN® CREAM, in the treatment of primitive chronic anal fissures (according to Lyndsay classification).

The scientific rationale for the study was based on the composition of the (Ozoile®, cera alba, arginine, ribes nigrum, hyaluronic acid, glycyrrhetinic acid, melaleuca alternifolia Leaf oil etc).

In particular, the formulation claims the association of Ozoile® with Cera alba to form a protective natural barrier.

Ozoile® (stable Ozonides) is an exclusive pool of molecules obtained by a patented process, in which the ozone binds to olefinic bonds of organic olive oil forming the stable Ozonides.

In Literature there are molecular biology studies which put in evidence the anti-inflammatory, regenerating and repairing tissues action of Ozoile® even in comparison with Corticosteroids. In particular, the following is evident:

Ozoile® presents anti-inflammatory action through the COX-2 inhibition and the pro-inflammatory (TNF-α, IL 1β, IFN-γ) and anti-inflammatory (IL-13) cytokines expression modulation, contrasting pain, redness, itching, burning, swelling, degenerative process, radiation damages.

Ozoile® promotes the tissue regeneration because it regulates the proteins and enzymes transcription related to structural and morphological tissue alterations such as TG2 and NOS; in case of hypoxia, it increases the HIF-1α factor transcription responsible for the cellular resistance towards the oxygen deficiency, promotes the neovascularization increasing the VEGF transcription and contributes to a right and appropriate re-epithelialization positively regulating E-Cadherin transcription, responsible for the right adhesion between the forming neocells.

Ozoile® presents microbicidal action as broad spectrum for the high affinity towards the lipoproteic components of the bacterial and fungal wall and for the oxidative action of Bioperoxides.

In PROCTEN® CREAM, Ozoile® is associated, in addition to Cera Alba, also with other components already mentioned, of which the main functions are widely known. This preparation represents the unmissable opportunity to include in a single product for topical use all the researched properties in the treatment of the pathophysiology sequelae triggered by the conditions that generate the onset and the becoming chronic of the primitive anal fissures.

Materials and methods

85 patients suffering from primitive anal fissure were enrolled in the study. Average age of 44 (range 16-56), of which 51 males and 34 females. The patients enrolled in the study belonged to a homogeneous physiopathological and anatomopathological class. Patients with concomitant anorectal diseases were excluded from the study, with comorbidity such as to result in significant study loss, or already subjected to surgical treatments or previous pharmacological therapies in the previous three months.

All the patients are subjected to treatment with PROCTEN® CREAM twice a day for 45 days with a total posology of 80 ml in the reporting period.

The effectiveness has been evaluated at 20 and 45 days, at 3 and at 6 months starting from the treatment. The following parameters have been taken in:
clinical evidence, symptoms described by the patient such as tenesmus, pain (evaluate with Vas scale), burning, manometric feedback (made before and after the treatment).

Results

In consideration of the multifocality of the parameters taken into consideration in the study, it was decided to administer to enrolled patients, before the treatment, at 20 and at 45 days, a dedicated questionnaire and Vas. 6-months follow up was also performed, with the purpose to observe the stability of healing in the middle term.

Clinical evidence

Twenty days after treatment, 18 patients (21,2%) were found to have evidence of advanced anal fissure healing.
In 59 patients (69,4%) the healing of anal fissure was found.
In the remaining 7 patients (8,2%) there were still no satisfactory clinical results, although in this cluster of patients almost all reported a reduction in symptoms prior to treatment. Only in 1 patient (1,2%) improvement was not observed.
Clinical evidence 45 days after treatment shows that patients with an advanced healing lesion increased to 8 (9,4%). Patients clinically healed were 73 (85,9%). Only 4 patients (4,7%) had not found benefit on the anal fissure but they reported symptoms improvement.

- **Symptomatology**

a) Tenesmus

A reduction in tenesmus was observed in 5 patients 20 days after treatment (5.9%), the disappearance of tenesmus in 75 patients (88,2%), while there was no significant reduction in tenesmus in 5 patients (5,9%).
At 45 days from the treatment, instead, the tenesmus had disappeared in 76 patients (89.4%), reduced but still present in 5 patients (5.8%), on the other hand 4 patients (4.7%) did not significantly report improvement of the tenesmus after the treatment with PROCTEN® CREAM.

b) Pain

At 20 days after the treatment, 69 patients reported no painful symptoms, or the presence of mild symptoms described ad manageable without the need to take drugs (“0” and “2” according to Vas Scale).

For 9 patients (10.6%) the painful symptoms were significantly improved but still worthy of attention (Vas 4 Scale).
Only for 7 patients (8,2%) the painful symptoms were not significantly improved (Vas 6 Scale).
At 45 days from the treatment, 71 patients (83,5%) reported Vas "0" Scale; 9 patients (10,5%) described a strong improvement of the painful symptoms enumerating the Vas Scale at "2". Only 1 patient (1,12%) did not report a significant improvement in the symptoms.

- **Manometric feedback**

The study of anorectal manometric performed routinely in all patients enrolled in the study have shown a global improvement of the pressure of the anal channel at rest before the treatment (reference range 45-105 mmHg; range found (92-129 mmHg).
This date confirms what already reported in the literature, that is an anal pressure at rest > 90 mmHg is associated with the onset of anal fissures (Lestar et all. Int.J. Colorectal Dis 1898).
In our study, at 20 days from the treatment the endoanal pressure at rest presented a range of 69-111 mmHg; the date further improved at 45 days from the treatment exhibiting a range of 61-108 mmHg.

6-months Follow-up

A lot of studies presented in Literature described the encouraging results in the conservative treatment of anal fissures. However, few studies take in consideration the stability of the result during the time, not having middle and long term follow up. At the moment, there are not dates regarding to the possibility of resurgences or relapses of anal fissure in the patients already treated with success, with local conservative medical therapy in the middle and long term on the treatment.
In our study, we decided to introduce this specific valuation to understand well if the effectiveness of the product, that we tested, can determinate the total healing of anal fissure. This study analyses the presence of resurgences symptoms at 6 months to the end of the treatment or the relapse of the disease.
In our opinion, the follow up has to be further extended at least 12 months from the end of the treatment, eventually adding variables such as "maintenance therapy".
In this experience, it is demonstrated that in the 73 patients clinically healed, only 3 patients (4,1%) presented resurgence (sporadic) of the symptoms, moreover, reported as mild intensity one and not deserving of pharmacological support. While only 1 of them (1.3%) presented anal fissure again.

Discussion about the results

From our study, it is shown that in 20 days of treatment with PROCTEN® CREAM at total dosage of 40 ml in two daily administrations in patients affected by primitive chronic anal fissure, the clinic healing of anal fissure was observed in the 69,4% of the patients.

Continuing the treatment until 45 days, the healing rate rise significantly to 85,9%.

The results about the symptoms, instead, does not reveal substantial differences at 20 and at 45 days from the treatment (tenesmus: respectively 88,2% vs 89,4%; pain: respectively 81,1% vs 83,5%), this means that there is a faster effectiveness of PROCTEN® CREAM on the symptoms (peak within 20 days), respect to the complete healing (peak after 45 days of therapy). The manometric evaluation after six months of treatment, attests a range of 62-112 mmHg demonstrating that the effectiveness on the sphincter tone is stable in the next months after the treatment (61-108 mmHg at the end of a 45-days treatment). This date well connects with the follow up evidence at six months, which underlines as the obtained results are stable during the time in the 95,7% of patients.

Conclusions

In our experience, it is demonstrated that PROCTEN® CREAM is easily handy product, well tolerated and without side effects, able to determinate the complete and definitive healing of the primitive chronic anal fissure in the 85.9% of the treated patients, the resolution of the symptomatology range in almost all the patients.

Considering the obtained results, it is recommended to prescribe 45 days of treatment because not all patients presented an early favourable response to the treatment. The healing, once obtained, is stable and definitive at six months in the 95,7%.

Bibliography:

1. Tiziana Russo, Monica Currò, Nadia Ferlazzo, Daniela Caccamo, Patrizia Perrone, Salvatore Arena, Enrica Antonelli, Pietro Antonuccio, Riccardo Ientile, Carmelo Romeo, Pietro Impellizzeri. **Stable Ozonides with Vitamin E Acetate versus Corticosteroid in the Treatment of Lichen Sclerosus in Foreskin: Evaluation of Effects on Inflammation**. Urol Int, April 16 2019

2. Domenico Di Maria, **New therapeutic approach with Ozoile® to the EAC eczema, a chronic and annoying pathology**. Journal of Otolaryngology-ENT Research Volume 12 Issue 1 Published January 22, 2019

3. Monica Currò, Tiziana Russo, Nadia Ferlazzo , Daniela Caccamo, Pietro Antonuccio, Salvatore Arena, Saveria Parisi, Patrizia Perrone, Riccardo Ientile, Carmelo Romeo and Pietro Impellizzeri. **Anti-Inflammatory and Tissue Regenerative Effects of Topical Treatment with Ozonated Olive Oil/Vitamin E Acetate in Balanitis Xerotica Obliterans**. Molecules 2018, 23,645, 13 Marzo 2018

4. Zanardi, S. Burgassi, E. Paccagnini, M. Gentile, V. Bocci, and V. Travagli, **What Is the Best Strategy for Enhancing the Effects of Topically Applied Ozonated Oils in Cutaneous Infections?** Biomed Res Int. 2013 Oct 27

5. Nathália R. de Almeida, Adilson Beatriz, Ana Camila Micheletti and Eduardo J. De Arruda, **Ozonized vegetable oils and therapeutic properties: A review**. Orbital, The Electronic Journal Of Chemistry, Volume 4, Number 4, October-December 2012

6. Kim HS, Noh SU, Han YW, Kim KM, Kang H, Kim HO, Park YM.**Therapeutic effects of topical application of ozone on acute cutaneous wound healing.** J Korean Med Sci, 12 June 2009
7. V. Travagli, I. Zanardi, V. Bocci, **Topical applications of ozone and ozonated oils as anti-infective agents: an insight into the patent claims**. Recent Patents on Anti-Infective Drug Discovery, Volume 4, Number 2, June 2009, pp. 130-142(13)

8. J Korean Med Sci, 12 June 2009 N. Geweely. **Antifungal Activity of ozonized olive oil**. Int. J. Agri. Boil., Vol.8, No. 5, 2006

9. Koichi Tamoto, Akironi Yamazaki, Hiromi Nochi, Toshiaki Miura. **Ozonides of olive oil methyl oleate inhibit the expression of cyclooxygenase -2 through the suppression of IkB/NFkB-dependent pathway in lipopolysaccharide-stimulated macrophage-like THP-1 cells**. IOA17th World Ozone Congress- Strasbourg 2005

10. L.A. Sechi, I. Lezcano, N. Nunez, M. Espim, I. Duprè, A. Pinna, P. Molicotti,G. Fadda and S. Zanetti. **Antibacterial activity of ozonized sunflower oil**. Journal of Applied Microbiology 2001, 90, 279±284.

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