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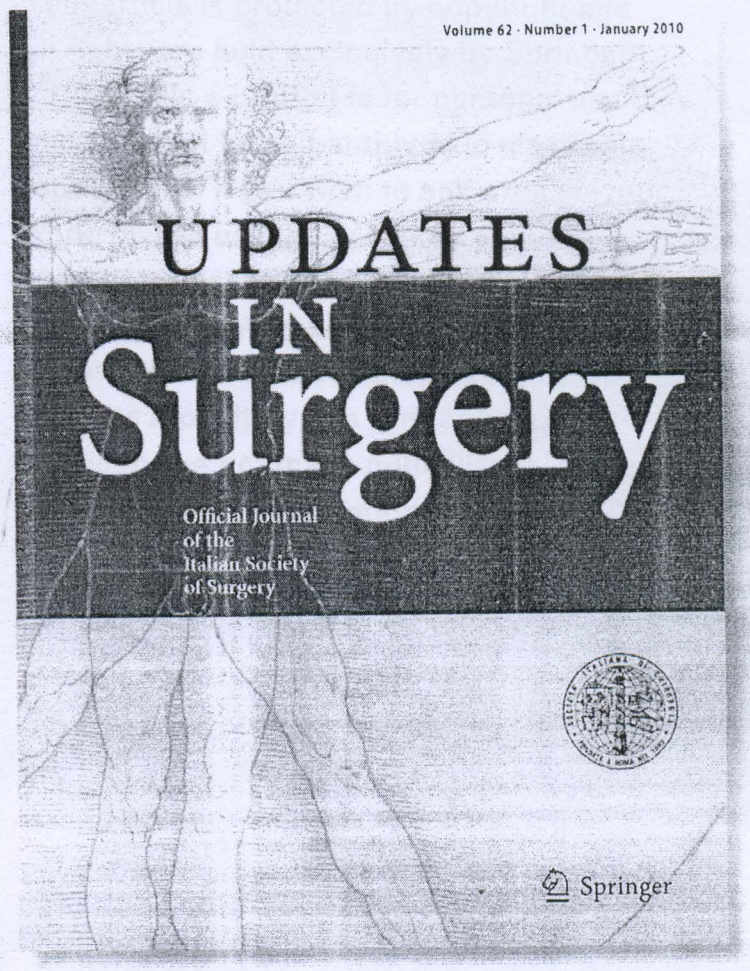

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ORIGINAL ARTICLE

Efficacy and tolerability of hyaluronic acid, tea tree oil and methyl-sulfonyl-methane in a new gel medical device for treatment of haemorrhoids in a double-blind, placebo-controlled clinical trial

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Abstract Topical formulations are widely used in anti-haemorrhoidal treatment, but often lacking controlled clinical trials. Here, we report the results from a controlled clinical trial performed with a new gel medical device (Proctoial) containing hyaluronic acid with tea tree oil and methyl-sulfonyl-methane as major components. The total number of 36 haemorrhoidal patients (grade 1–3) was enrolled in a double-blind, placebo-controlled clinical trial and divided into 2 equal parallel groups. The anal pain, pain during defecation, visible bleeding, pruritus and irritation/inflammation were recorded before and after 14-day treatment using a visual analogue scale both by the investigators and by the patients. Safety and tolerability of the treatments were also recorded. The new gel medical device statistically significantly reduced all the symptoms after the treatment compared to placebo. The results indicated also a very good tolerability and safety of the treatments.

Keywords Haemorrhoids · Hyaluronic acid · Tea tree oil · Methyl-sulfonyl-methane · Gel medical device · Clinical study

Introduction

Haemorrhoids are cushions of tissue with a rich submucosal vascular plexus and are suspended in the anal canal by connective tissue [1, 2]. The fragmentation of the extracellular matrix and the connective tissue that supports these cushions, due to age and the passage of hard stools, determines their descent with a protrusion and congestion [3]. Recently it has been suggested that haemorrhoids may be closely related with a disorder of the collagen metabolism, since a clear reduction in collagen amount was demonstrated in haemorrhoidal disease [4]. The mucosal inflammation is a hallmark of haemorrhoids, and the classic symptoms are represented by bleeding, protrusion and anal pain which are particularly exacerbated by defecation [2]. A conservative treatment of haemorrhoids is highly desirable, and therefore, in the first instance, the use of gels or creams with their predominant mechanical actions, which may protect anus-rectal mucosa, and may produce a smoothing effect to the passage of hard stools are widely used. Moreover, additional active components able to increase and/or induce the physiological repairing processes would be of great help. In this regard, we investigated the efficacy and tolerability of a new topical gel medical device containing additional components: hyaluronic acid (HA); methyl-sulfonyl-methane (MSM) and the essential oil extracted from *Melaleuca alternifolia* (TTO).

Hyaluronic acid is a ubiquitous polysaccharide with a remarkable capacity of restructuring the extracellular matrix, being currently used as medical device filler in

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cosmetic surgery to increase the volume of intradermal tissues [5]. It is a high molecular weight molecule with negative charges capable of forming highly viscous gel in the presence of H_2O. It contributes to stabilize the intracellular structures and produces an interconnection with the collagen fibres [6]. Depolymerisation of HA occurs through two ways: enzymatically by hyaluronidase, and through a chemical oxidation by free radicals. HA has a remarkably rapid turnover, and the total amount of about 15 g present in the human body had a 5 g daily turnover [7]. MSM is a natural compound and takes part in the terrestrial sulphur cycle, and it has also shown anti-inflammatory and antioxidant effects in vitro in murine macrophages activated by lipopolysaccharides to express pro-inflammatory mediators such as NO, prostaglandins and pro-inflammatory cytokines. In addition, MSM inhibited the release of pro-inflammatory mediators through a signal mediated by down regulation of NF-kB. Moreover, the topical administration of MSM significantly reduced experimentally induced ear oedema [8]. TTO showed a relevant antibacterial activity with a broad spectrum on both gram+ and gram− [9]. Most bacterial strains are susceptible to TTO with MIC (minimum inhibitory concentration) equal to or <1 % [10], and it has mainly antibacterial activity, but at lower doses it may be also bacteriostatic [9].

The particular viscous-elastic characteristics of HA may probably contribute to the physical protection of the anus-rectal mucosa, but the efficacy of HA in the restructuring of connective tissues [6], healing of tissues in various organs and apparatus [11], as well as, wound healing efficacy of HA is also very well known [12]. The leading action of HA in the medical device under investigation is supported by the interaction with the ancillary activities of the two other major components of the formulation, since both MSM and TTO may prevent the depolymerisation of HA.

Aims of the study

The primary objective was to assess the efficacy of Proctoial on anal pain, pain during defecation, visible bleeding, pruritus and irritation.

To assess the safety and tolerability of Proctoial, the occurrence of any adverse effects were recorded.

The secondary objective was to assess the global compliance of the treatment.

Materials and methods

The clinical study is a randomised, double-blind, parallel group, placebo-controlled mono-centre trial. The study was approved by ethics committees of Clinical centre Skopje (Macedonia) and a total number of 36 patients were enrolled (18 for each treatment arm), the sample size was calculated supposing a decrease of 60 % of the main symptoms (pain, pruritus and irritation) at the end of treatment with 80 % of power and a drop out of maximum 10 %.

The inclusion criteria were: written informed consent; both sexes, >18 years old, with 1°–3° haemorrhoids. The exclusion criteria were: suspected hypersensitivity and/or contraindication to any ingredients of the study product; pregnancy, breast feeding, oocyte donation or oocyte implantation planned during the study, patients not able to follow study procedures, e.g. language problems, psychological disorders; female patients of childbearing potential, not using and not willing to continue using a medically reliable method of contraception for the entire study duration; any other untoward medical condition that could interfere with the participation of the patient in the trial, patients under any study medication treatment in the last 30 days previous anal surgery, and inflammatory anal diseases.

At the 1° visit, if inclusion/exclusion criteria were fulfilled, patients were randomly assigned to one of the two treatment groups according to a four block randomization list prepared by R&D Unit of BSD pharma, and the blindness was assured by the identity of the two treatments. The placebo gel was identical to active gel (Proctoial™, BSD pharma—Italy) but lacked of HA, TTO and MSM, the two gels were indistinguishable. The patients were treated at home and the gel was applied every 12 h for 14 days at the dose of 1–1.5 g which corresponds to approximately the amount of gel squeezed from 1/2 cm of the tube.

At the end of treatment period (14 days), the patients returned to the hospital for the final visit and evaluated. The choice of placebo was justified by the relatively minor clinical symptoms.

The primary efficacy endpoints were: the anal pain intensity, pain during defecation, visible bleeding, pruritus and irritation were recorded by the patients and investigators (anal pain, inflammation and visible bleeding) using a visual analogue scale (VAS 0–10) at the 1° visit and at the end of treatment (final visit). A score of 0 corresponds to the absence of specific symptom and a score of 10 represents the maximum severe degree of the symptom. The differences between the score at visit one and final visit were recorded and statistically analyzed.

The primary safety endpoint was the evaluation of the safety and tolerability of the treatment and was evaluated by recording the occurrence of any adverse effects. The global tolerability judgement of the treatment by patients and investigators was recorded on the base of a 4 score scale: very good, good, poor, a very poor.

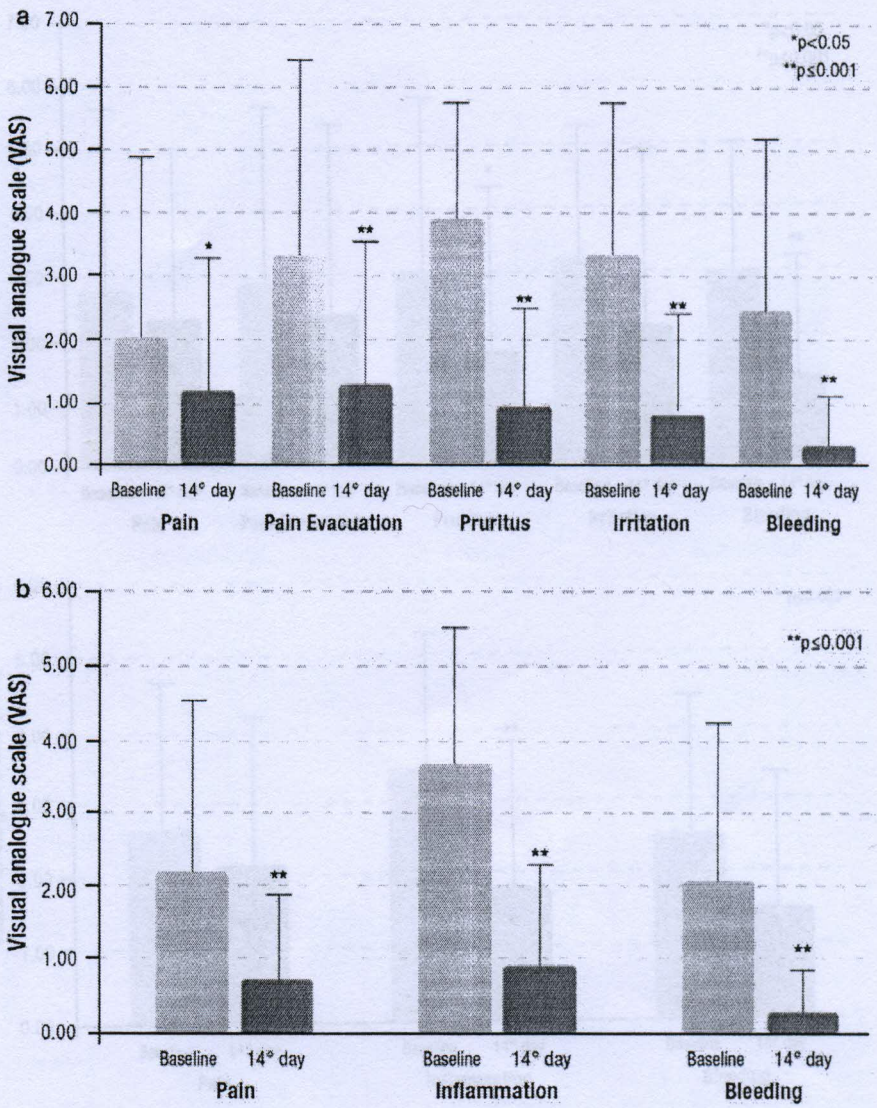

Fig. 1 **a** Patient evaluation on Proctoial treatment, **b** investigator evaluation on Proctoial treatment

The secondary endpoint was the global assessment of the disease, and was performed by asking the patients to evaluate their symptoms at the end of the treatment to the period of time before the treatment using three scores: better, no changes, worst.

Descriptive and statistical analysis (Student t test) has been performed within and between groups. Score values were analysed by Mann–Whitney test. A $p \leq 0.05$ has been considered statistically significant.

Results

The 14 days twice a day active gel treatment resulted in a statistically significantly decrease over the 1° visit of all measured parameters both from patients and investigators evaluations (Fig. 1a, b). In particular, the statistical difference calculated from pre-treatment and post-treatment (D) was highly statistical significant for: pain during evacuation, pruritus, irritation and visible bleeding ($p < 0.001$) and statistically significant for pain ($p < 0.05$) by the patient evaluation (Fig. 1a), whereas the difference was also significant ($p < 0.001$) for any symptom reported by the investigators like pain, inflammation and visible bleeding (Fig. 1b).

Placebo administration per se resulted in reduction of some symptoms and the difference between before- and end-treatment was statistically significant on the signs of inflammation evaluated by the investigators and pruritus and bleeding by the patients (Fig. 2a, b). However, comparing the efficacy of the two treatments (active vs. placebo) on the difference in VAS values between before- and

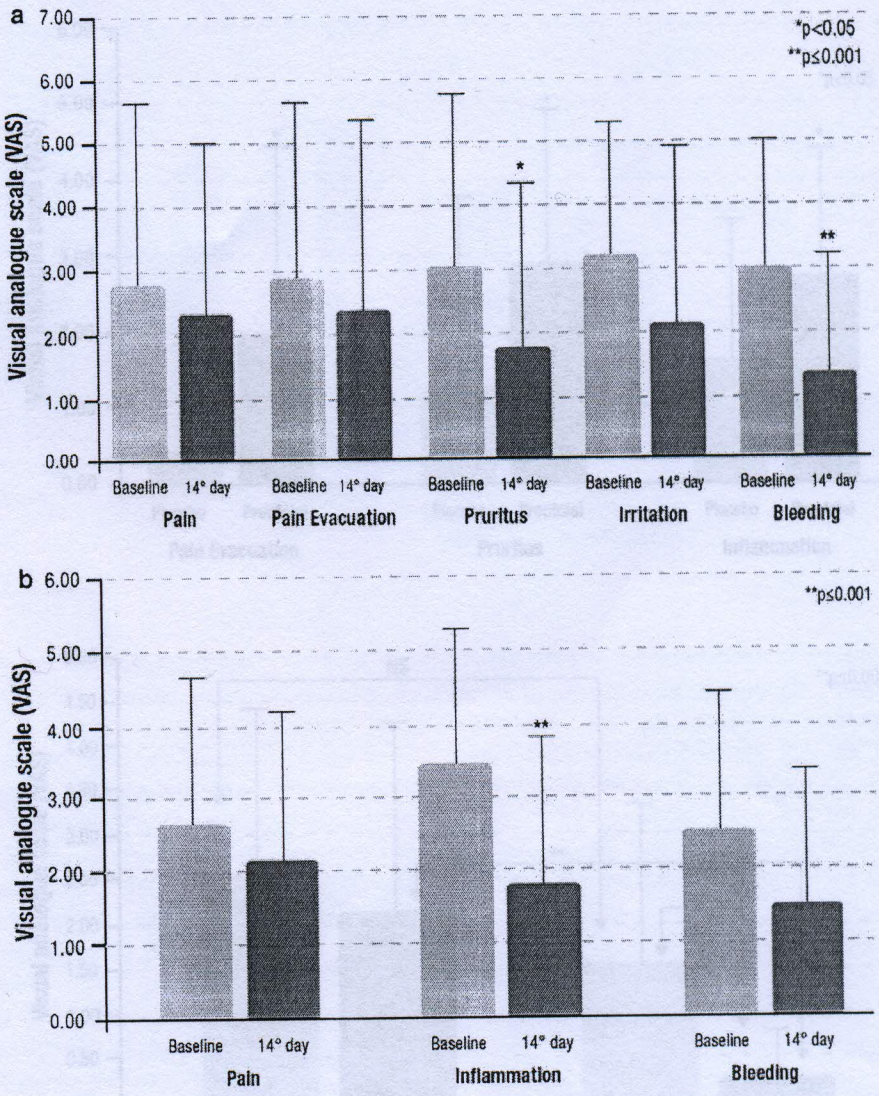

Fig. 2 a Patient evaluation on placebo treatment, b investigator evaluation on placebo treatment

end-treatment resulted with a statistically significantly better efficacy of the active treatment of pain after evacuation and pruritus as judged by the patients and inflammation end bleeding evaluated by the investigators (Fig. 3). Comparing the VAS actual data obtained by the patients and investigators for the symptom of visible bleeding, resulted in a statistically significant decrease in the actual values after active treatment as compared to placebo treatment, and indeed, the active treatment almost completely stopped bleeding (Fig. 4). The safety of the two treatments was confirmed by the complete absence of any adverse device effects, either device or not device related. Moreover, the global assessment of the compliance of the treatment by the patients resulted with a statistical significant improvement by the active gel as compared to the placebo gel. Similar statistical significant differences were observed for the global efficacy and assessment of the disease (Fig. 5).

Discussion

The 14-day treatment with Proctoial gel in patients suffering from haemorrhoids (1°–3°) markedly reduced all the symptoms (pain, irritation/inflammation, pruritus and bleeding), which are indeed considered as the major symptoms of haemorrhoids. However, also placebo treatment showed, in some way, an efficacy in decreasing some symptoms of haemorrhoids, indicating that the mere use of any type of gel or cream may, at least in part, reduce the haemorrhoid symptoms. But the statistical difference in the efficacy observed between the active and placebo

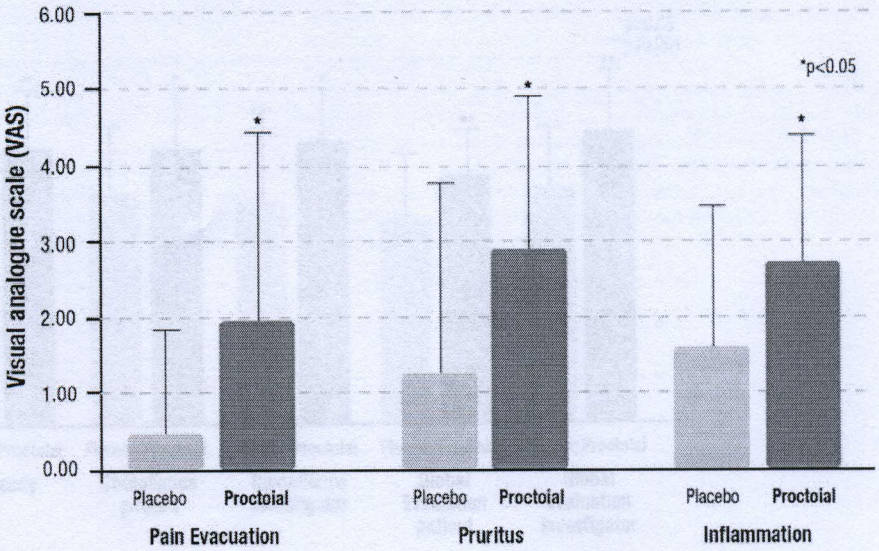

Fig. 3 Difference between baseline and 14 days treatment

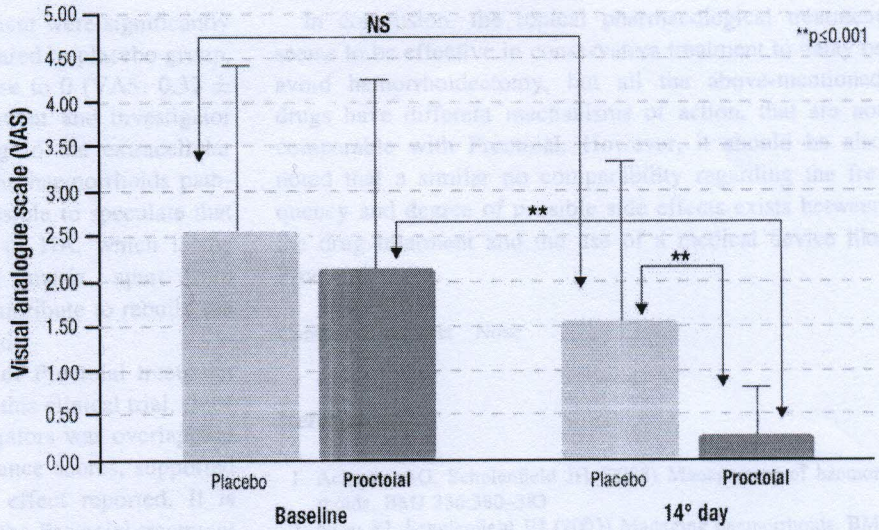

Fig. 4 Bleeding evaluation

treatments clearly showed that the presence of HA, and the additional presence of TTO and MSM in the Proctoial formulation provided to this medical device a clear-cut therapeutic efficacy. The well-known chemical and physical characteristics of HA may explain, at least in part, the efficacy of this new medical device, and indeed, MSM and TTO may act in preventing of HA degradation by different mechanisms. MSM may prevent the breakdown of HA not only through its anti-oxidative efficacy but also by a direct hyaluronidase inhibition, with an IC 50 = 3.5 mM (BSD-pharma date on file, 2007). On the other hand, MSM acts in the human body as a source of organic sulphur, which is involved in the formation of glycosaminoglycans (GAG) of the extracellular matrix [13], which together with HA allows the reconstruction of damaged tissues.

The fragmentation of the HA is not due only to the action of endogenous enzymes and free radicals but also by hyaluronidase and free radicals produced by pathogen and non-pathogen bacteria. The germicidal and antibacterial activity of TTO has been demonstrated also against faecal bacteria such as *Escherichia coli* and *Enterococcus foecalis* [9].

Therefore, TTO may also exert a dual effect, on one site the eradication of bacteria capable of producing hyaluronidase and free radicals results in a reduction in depolymerisation of HA and may have an important role in protecting the microenvironment of the wound in bleeding haemorrhoids. Moreover, the well-known wound healing efficacy of HA well correlates with the data obtained in the bleeding symptom. Proctoial gel treatment completely stopped the observable bleeding and the actual values

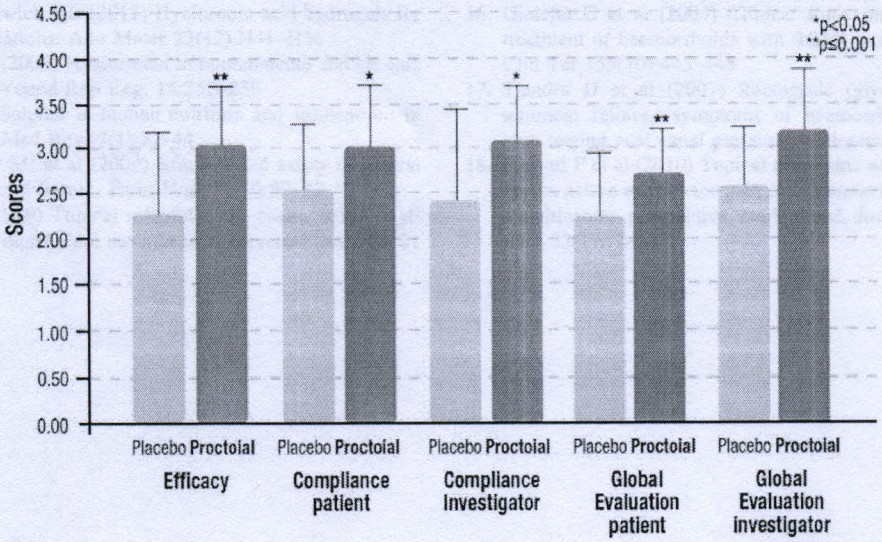

Fig. 5 Global efficacy and assessment of the disease

(VAS) observed at the end of treatment were significantly reduced in the active group as compared to placebo group, and the actual values were very close to 0 (VAS: 0.32 ± 0.8 and 0.32 ± 0.51 cm for the patient and investigator evaluation, respectively). According to the extracellular matrix degradation hypothesis for the haemorrhoids pathogenesis [4], from our data it is possible to speculate that also the exogenous administration of HA, which is the major component of extracellular matrix, apart from reducing the symptoms, may also contribute to rebuild the structures anchoring the haemorrhoids.

The safety and well tolerability of Proctoial treatment was also confirmed by the results of this clinical trial, since the global judgement of the investigators was overlapping with all the tolerability and compliance scores, supported also by the absence of any side effect reported. It is therefore indisputable to assert that the Proctoial treatment is safe and effective. However, it is difficult to compare the clinical data obtained in this trial with those obtained in other recent clinical studies. The topical treatment of haemorrhoids includes smooth muscle relaxing drugs such as the Ca-antagonists diltiazem, nifedipine [14, 15] or local anaesthetics [16]. Smooth muscle relaxing drugs seem to be very active in haemorrhoids associated with anal sphincter spasm and anal fissure [14, 17]. Local anaesthetics are also effective in relieving pain after hemorrhoidectomy [18]. The limitation of our study is the spectrum of haemorrhoid grade severity chosen (1°–3°). Since the study has the characteristics of the pilot study, it was considered that a wide range grade could give more information. A second limitation is the lack of an adequate time of follow-up and in this regard a new study looking at this aspect is in progress.

In conclusion, the topical pharmacological treatment seems to be effective in conservative treatment to delay or avoid hemorrhoidectomy, but all the above-mentioned drugs have different mechanisms of action, that are not comparable with Proctoial. However, it should be also noted that a similar no comparability regarding the frequency and degree of possible side effects exists between the drug treatment and the use of a medical device like Proctoial.

Conflict of interest None.

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