Journal of Clinical & Experimental Dermatology Research

Georges et al., J Clin Exp Dermatol Res 2017, 8:4
DOI: 10.4172/2155-9554.1000403

Rsearch Article Open Access

Clinical Efficacy of a New Generation of Multi-Target, Anti-Edematous, Anti-Inflammatory, Tissue Repairing Topical Polymeric Liquid Bandage for the Treatment of Internal Hemorrhoids

Marjorie Georges[1], **Houda Miled Ben Achour**[2], **Sara Adel Adly**[3], **Robin Trouiller**[1] **and Ravi Shrivastava**[1]

[1]*Vitro-Bio Research Institute, Issoire, France*

[2]*SHB Pharma, 81 Ennouiri, La Soukra, Tunisia*

[3]*Al Ansar, 9 Abrahim Sherif Str. Mostafa Kamal, Alexandria, Egypt*

[*]**Corresponding author:** Shrivastava Ravi, Vitro-Bio Research Institute, Issoire, France, Tel: +3304735505 05; Fax: +330473550011; E-mail: rs@vitrobio.com

Received date: June 15, 2017; **Accepted date:** July 06, 2017; **Published date:** July 10, 2017

Abstract

Objective: Internal hemorrhoids are a widespread vascular disease for which currently there is no satisfactory curative treatment available. The pathology involves the disintegration of the supporting tissue of the anal cushions, causing venous dilation, blood stagnation in the hemorrhoid, formation of edematous venous plexus covered by mucosa, and inflammation. An effective treatment must therefore be multi-target and capable of acting on all the pathology parameters simultaneously. We evaluated the clinical efficacy of a topical, osmotically active filmogen medical device (VB-Gy-ip) directed at minimizing edema, inflammation and volume of the lesions, concomitantly.

Methods: The study was a multi-centric, randomized, placebo-controlled, double-blind trial on patients suffering from internal hemorrhoids. 1 to 2 ml of test product, presented as a viscous solution containing VB-Gy-ip, presented in 50 ml tubes, was applied manually into the rectum, 3 to 4 times per day, for 14 consecutive days. Xanthan gum solution was used, in identical manner, as placebo or comparator product. The effects on the hemorrhoidal size, pain intensity, rectal bleeding, prolapse, defecation discomfort, irritation and itching were quantified using a 0 (no symptoms) to 10 (severe symptoms) scoring scale. Study design included 36 test product patients versus 18 placebo patients. Product safety and acceptability were also evaluated. All patients were re-examined on Day 21 to assess the eventual reversibility of the effects observed.

Results: Although regular and frequent use of xanthan gum gel helped reduce internal hemorrhoid symptoms appreciably, the test product remarkably induced very fast and statistically significant regression of all the clinical signs without any side effects.

Conclusion: An ideal treatment for internal hemorrhoid should simultaneously reduce edema, pain, inflammation, and the size of the lesion without any irritation or side effects. VB-Gy-ip is a completely new class of multi-target treatment for internal hemorrhoids, representing a big hope for millions of patients suffering from this pathology.

Keywords: F-VB-Gy; Clinical; Chronic; Haemorrhoids; Osmotic, Filmogen; Anti-edematous

Introduction

Hemorrhoids affect nearly 4% of the world population, causing considerable discomfort and affecting the quality of life of the patients. They manifest as oedematous blood vessels at the level of the anal opening, and depending upon their location, they may be classified as internal or external [1,2]. The anal dentate line differentiates external and internal hemorrhoids. External hemorrhoids are located below the dentate line and drain via the inferior rectal veins into the pudendal vessels and then into the internal iliac vein. These vessels are covered by anoderm that is comprised of modified squamous epithelium containing pain fibers. Internal hemorrhoids lie above the dentate line and are covered by columnar cells that have visceral innervations. They drain via the middle rectal veins into the internal iliac vessels. Internal hemorrhoids are classified further into their degree of prolapse. First-degree hemorrhoids protrude into the anal canal, but do not prolapse out of the canal. Second-degree hemorrhoids prolapse outside of the canal, but reduce spontaneously. Third-degree hemorrhoids prolapse out of the canal and require manual reduction; fourth-degree hemorrhoids are irreducible [3]. The hemorrhoidal wall is made up of elastic connective tissue but due to dilation and thinning of the muscle wall, the hemorrhoidal cushions may be called sinusoids instead of arteries or veins. When blood stays stagnant in a live organ, this may cause severe pain and irritation, along with occasional bright red bleeding upon strain [4].

Due to the differences in anatomical structure, location, and physiopathology of internal and external hemorrhoids, the treatment strategies must also be different. Although, new treatment strategies are suggested continuously [5,6], in the absence of any effective treatment, hemorrhoids become usually chronic, involving formation of edematous vascular sinusoids, tissue destruction, inflammation, pain, irritation, difficulty defecating, and bleeding [7]. To be effective, a treatment should first reduce edema to alleviate pressure on the vessels, which should consequently allow regression of the lesion and initiation of the natural healing process. In case of internal hemorrhoids, the

location of lesions does not permit using any long-acting topical medication. And in the absence of any safe and efficacious anti-edematous drug, only operative treatments, with multiple drawbacks, are currently employed [8,9].

We evaluated a newly conceived glycerol-based hypertonic solution (VB-Gy), 18 times more osmotic than sea water yet not irritant, capable of attracting hypotonic liquid from any live semi-permeable biological membrane, and thus acting as a strong anti-edematous drug for topical application [10]. As VB-Gy eventually becomes diluted with the strong hypotonic liquid outflow it generates, it was rendered filmogen, flexible and resistant to dilution, by adding a small quantity of Pileseptine-i premix, containing a specific association of natural polymeric ingredients and hydrophobic essential oils. The resulting composition was termed VB-Gy-ip [11]. We postulated that the topical application of such a filmogen hypertonic solution should exert sufficient osmotic pressure on the surface of the dilated, edematous hemorrhoid to create a strong exudation of hypotonic liquid from the hemorrhoidal mucosa, and reduce the hemorrhoid size. This mechanical effect should empty the hemorrhoidal sinusoids of exudates to provide symptomatic relief and allow hemorrhoidal tissue to resume its normal shape and functions.

A randomized, placebo-controlled, double-blind clinical study was then conducted, with the aim of verifying the efficacy of filmogen VB-Gy-ip Test Product (TP) compared to a physically identical xanthan gum gel as placebo or Comparator Product (CP).

Materials and Methods

Investigational products

The Test Product (TP) consisted in the hypertonic, glycerol-based solution VB-Gy-ip, rendered filmogen with natural polymer premix and mint and linseed oils as hydrophobic excipients. A placebo viscous gel containing 0.5% xanthan gum in water served as comparator product (CP). The TP and CP gels were identical with respect to color and consistency, and were presented in 50 ml plastic tubes with a canula, with individual product identification codes.

The primary objective of the study was to evaluate the efficacy of the TP on hemorrhoidal symptoms, and the secondary objectives were to verify its safety and absence of side-effects.

Study organizer

The clinical part of this research was conducted at Nexus Clinical Research Center in India, affiliated to Nexus Clinical Research LLC, USA. The protocol and study design were approved by the Institutional Ethical Committee of India – Rajiv Gandhi Institute of medical sciences (EC Registration N° ECR/492/Inst/AP/2013, dated 05/12/2013) and the trial was conducted following the ICH-GCP guidelines as per the declaration of Helsinki concerning ethical principles for medical research involving human subjects.

Study design and rationales

The study was designed as a multi-centric, randomized, placebo-controlled, double-blind, clinical trial. The aim of the study was to compare the efficacy and safety of filmogen VB-Gy-ip osmotic topical gel compared to a placebo gel for the treatment of internal hemorrhoids. The doses were selected based on a previous pilot, dose range finding, observational study on patients suffering from hemorrhoids where VB-Gy-ip gel was applied topically over the hemorrhoidal surface 4 times per day for 14 days without any side effects. Xanthan gum gel was chosen as a placebo or comparator product as it is safe, non-irritant, and has nearly identical physical characteristics to the TP. Products were applied topically with a finger because hemorrhoids are very painful and the patients could thus apply the product at their convenience and exactly on the internal hemorrhoidal surface.

Number of patients

The aim was to conduct the study on at least 50 patients so as to obtain statistically significant results. As the use of xanthan gum as excipient in various topical preparations is common and its mode of action as a neutral viscosity enhancer/filmogen agent is known, it was decided to include twice more patients in the TP group compared to the xanthan gum-containing CP group. Final complete sets of results were collected on 18 patients in the CP group and 36 in the TP group.

Inclusion and exclusion criteria

At the time of recruitment at the study centers, patients were examined physically, and patient's medical, surgical, and allergic history was checked. Vital signs such as blood pressure, pulse rate, and respiratory rate were recorded. Patients not suffering from any serious pathology were then examined for enrollment in the study. The main inclusion criteria comprised: signed informed consent for participation in the study; males or females, aged 18-65 years; not under any treatment which may affect study outcome; having clinical manifestations of grade I to III internal hemorrhoids; and ready for manual rectal and proctological examinations as per the study protocol. The key exclusion criteria were: hypersensitivity or allergy to investigational product ingredients; gastro-intestinal diseases; under hemorrhoidal treatment; presence of other anorectal pathologies such as inflammatory bowel disease; sphincter lesions; anal fistula; records of previous anorectal surgery; as well as pregnant and nursing women.

Randomization

After screening, patients satisfying all the inclusion criteria were enrolled and randomly allocated, in a 2:1 ratio, to either TP or CP group (Figure 1). Treatments were allocated to patient by carrying out randomization using SAS Version 9.1.3 following a randomization schedule. Block Randomization methodology was employed for generating the list. Each patient received a unique screening identification number, randomization code, and enrollment identification number.

Product presentation and administration

TPs and CPs were supplied by Naturveda Research Institute (ZAC de Lavaur 63500 Issoire, France) and, for blinding purpose, were presented identically (50 ml tubes containing a viscous gel) except for the product code and the batch number which were different.

Patients were asked to apply a small quantity (1-2 ml) of gel directly over the internal hemorrhoidal surface with a clean finger, 4 times per day (morning, mid-day, evening, and before night rest) from Day 1 to Day 14 or till complete recovery (whichever was earlier). 1st treatment was administered just after the patient's inclusion in the study (Day 1). Although, treatment was stopped on Day 14, patients were re-

examined on Day 21 to evaluate the stability of results or rebound effects, if any.

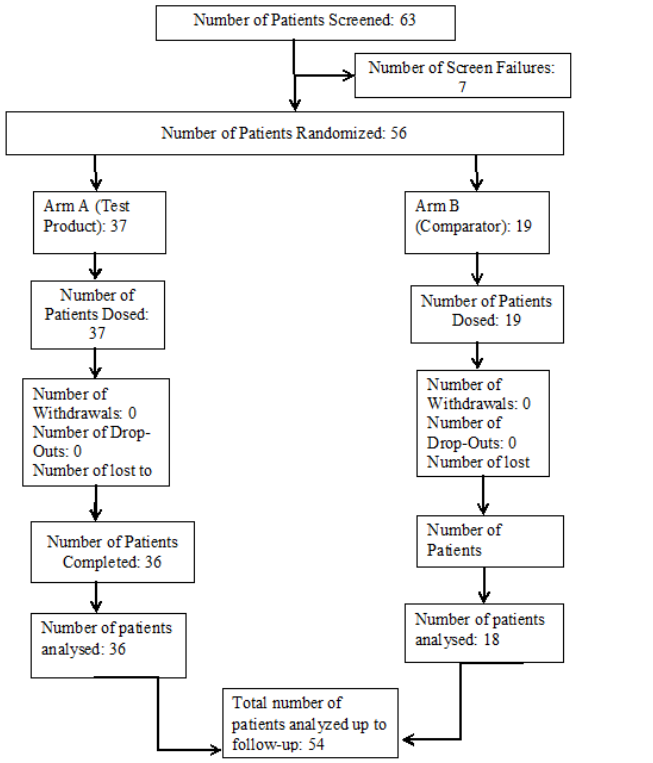

Figure 1: Flow chart of population distribution from screening up to the end of the treatment (Day 14) and follow–up visit (Day 21).

Parameters studied

The key parameters evaluated were the products' effects on the size of hemorrhoids, pain intensity following bowel movements, rectal bleeding, prolapse, defecation discomfort, and change in itching/irritation compared to baseline, at the following time-points: 2 h post dose on Day 1, on Day 2 (Visit 2), Day 3 (Visit 3), Day 8 (Visit 4), Day 14 (Visit 5/end of therapy visit). The secondary parameters checked were: change in irritation/itching after defecation and redness (sign of inflammation) around the anal area. Treatment was stopped on Day 14 but the patients were asked for a follow-up visit on Day 21 to evaluate progression, stabilization, and recovery/non-re-occurrence of hemorrhoid compared to the observations made at the end of the treatment course (Day 14). These parameters were evaluated on a 0 (no symptoms) to 10 (severe symptoms) scoring scale and were recorded in the patient's diary. Product's global efficacy, safety, and acceptability assessment by the patients and the investigator were also recorded on Day 14.

Statistical analysis of results

The analyses were conducted with Microsoft Excel and XLStat using the available data. Significant effects were those with a probability lower than $\alpha=0.05$. For each score, repeated measures analysis of variance (RMANOVA) determined differences in symptoms scores across study visits. Nemenyi post-hoc test provided pairwise comparisons in a group between baseline and the end of the study.

Results were compared with baseline values (before 1st treatment on Day 1) in the same group and between the groups, at each time point.

Pain intensity during bowel movements	**Time-points**					
	Day 1 - T0 before treatment (baseline Visit 1)	**Day 2 (Visit 2)**	**Day 3 (Visit 3)**	**Day 8 (Visit 4)**	**Day 14 (Visit 5)**	**Day 21 (Follow up Visit 6)**
Means						
Comparator group	6.89	6.56	6.33	6.00	5.61	5.83
SD ±	*1.37*	*1.42*	*1.33*	*1.24*	*1.04*	*1.34*
Test group	6.89	5.86	4.78	3.69	2.72	2.94
SD ±	*1.45*	*1.44*	*1.42*	*1.35*	*1.32*	*1.47*
Change versus T0 (baseline)						
Comparator group %	-	-4.84%	-8.06%	-12.90%	-18.55%	-15.32%
p value	-	*0.739*	*0.174*	*0.002*	*< 0.0001*	*< 0.0001*
Test group %	-	-14.92%	-30.65%	-46.37%	-60.48%	-57.26%
p value	-	*0.211*	*0.0001*	*< 0.0001*	*<0.0001*	*<0.0001*
Severity Difference: Test group versus Comparator group						

% Severity Difference	-	-10.59%	-24.56%	-38.43%	-51.49%	-49.52%
p value	-	*0.099*	*0.0003*	*<0.0001*	*<0.0001*	*<0.0001*
results are significant when p<0.05						

Table 1: Pain intensity during bowel movements: Mean Values (± S.D.) in CP (n=18) and TP (n=36) groups at each time point, with % change compared to baseline scores and difference in severity in TP group compared to CP at each time point, with statistical significance (p value).

Results

Effect on pain intensity during bowel movements

Mean results for pain intensity (Table 1) clearly show that the CP helps reduce pain progressively during the study period: this reduction is slight (about 2% per day) but becomes statistically significant between Days 8 and 21. The pain reduction in this group is about 18.5% on Day 14 compared to Day 1. When the mean results of the TP group are compared with those of the CP group, whereas both started with the same value (6.89/10), a notable difference in pain severity is observed between the groups right from Day 2 (-10.5%, p<0.09) onwards, indicating a strong antalgic effect of the TP right after the 1st day of treatment. This difference between CP and TP groups increased substantially up to the end of the treatment period (Day 14) with 24%, 38%, and 51% lower severity in TP group compared to CP group, on Days 3, 8, & 14 respectively. When the treatment was stopped on Day 14, the mean value for pain intensity observed on Day 21 had gone up by only 2% and the severity difference remained statistically highly significant compared to the CP group, showing that the results obtained on Day 14 were rather maintained up to Day 21 even in the absence of treatment.

6/36 in the TP group still had a score between 0 and 1 on Day 14, indicating that the treatment period should be extended beyond 2 weeks to obtain complete recovery.

Effect on rectal bleeding

In the CP group, the mean scores show that hemorrhoidal bleeding was not affected in this group in the first 2 days, decreased slightly but with statistically significant difference compared to baseline between Days 8 and 14. Stopping the treatment for a week (between Days 14 and 21) did not much affect the bleeding rate.

Rectal bleeding	**Time-points**					
	Day 1 - T0 before treatment (baseline Visit 1)	**Day 2 (Visit 2)**	**Day 3 (Visit 3)**	**Day 8 (Visit 4)**	**Day 14 (Visit 5)**	**Day 21 (Follow up Visit 6)**
Means						
Comparator group	6.39	6.33	6.06	5.61	5.33	5.39
SD ±	*1.42*	*1.46*	*1.35*	*1.33*	*1.28*	*1.33*
Test group	6.81	5.75	4.72	3.75	2.69	2.83
SD ±	*1.35*	*1.364*	*1.32*	*1.30*	*1.22*	*1.46*
Change versus T0 (baseline)						
Comparator group %	-	-0.87%	-5.22%	-12.17%	-16.52%	-15.65%
p value	-	*1.000*	*0.765*	*0.011*	*0.0001*	*0.0002*
Test group %	-	-15.51%	-30.61%	-44.90%	-60.41%	-58.37%
p value	-	*0.239*	*0.0001*	*<0.0001*	*<0.0001*	*<0.0001*
Severity Difference: Test group versus Comparator group						
% Severity Difference	+6.52%	-9.21%	-22.02%	-33.17%	-49.48%	-47.42%
p value	*0.298*	*0.153*	*0.001*	*<0.0001*	*<0.0001*	*<0.0001*
results are significant when p<0.05						

Table 2: Rectal bleeding- Mean Values (± S.D.) in CP and TP groups at each time point, with % change compared to baseline scores and difference in severity in TP group compared to CP at each time point, with statistical significance (p value).

In the TP group, a strong and progressive reduction in hemorrhoidal bleeding was observed right from Day 2 ($p<0.24$ compared to baseline and $p<0.15$ compared to CP) through Day 14 as the mean scores on Days 2, 3, 8, and 14 had decreased by nearly 15%, 30%, 45% and 60%, respectively, compared to baseline value, with statistical significance from Day 3 (i.e. within 48h of treatment initiation). Bleeding did not show any notable increase by Day 21, after stopping the treatment on Day 14.

When compared with the CP group mean values, the bleeding severity in the TP group was 9%, 22%, 33% & 49% lower on Days 2, 3, 8, & 14 than in CP group respectively, with statistically significant difference from Day 3 onwards. These results (Table 2) demonstrate strong healing properties of the TP with regard to internal hemorrhoids. As bleeding was not totally stopped in all the patients on Day 14, it was suggested to continue applying the product until bleeding had totally stopped and other symptoms had also receded.

Effect on hemorrhoidal prolapse

NB: In the CP group, 12 out of 18 patients showed prolapse, and 22/36 patients in the TP group. Therefore, the mean values and statistical analyses are calculated on the Prolapse sub-groups CP n=12 and TP n=22. In the CP group, only some slight and not statistically significant reduction in the extent of prolapse was observed between Days 3 and 14, (-14%, $p>0.57$) compared to baseline value. When the treatment was stopped between Days 15 and 21, the severity of prolapse re-increased (+7.0%) indicating that application of the comparator gel on internal hemorrhoids has no meaningful effect on prolapse.

Irritation/Itching after Defecation	Time-points					
	Day 1 - T0 before treatment (baseline Visit 1)	Day 2 (Visit 2)	Day 3 (Visit 3)	Day 8 (Visit 4)	Day 14 (Visit 5)	Day 21 (Follow up Visit 6)
Means						
Comparator group	4.83	4.72	4.56	4.22	3.78	3.94
SD ±	*1.50*	*1.41*	*1.34*	*1.17*	*1.22*	*1.43*
Test group	4.89	3.69	2.69	1.72	0.78	0.86
SD ±	*0.89*	*0.79*	*0.79*	*0.81*	*0.76*	*0.90*
Change versus T0 (baseline)						
Comparator group %	-	-2.30%	-5.75%	-12.64%	-21.84%	-18.39%
p value	-	*1.000*	*0.924*	*0.144*	*0.0004*	*0.0003*
Test group %	-	-24.43%	-44.89%	-64.77%	-84.09%	-82.39%
p value	-	*0.211*	*0.0001*	*<0.0001*	*<0.0001*	*<0.0001*
Severity Difference: Test group versus Comparator group						
% Severity Difference	+1.15%	-21.76%	-40.85%	-59.21%	-79.41%	-78.17%
p value	*0.865*	*0.001*	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*
results are significant when $p<0.05$						

Table 3: Prolapse: Mean Values (± S.D.) in CP and TP groups at each time point, with % change compared to baseline scores and difference in severity in TP group compared to CP at each time point, with statistical significance (p value).

In the TP group, although the mean score for the total group (36 patients) was 2.25/10, some of them did not exhibit any symptom of prolapse, therefore the mean score was actuality 3.68 for n=22 patients showing prolapse (compared to 3.0 for the 12 patients showing prolapse in the CP group). Prolapse scores were not very high because only patients with grade I, II, and III with potential of re-absorption were included in this study. The mean values recorded at the different time-points (Table 3) show that the TP does not drastically reverse prolapse, as the baseline mean value was reduced only by 5%, 13%, 22%, and 27% on Days 2, 3, 8, & 14 respectively, and due to the fairly low population sample (n=22), the reduction is statistically significant ($p \leq 0.009$) only from Day 8. The resorption effect is still relatively modest which is probably due to the fact that prolapsing tissue is usually highly damaged and remains deformed even a few weeks after complete healing. It is quite noteworthy, though, that whereas the modest effect obtained with the CP (13.9% reduction on Day 14) is quickly reversed with one week of treatment interruption (only 5.6% reduction compared to baseline on Day 21), the beneficial effect exerted by the TP actually persists beyond the 14-day treatment course, and this solid benefit is even further verified on Day 21 with 30.8% reduction compared to pre-treatment value. Therefore, we recommend that for the treatment of prolapsing internal hemorrhoids, the product should be used for longer than 14 days, and the long term clinical efficacy of TP should be evaluated.

Defecation Discomfort	**Time-points**					
	Day 1 - T0 before treatment (baseline Visit 1)	**Day 2 (Visit 2)**	**Day 3 (Visit 3)**	**Day 8 (Visit 4)**	**Day 14 (Visit 5)**	**Day 21 (Follow up Visit 6)**
Means						
Comparator group	5.44	5.28	4.89	4.61	4.22	4.33
SD ±	*1.38*	*1.23*	*1.18*	*1.14*	*1.11*	*1.33*
Test group	5.86	4.81	3.78	2.78	1.78	1.81
SD ±	*1.05*	*0.98*	*1.02*	*0.96*	*0.96*	*1.19*
Change versus T0 (baseline)						
Comparator group %	-	-3.06%	-10.20%	-15.31%	-22.45%	-20.41%
p value	-	*0.996*	*0.294*	*0.012*	*<0.0001*	*0.0002*
Test group %	-	-18.01%	-35.55%	-52.61%	-69.67%	-69.19%
p value	-	*0.211*	*0.0001*	*<0.0001*	*<0.0001*	*<0.0001*
Severity Difference: Test group versus Comparator group						
% Severity Difference	+7.65%	-8.95%	-22.73%	-39.76%	-57.89%	-58.33%
p value	*0.221*	*0.131*	*0.001*	*<0.0001*	*<0.0001*	*<0.0001*
results are significant when p<0.05						

Table 4: Defecation Discomfort: Mean Values (± S.D.) in CP and TP groups at each time point, with % change compared to baseline scores and difference in severity in TP group compared to CP at each time point, with statistical significance (p value).

Effect on defecation discomfort

The mean scores (Table 4) for difficulties passing stools (defecation) show only slight improvement in the CP group from Day 3 up to Day 14, which was nonetheless maintained up to Day 21 (statistically significant from Day 8 onwards, as compared to baseline). In the TP group, a strong and continuous reduction of the mean severity score for defecation difficulty was observed right from Day 2 with 18% reduction. Thereafter, the reduction was very strong and statistically significant ($p \leq 0.0001$) on Day 3 (-35.5%), Day 8 (-52.6%) and Day 14 (-69.7%), compared to corresponding time-points comparator values as well ($p=0.001$ on Day 3 and $p<0.0001$ thereafter). 4/36 patients in the TP group scored 0 on a scale of 10 for defecation difficulties on Day 14. These results show clearly the efficacy of TP in reducing defecation discomfort rapidly. These effects were maintained during the follow-up observation period, as assessed on Day 21.

Irritation/Itching after Defecation	**Time-points**					
	Day 1 - T0 before treatment (baseline Visit 1)	**Day 2 (Visit 2)**	**Day 3 (Visit 3)**	**Day 8 (Visit 4)**	**Day 14 (Visit 5)**	**Day 21 (Follow up Visit 6)**
Means						
Comparator group	4.83	4.72	4.56	4.22	3.78	3.94
SD ±	*1.50*	*1.41*	*1.34*	*1.17*	*1.22*	*1.43*
Test group	4.89	3.69	2.69	1.72	0.78	0.86
SD ±	*0.89*	*0.79*	*0.79*	*0.81*	*0.76*	*0.90*
Change versus T0 (baseline)						
Comparator group %	-	-2.30%	-5.75%	-12.64%	-21.84%	-18.39%

p value	-	*1.000*	*0.924*	*0.144*	*0.0004*	*0.0003*
Test group %	-	-24.43%	-44.89%	-64.77%	-84.09%	-82.39%
p value	-	*0.211*	*0.0001*	*<0.0001*	*<0.0001*	*<0.0001*
Severity Difference: Test group versus Comparator group						
% Severity Difference	+1.15%	-21.76%	-40.85%	-59.21%	-79.41%	-78.17%
p value	*0.865*	*0.001*	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*
results are significant when p<0.05						

Table 5: Irritation/Itching after Defecation: Mean Values (± S.D.) in CP and TP groups at each time point, with % change compared to baseline scores and difference in severity in TP group compared to CP at each time point, with statistical significance (p value).

Effect on irritation after defecation

Mean results of the CP group show a slow progressive reduction in itching & irritation during the study period. Itching intensity decreased by about 5.7% on Day 3 and 12.6% on Day 8; with statistical significance only from Day 14, with 21.8% reduction, compared to baseline. These effects were more or less maintained till the follow-up visit (on Day 21).

In the TP group, there was a drastic reduction in itching and irritation after defecation as the mean scores were decreased by approximately 24%, 45%, 64.7% and 84% on Days 2, 3, 8, and 14 respectively, compared to baseline value, a reduction statistically significant from Day 3 onward (p<0.0001). Even when the TP mean scores are compared with the CP scores, the severity of itching and irritation in the TP group is significantly lower early on, by about 20% (p=0.001), then 40%, 60% and 80% (p<0.0001) on Days 2, 3, 8 and 14 respectively. All patients complained about irritation at the start of the study, but only 1/18 in the CP compared to 15/36 in the TP scored 0 (no irritation at all) at the end of the study. These results (Table 5) show a very strong efficacy of the TP in reducing internal hemorrhoidal itching and irritation. This effect may be related to the TP's soothing and hydrating properties.

Redness / inflammation around anal area	**Time-points**					
	Day 1 - T0 before treatment (baseline Visit 1)	**Day 2 (Visit 2)**	**Day 3 (Visit 3)**	**Day 8 (Visit 4)**	**Day 14 (Visit 5)**	**Day 21 (Follow up Visit 6)**
Means						
Comparator group	4.72	4.61	4.06	3.83	3.39	3.50
SD ±	*1.45*	*1.38*	*1.16*	*1.15*	*1.09*	*1.42*
Test group	4.67	3.61	2.563	1.53	0.69	0.81
SD ±	*1.01*	*1.02*	*1.03*	*1.03*	*0.82*	*0.98*
Change versus T0 (baseline)						
Comparator group %	-	-2.35%	-14.12%	-18.82%	-28.24%	-25.88%
p value	-	*0.999*	*0.105*	*0.005*	*<0.0001*	*< 0.0001*
Test group %	-	-22.62%	-45.83%	-67.26%	-85.12%	-82.74%
p value	-	*0.211*	*0.0001*	*<0.0001*	*<0.0001*	*<0.0001*
Severity Difference: Test group versus Comparator group						
% Severity Difference	-1.18%	-21.69%	-37.67%	-60.14%	-79.51%	-76.98%
p value	*0.870*	*0.004*	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*
results are significant when p<0.05						

Table 6: Redness/inflammation around anal area: Mean Values (± S.D.) in CP and TP groups at each time point, with % change compared to baseline scores and difference in severity in TP group compared to CP at each time point, with statistical significance (p value).

Effect on redness around anal area

The mean values in the CP group show a progressive but moderate reduction of redness around anal area from Day 3 (-14%), with statistical significance from Day 8 (19% reduction, p=0.005), and attaining 28% on Day 14 (p<0.0001), compared to baseline mean value. Although modest, this improvement was rather maintained until Day 21 (-26%, p<0.0001). These results indicate that the CP does help reduce hemorrhoidal redness to some extent, but that these effects remain limited. In the TP group, the reduction was strong right after the 1st treatment (22% on Day 2) showing statistically significant difference of effect compared to the CP (p<0.004), and continued progressing with statistically significant (p<0.0001) difference compared to CP on Day 3 (37%), Day 8 (60%), and Day 14 (77%). The effects were maintained until Day 21 (82.7% reduction compared to baseline, 77% lesser severity compared to CP) indicating that the TP reduce significantly topical anal inflammation (Table 6).

Product acceptability

The treatment with CP was found to be fair by 94% and good by 6% of participants (patients and investigators), but no one found the treatment very good or excellent. The effects on internal hemorrhoids parameters measured in this study also show a limited efficacy of the xanthan gum gel. In the TP group, product was scored as good (56%) or very good (44%), indicating a rather high satisfaction rate, in correlation with the efficacy results observed with regard to all parameters.

Safety parameters

No undesirable or side effects were reported by any of the patients, whether in the TP or CP groups.

Discussion

Internal hemorrhoids are a very common anorectal condition affecting millions of people around the world, and for which there is no curative treatment despite regularly claimed invention of modern remedies [12,13]. This pathology has a strong economic, social and even historical importance as the emperor of France, Napoleon Bonaparte, suffered from strong hemorrhoidal pain on the day of the decisive battle of Waterloo in 1815 and lost the battle [14]. 200 years later, there is still no effective treatment for internal hemorrhoids, a lack primarily related to the fact that this is a chronic and multifactorial pathology involving downward displacement of anal cushions causing venous congestion and leading to the protrusion of venous plexus.

Mucosal damage induces local inflammation and swelling which constricts the blood vessels. As venous blood cannot flow rapidly any longer, the venous dilation produces edema which continues increasing in volume and causes hemorrhoidal swellings [3,4]. When this condition starts becoming chronic, the affected anal and vascular tissue shows signs of collagen and fibroelastic tissue degeneration, distortion and rupture of the anal sub-epithelial muscles, strong important release of inflammatory and pro-inflammatory cytokines and matrix metalloproteinases (MMPs) which may be followed by thrombosis, necrosis, and neo-vascularization [6]. Bowel movements induce irritation, itching, pain and discomfort. The localization of the lesions in the anal canal offers a perfect environment for microbial growth and lesions tend to become chronic [15]. Internal hemorrhoids thus involve multiple physio-pathological changes, all originating from the initial vascular protrusion, edema, and the inability of edematous tissue to regress and resume its normal physiology. Taking into consideration internal hemorrhoidal physiopathology, no complicated research is needed to understand that an ideal treatment should first reduce the volume of the hemorrhoids, either surgically or by removing the liquid from the lesions which should help diminish their size [8]. Surgical treatment is commonly practiced but this this is an expensive and painful technique offering only temporary relief as once cauterized vessels are healed, new vessels emerge from the damaged tissue and the disease process resumes [16]. Up till now, there was no anti-edematous drug which could preferably be applied directly on the lesion so as to avoid systemic side effects and which wasn't irritant or cytotoxic to anal tissue. To be effective, the anti-edematous treatment should also possess soothing properties to minimize irritation, itching, and pain, and be capable of humecting the anal passage. It should also act as an antiseptic to hamper microbial growth, and have tissue healing properties to allow edematous vessels to resume their normal physiology and functions. Topical pro-inflammatory cytokine-inhibiting properties should complete the profile of this ideal treatment. Unfortunately, even after continuous research over many decades to find a curative and effective treatment for internal hemorrhoids, results were never convincing [17,18].

Currently there is no drug, natural or synthetic, systemic or topical, surgical or therapeutic, capable of fulfilling all these basic yet essential requirements simultaneously to treat internal hemorrhoids. The use of multiple approaches to treat hemorrhoids such as various hydrating and soothing creams and ointments [19], antiseptics, pain killers, anti-inflammatory drugs [20], oral flavonoids [21,22], calcium antagonists such as nifedipine [23,24], as well as sclerotherapy [25], rubber band and other legations to cut-off the hemorrhoidal tissue, and multitudes of natural therapies [26,27], itself indicates that there is no one therapy which is relatively effective to treat this disease. Many non-surgical preparations contain chemicals and one should not forget that almost all chemicals are cytotoxic at therapeutic concentrations and cells cannot grow, nor an injury can heal in the presence of any chemical. Glycerol was not used as a therapeutic agent to treat hemorrhoids even though glycerol is highly osmotic and cell-friendly, only due to the fact that osmosis created by glycerol on a live semi-permeable membrane reduces the concentration of glycerol within a few minutes, stopping the process of osmosis and its therapeutic advantages [28]. The aim of our research was to conceive a glycerol base, which is rendered filmogen to increase the flexibility and resistance of the film to outcoming liquid flow.

The results of this study clearly show that applying an osmotically active, resistant and flexible film over the internal hemorrhoidal surface generates an instant and strong outflow of the hypotonic liquid accumulated inside the hemorrhoidal lesions. Liquid exudation progressively reduces the volume of the lesion and within a few days, the regression of the lesion in turn alleviates the pressure over the surrounding area, thereby reducing pain and improving stool passing. Counteracting edema and decreasing the volume of the lesion equally lessen vascular exudation and bleeding episodes. The F-VB-Gy solution generates a continuous outward flow of hypotonic liquid that hampers microbial attachment and growth. Cleaning the lesions favors the healing process and improves local defense mechanisms. F-VB-Gy being totally non-cytotoxic and cell-friendly does not interfere with the cell growth and the repair process; on the contrary, it protects the cells against external aggressions and prepares a favorable ground for the hemorrhoidal tissue to resume its normal physiological form and

functions. To our knowledge, this is the 1st time in the scientific world, that a single topical, multi-target treatment for internal hemorrhoids is conceived which can mechanically and nearly instantly reduce the volume of the hemorrhoids, as well as pain, irritation, bleeding, and lead to nearly complete recovery within 2-3 weeks without any undesirable effect.

The therapeutic potential of this new generation of simple but scientific and logical treatment needs to be exploited for other similar topical pathologies.

References

1. Mounsey AL, Halladay J, Sadiq TS (2011) Hemorrhoids. Am Fam Physician 84: 204-210.
2. Lohsiriwat V (2013) Approach to hemorrhoids. Curr Gastroenterol Rep 15: 332.
3. Lohsiriwat V (2012) Hemorrhoids: from basic pathophysiology to clinical management. World J Gastroenterol 18: 2009-2017.
4. Gulati OP (2014) Pycnogenol® in chronic venous insufficiency and related venous disorders. Phytother Res 28: 348-362.
5. Altomare DF, Giannini I (2013) Pharmacological treatment of hemorrhoids: a narrative review. Expert Opin Pharmacother 14: 2343-2349.
6. Varut Lohsiriwat (2015) Treatment of hemorrhoids: A coloproctologist's view. World J Gastroenterol 21: 9245–9252.
7. Mounsey AL, Henry SL (2009) Clinical inquiries. Which treatments work best for hemorrhoids? J Fam Pract 58: 492-493.
8. Maloku H, Gashi Z, Lazovic R, Islami H, Juniku-Shkololli, et al. (2014) A. Laser Hemorrhoidoplasty Procedure vs Open Surgical Hemorrhoidectomy: a Trial Comparing 2 treatments for Hemorrhoids of Third and Fourth Degree. Acta Inform Med 22: 365-367.
9. Lu M, Yang B, Liu Y, Liu Q, Wen H, et al. (2015) Procedure for prolapse and hemorrhoids vs traditional surgery for outlet obstructive constipation. World J Gastroenterol 21: 8178-8183.
10. Shrivastava R (2005) Non-solid composition for local application. Patent PCT/FR99/01340, International publication N°WO 00/74668 A1 on 14/12/2000.
11. Shrivastava R, Shrivastava L (2016) Composition for topical application comprising glycerol and tannins. International PCT application N° PCT/EP2013/061835, Publication N° WO 2014/194966 A1 of 11.12.2014.
12. Hollingshead JR, Phillips RK (2016) Haemorrhoids: modern diagnosis and treatment. Postgrad Med J. 92: 4-8.
13. Herman V, Abbas MA (2007) Hemorrhoids: Modern Remedies for an Ancient Disease. Perm J 11: 74–76.
14. Welling DR, Wolff BG, Dozois RR (1988) Piles of defeat: Napoleon at Waterloo. Dis Colon Rectum 31: 303-305.
15. Kiuchi T, Asakura K, Nakano M, Omae K (2017) Bidet toilet use and incidence of hemorrhoids or urogenital infections: A one-year follow-up web survey. Prev Med Rep 16: 121-125.
16. Sanchez C, Chinn BT (2011) Hemorrhoids. Clin Colon Rectal Surg 24: 5–13.
17. Ohning GV, Machicado GA, Jensen DM (2009) Definitive therapy for internal hemorrhoids--new opportunities and options. Rev Gastroenterol Disord 9: 16-26.
18. Rakinic J, Poola VP (2014) Hemorrhoids and fistulas: new solutions to old problems. Curr Probl Surg 51: 98-137.
19. Gurel E, Ustunova S, Ergin B, Tan N, Caner M, et al. (2013) Herbal haemorrhoidal cream for haemorrhoids. Chin J Physiol 56: 253-262.
20. Hernández-Bernal F, Castellanos-Sierra G, Valenzuela-Silva CM, Catasús-Álvarez KM, Martínez-Serrano O et al. (2015) Recombinant streptokinase vs hydrocortisone suppositories in acute hemorrhoids: A randomized controlled trial. World J Gastroenterol 21: 7305-7312.
21. Belcaro G, Gizzi G, Pellegrini L, Dugall M, Luzzi R, et al. (2014) Pycnogenol® in postpartum symptomatic hemorrhoids. Minerva Ginecol 66: 77-84.
22. Newton GD, Pray WS, Popovich NG (1996) New OTC drugs and devices: a selected review. Am Pharm 35: 108-116.
23. Silverman R, Bendick PJ, Wasvary HJ (2005) A randomized, prospective, double-blind, placebo-controlled trial of the effect of a calcium channel blocker ointment on pain after hemorrhoidectomy. Dis Colon Rectum 48: 1913-1916.
24. Tomiki Y, Ono S, Aoki J, Takahashi R, Ishiyama S, et al. (2015) Treatment of Internal Hemorrhoids by Endoscopic Sclerotherapy with Aluminum Potassium Sulfate and Tannic Acid. Diagn Ther Endosc. 2015: 517-690.
25. Gupta PJ (2009) Current guidelines for anal fissure treatment and evidence-based approach towards hemorrhoids. Chir. 30: 461-471.
26. Hall JF (2013) Modern management of hemorrhoidal disease. Gastroenterol Clin North Am. 42: 759-772.
27. Fluhr JW, Darlenski R, Surber C (2008) Glycerol and the skin: holistic approach to its origin and functions. Br J Dermatol. 159: 23-34.