Journal of Surgery
Giarratano G, et al. J Surg 9: 11065
www.doi.org/10.29011/2575-9760.011065
www.gavinpublishers.com
Research Article

Efficacy and Safety of CONAN® Proctological Cream Formulation in the Topical Treatment of Haemorrhoidal Disease and Anal Fissures: A Randomized Controlled Clinical Trial

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Citation: Giarratano G, Saraceno F, Toscana C, Sileri P, Di Lorenzo N (2024) Efficacy and Safety of CONAN® Proctological Cream Formulation in the Topical Treatment of Haemorrhoidal Disease and Anal Fissures: A Randomized Controlled Clinical Trial. J Surg 9: 11065 DOI: 10.29011/2575-9760.11065

Received Date: 01 June 2024; **Accepted Date:** 05 June 2024; **Published Date:** 08 June 2024

Abstract

Background: To evaluate the role of CONAN® Proctological Cream containing escin, hesperidin and hyaluronic acid in topical treatment of haemorrhoidal disease and anal fissures and its potential efficacy in reducing related symptoms. **Methods:** Forty patients with haemorrhoidal disease and anal fissures were enrolled. Of them, 20 were randomized to receive the medical device CONAN® Cream (Group A) and 20 to the untreated control group (Group B). At each scheduled visit, total symptoms were assessed and recorded by assigning a Numerical Rating Scale score from 0 to 10. The adverse events reported by study subjects were also assessed and recorded. **Results:** At the end of observational period the group treated with CONAN® Proctological Cream obtained a statistically significant improvement ($p<0.001$) in total symptoms calculated using the NRS score compared to the untreated group. No adverse effects were reported.

Conclusions: CONAN® Proctological Cream is safe and efficacious in the treatment of symptoms associated with haemorrhoidal disease and anal fissures.

Keywords: Anal Fissure; Controlled Clinical Trial; Conservative Treatment; Haemorrhoids; Proctological Cream; Topic Treatment

Introduction

Haemorrhoidal Disease (HD) and Anal Fissure (AF) are two of the most common diseases referred to the proctologist. The prevalence of haemorrhoids in Western is very high, between 4,4% and 12,8% in normal adult population [1,2], this pathology affects adults of any age and sex [3], luckily however only a poor percentage of this population need surgical treatment; most patients with HD can be treated by conservative therapy [4,5]. Haemorrhoids are categorized in four degrees (from 1 to 4) by Goligher's Classification [6] and this classification is still used for the treatment planning. Conservative treatments are preferred in grade 1-2 and in selected grade 3 of HD and include high-fibres diets, topical medicament, stool softeners, oral venotonic [7,8]. The mucosal inflammation of vascular plexus is cause of main symptoms of HD: rectal bleeding and/or pain during defecation and itching. The AF typically affects young adults with similar incidence in both sexes [9,10]. It consists of a longitudinal ulcer in the squamous epithelium of the anus and the most frequent symptoms are pain during and after defecation, associated with rectal bleeding and sphincter spasm [11]. AF is classified as acute with a duration about 2-4 weeks [9] or chronic when it persists more than 8-12 weeks. Chronic Anal Fissure (CAF) is characterized of less pain during defecation and it is associated to a sentinel pile or skin tag [12]. In patients affected by acute or chronic AF the first line of treatment is based on topical medicament and bowel-function regulation [13]. In the clinical practice a lot of topical medicaments are used for most common proctologic disease. Different topical formulations have been evaluated in study with patient affected by HD and AF but sometimes studies are heterogeneous [14].

In our study we tested CONAN® (Proctological Cream, Medical Device, Omikron Italia Srl) a proctological cream containing 2.5% glycerin macerate from horse chestnut buds (escin), 1% hesperidin, 0.1% hyaluronic acid, 0.1% centella asiatica and 2.5% glycerinic extract of mallow. These substances have documented effects on the microcirculation and inflammation with a decongesting [15], venotonic [16] and trophic-healing action [17]. Escin has a vasoprotective action by inhibiting the activity of elastase and hyaluronidase, two enzymes that damage the vessel endothelium and the extracellular matrix, consequently weakening their structure. By reducing the activity of these enzymes, the vessels regain their normal resistance and permeability [18]. Flavonoids like hesperidin are a class of naturally-occurring compounds with a proven action on wall tone, vessel permeability and the inflammatory process [19]. Hyaluronic acid supports tissue regeneration by promoting cell proliferation and migration [20]. Centella Asiatica extract counteracts the effects of oxidative damage [21] Glycerin extract of mallow has antioxidant property [22]. Aim of the study is to assess the efficacy, safety and tolerability of CONAN® on most frequent symptoms in grade 1-2 HD and in AF.

Matherials and Methods

Study Design

Between March to September 2022, forty consecutive patients (pts) were recruited for this study. The trial was conducted as a single center, prospective, randomized, controlled, parallel group. Study approval was achieved from the local ethical committee according to the Italian bioethics laws in concordance with the Helsinki Declaration Principles. A signed informed consent was obtained from every patient for the utilization of her/his anonymized data for research purposes.

Inclusions and Exclusions

We included adult patients aged between 18-70 years who were affected by HD grade 1-2 and AF. The exclusion criteria were HD grade 3-4, proctitis, on-going therapy with topical treatments containing phlebotropic and/or anti-inflammatory substances, surgical treatment less than one year prior to inclusion, pregnancy and breastfeeding as well as known hypersensitivity to the ingredients of the study product.

Work Up

The study population was randomized into two treatment arms: Group A, active treatment (CONAN® Proctological Cream, Medical Device, Omikron Italia Srl) and Group B, the control group (bowel-function regulation). The patients of both groups were instructed to follow a healthy diet including an adequate fibre intake and general advice for facilitating evacuation using stool softeners. The active treatment samples used for the duration of the study were allocated at the site involved and consisted in 30 g tubes with an endorectal applicator, identified by the batch number, expiry date and information on the study on dedicated labels.

The treatment of patients randomized to Group A consisted in applying the local treatment (1 application 3 times/day) for 30 days.

The study plan involved 3 visits:

- V1 patient enrolment;
- V2 after a 15 day follow-up period;
- V3 after 30 days, last patient follow-up.

During the first outpatient clinic visit (V1), the principal investigator of the study provided each patient with the information sheet and informed consent form and illustrated the aims of the study.

Once the consent form had been signed, the clinical details of all patients, such as general, family and vascular information, as well as information on any on-going topical and/or systemic therapies, were collected. A full proctology examination was then carried out to ensure the inclusion criteria were met. Eligible patients were subsequently enrolled, randomized to one of the two study groups and underwent the procedures required by the protocol: proctology examination and collection of the clinical data relating to total symptoms using the one-dimensional quantitative NRS – Numerical Rating Scale (a numerical scale with arbitrary scores from 0 to 10 for symptom intensity, 0 absent – 10 extreme) to rate symptoms such as burning, itch, heavy feeling and foreign body sensation. At the end of the proctology examination (V1), patients in Group A were given 3 packs of the medical device CONAN® Proctological Cream and the relevant instructions for application: 1 application 3 times a day for 30 days on the affected area. The patients underwent another full proctology examination and total symptom severity rating using the NRS after 15 days (V2) and 30 days (V3) of treatment. At the end of each visit, information on symptoms and any adverse events was recorded in a dedicated case report form (CRF) maintaining patient anonymity. Patients affected by HD were divided on predominant symptoms: bleeding, itching/anitis, pain/thrombosis. Patients affected by AF were divided in acute and chronic. The primary outcome was the change in the symptom numerical rating scale (NRS) score after one month (V3) of treatment compared to the baseline in the two groups.

Safety Analysis

The safety of the treatment was investigated by recording and systemic and local adverse events such as systemic allergic reactions, skin sensitisation and discomfort, etc. Treatment compliance was evaluated through assessment by the investigator of the empty study treatment cream tubes returned by patients at the end of the study.

Statistical Analysis

The quantitative data were presented as mean and standard deviation. The categorical data were presented as number and percentage.

The Chi-squared test was used to analyse the difference between the two groups for the categorical variables and the T-test was used to analyse the quantitative variables.

The mixed-effect Poisson model with robust standard error was used to compare the changes in NRS score between the two groups between V3 and V1 (primary outcome). Time, treatment and their interactions were considered fixed effects, whereas the subject was considered a random effect.

The same model was used to compare the change in the NRS score at the 3 time-points.

The estimated means, changes and the differences between the changes were estimated using the models.

The data were analysed using STATA 16.1 software and a p value <0.05 was considered statistically significant.

Results

A total of 40 patients, 25 females and 15 males, between 24 and 71 years of age, were enrolled and randomized 1:1 to the two groups. Twenty patients were randomized to the active treatment with CONAN® Proctological Cream (Group A) and twenty to the untreated control group (Group B).

No significant difference was observed between the two groups in terms of sex and age distribution.

In Table 1 we reported all demographic data. At baseline (V1) the mean (sd) NRS symptom rating scale score was 6.75 (1.1) points in Group A and 6.15 (1.04) points in Group B (p=0.098).

		Group A (n=20)		Group B (n=20)		p
Sex (n, %)						0.744
	Females	12	60	13	65	
	Males	8	40	7	35	
Age (mean, sd)		44	10.6	45	13.5	0.782
Condition (n, %)						0.474
	HAEMORRHOIDS	17	85	15	75	
	ANAL FISSURES	3	15	5	25	
Comorbidities						0.661
	Hypertension	1	5	3	15	
	Psoriasis	1	5			
	Hypercholesterolaemia			1	5	

Table 1: Sample characteristics.

After 30 days (V3), the mean NRS score had changed from 6.75 to 3.95 points in Group A and from 6.15 to 4.85 points in Group B; there was a mean decrease in the NRS score of -2.8 (0.17) points in Group A and of -1.3 (0.15) points in Group B (Figure 1) this difference is statistically significant (1.5, 95% CI: 1.06-1.94; p<0.001). (Table 2; Figure 1).

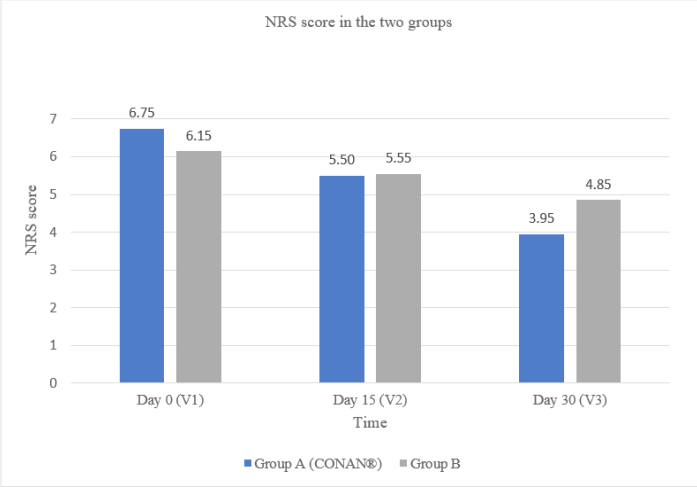

Figure 1: NRS score at V1, V2 and V3 in the two groups.

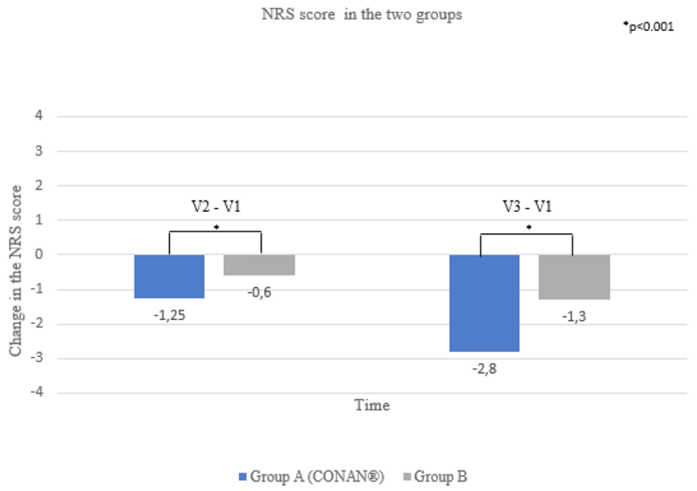

Figure 2: Change in the NRS score between V2/V1 and V3/V1 in the two groups.

	Group A (Conan®)		Group B		
	mean	SE	mean	SE	p
V1	6.75	0.25	6.15	0.23	
V3	3.95	0.32	4.85	0.23	
V3-V1	-2.8	0.17	-1.3	0.15	<0.001

Estimated by the mixed-effect Poisson

Table 2: Change in the NRS score between V1 and V3 in the two groups.

This trend was already evident after 15 days of treatment (0.65, 95% CI: 0.33-0.97; p<0.001). The results are shown in Table 3 and Figure 2.

	Group A (Conan®)		Group B		
	mean	SE	mean	SE	p
V1	6.75	0.25	6.15	0.23	
V2	5.50	0.24	5.55	0.23	
V2-V1	-1.25	0.1	-0.6	0.13	<0.001

Estimated by the mixed-effect Poisson

Table 3: Change in the NRS score between V1 and V2 in the two groups.

We also analyzed the subgroup of haemorrhoidal disease and anal fissure as group A (treated) and group B (untreated). At V1 there was no difference in NRS score between group A and group B in both groups. For haemorrhoidal disease the NRS score changed from 6.59 (V1) to 5.35 (V2) to 3.65 (V3) points in Group A and from 6.07 (V1) to 5.47 (V2) to 4.80 (V3) points in Group B, with a mean decrease (SE) of -1.24 (0.10) points at V2 and -2.9 (0.18) points at V3 in Group A and of -0.6 (0.16) points at V2 and -1.3 (0.15) points at V3 in Group B compared to the baseline. (Table 4; Figure 3).

	Haemorrhoidal Disease				
	Group A (Conan®)		Group B		
	mean	SE	mean	SE	p
V1	6.59	0.25	6.07	0.26	
V2	5.35	0.24	5.47	0.27	
V3	3.65	0.32	4.80	0.29	
V2-V1	-1.24	0.1	-0.6	0.16	0.001
V3-V1	-2.94	0.18	-1.27	0.15	<0.001

Estimated by the mixed-effect Poisson model

Table 4: Change in the NRS score between V2/V1 and V3/V1 in patients with Haemorrhoidal Disease.

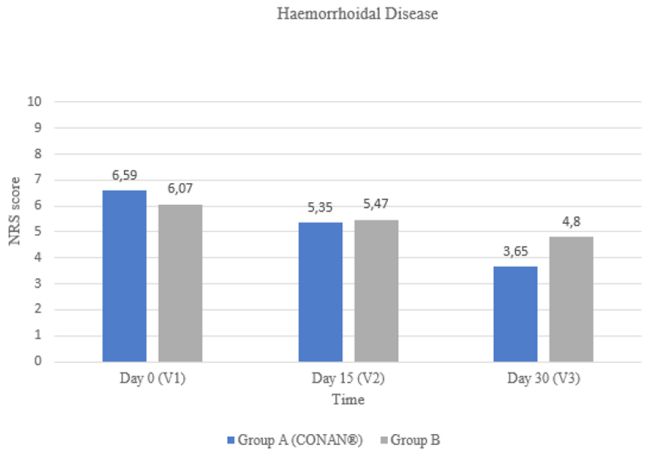

Figure 3: NRS score at V1, V2 and V3 in patients with Haemorrhoidal Disease.

The difference in change between the two groups is statistically significant at V2 (0.64 CI95% 0.26-1.01 P=0.001) and at V3 (1.67, CI95% 1.22-2.13; p<0.001), indicating a statistically significant greater reduction in symptoms in the group treated with CONAN® Proctological Cream compared with the Group B (Figure 4). For Anal fissures the NRS score changes from 7.67 (V1) to 6.33 (V2) to 5.67 (V3) points in Group A and from 6.4 (V1) to 5.80 (V2) to 5.00 (V3) points in Group B, with a mean (SE) decrease of – 1.33 (0.29) points at V1 and -2.0 (0.0) points at V2 in the group treated with CONAN® Proctological Cream and of -0.6 (0.23) points at V1 and -1.4 (0.38) points at V2 in Group B (Table 5; Figure 5). Although a considerable difference in change was observed between the two groups, in this case statistical significance was not achieved (0.60, CI95% -0.151;1.35; p=0.117).

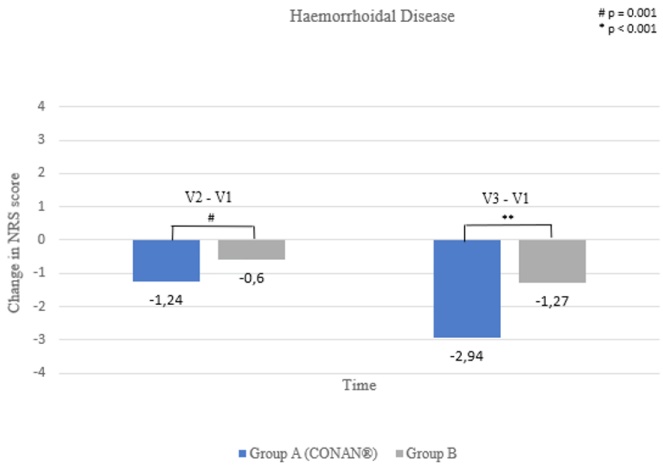

Figure 4: Change in NRS score between V2/V1 and V3/V1 in patients with Haemorrhoidal Disease.

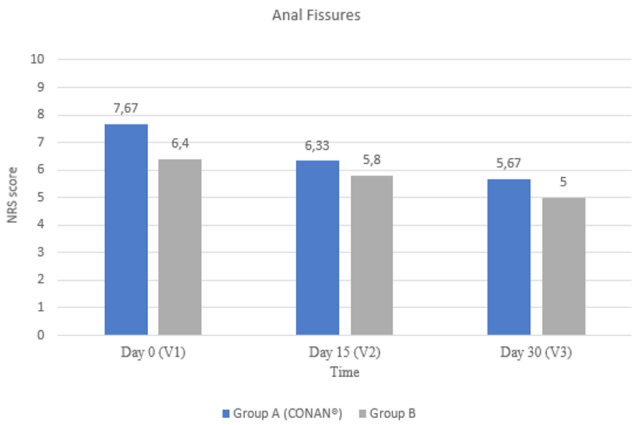

Figure 5: NRS score at V1,V2 and V3 in patients with Anal fissures.

Anal Fissures					
	Group A (Conan®)		Group B		
	mean	SE	mean	SE	p
V1	7.67	0.58	6.4	0.49	
V2	6.33	0.77	5.8	0.47	
V3	5.67	0.58	5	0.3	
V2-V1	-1.33	0.29	-0.6	0.23	0.05
V3-V1	-2	0	-1.4	0.38	0.117

Estimated by the mixed-effect Poisson model

Table 5: Change in the NRS score between V2/V1 and V3/V1 in patients with Anal fissures.

The two pathologies had also classified according to the symptoms obtaining 4 classes: 1A Anitis itching in patients with HD; 1B Bleeding in patients with HD; 2A Acute in patients with AF; 2B Chronic in patients with AF (Table 6).

Haemorrhoidal Disease	**Group A (n=17)**		**Group B (n=15)**	
	n°	(%)	n°	(%)
Anitis - Itching (1A)	7	41.2	4	26.7
Bleeding (1B)	10	58.8	11	73.3
Anal Fissures	**Group A (n=3)**		**Group B (n=5)**	
	n°	(%)	n°	(%)
Acute Fissure (2A)	1	33.3	2	40
Chronic fissure (2B)	2	66.7	3	60

Table 6: Symptom Classification.

The largest group was 1B in which there were 10 patients with treatment A and 11 patients with treatment B, followed by group 1A with 7 patients in group A and 4 patients in group B.

Group 2A consisted of only 3 patients (1 with treatment A and 2 with treatment B) and group 2B consisted of 5 patients, 2 with treatment A and 3 with treatment B.

The comparison between treatments and over time was made only for groups 1A and 1B; groups 2A and 2B given the low number only descriptive statistics was reported (Table 7).

	Patients with Acute Fissures in AF (Group 2A)							
	A (n=1)				B (n=2)			
	mean	SD	median	min-max	mean	SD	median	min-max
V1	9				6.5	0.71	6.5	6-7
V2	8				6	0	6	6-7
V3	7				5.5	0.71	5.5	5-6
	Patients with Chronic Fissures in AF (Group 2B)							
	A (n=2)				B (n=3)			
	mean	SD	median	min-max	mean	SD	median	min-max
V1	7.00	0	7.0	07-Jul	6.33	1.53	6.0	5-8
V2	5.50	0.7	5.5	05-Jun	5.70	1.53	6.0	4-7
V3	5.50	0	5.0	05-May	4.67	0.58	5.0	4-5

Table 7: NRS score at V1,V2 and V3 in patients with Acute Fissure in patients with Anal Fissures (2A)/ Chronic fissure in patients with Anal Fissures (2B).

At V1 the NRS score did not differ between treatment A and treatment B either in symptom 1A or symptom 1B. In particular, the mean (sd) is 6.57 (0.98) in group A and 5.75 (0.96) in group B for symptoms 1A (p=0.210), 6.6 (1.17) in group A and 6.18 (1.08) in group B for symptoms 1B (p=0.405).

Results in 1A Anitis Itching in Patients with Haemorrhoidal Disease

For symptoms 1A the NRS score changed from 6.57 (V1) to 3.71 (V3) in group A and from 5.75 (V1) to 4.50 (V3) in group B, there was therefore an average reduction (SE) of - 2.9 (0.39) point at V3 in A and 1.3 (0.23) points at V2 in B. The difference in variation between the two groups was statistically significant (1.61 CI95% 0.72-2.50 p<0.001) indicating a significantly greater reduction in A than in B (Table 8; Figures 6-7).

	Anitis-itching (Group 1A)					Bleeding (Group 1B)				
	A		B			A		B		
	mean	SE	mean	SE	p	mean	SE	mean	SE	p
V1	6.57	0.36	5.75	0.43		6.60	0.36	6.18	0.32	
V2	5.29	0.35	5.25	0.57		5.40	0.33	5.55	0.31	
V3	3.71	0.59	4.5	0.59		3.60	0.36	4.91	0.33	
V2-V1	-1.29	0.18	-0.5	0.26		-1.20	0.13	-0.63	0.2	
V3-V1	-2.86	0.39	-1.25	0.23	<0.001	-3.00	0.14	-1.27	0.19	<0.001

Table 8: Change in the NRS between V2/V1 and V3/V1 in patients with Anitis-itching (Group 1A) and Bleeding (Group 1B).

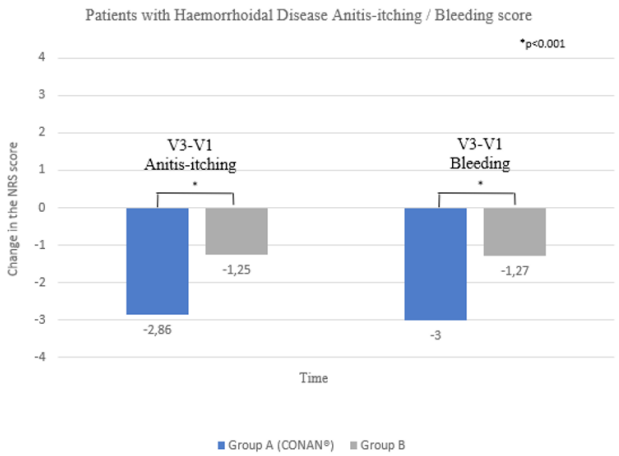

Figure 6: Change in NRS score at V3 between the two groups in patients with Haemorrhoidal Disease Anitis-itching (1A) / Bleeding (1B).

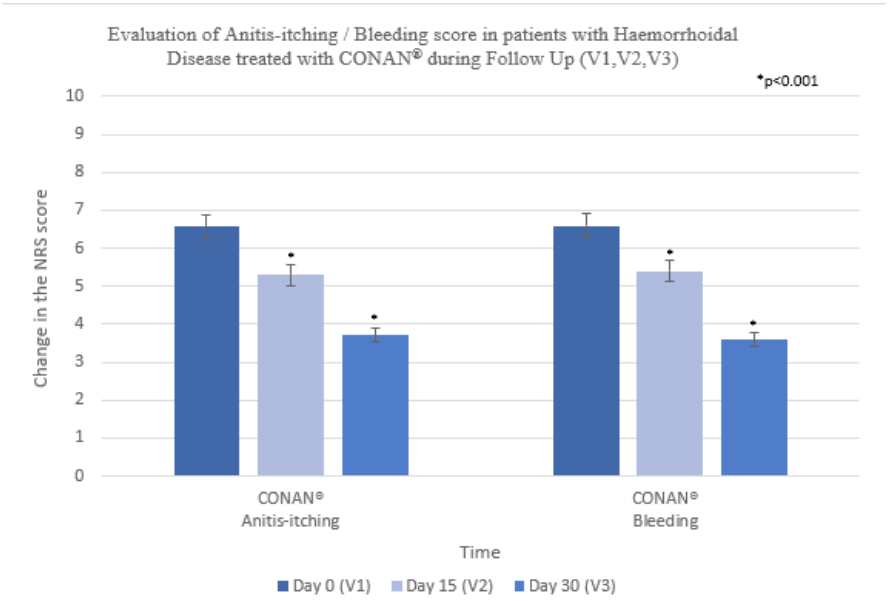

Figure 7: Evaluation of Anitis-itching / Bleeding score in patients with Haemorrhoidal Disease treated with CONAN® during Follow Up (V1,V2,V3).

Results in 1B Bleeding in Patients with Haemorrhoidal Disease

For symptoms 1B the NRS score changed from 6.60 (V1) to 3.60 (V3) in group A and from 6.18 (V1) to 4.91(V3) in group B, there is therefore an average reduction (SE) of -3.0 (0.14) points at V3 in A and -1.3 (0.19) points at V3 in B. The difference in variation between the two groups was statistically significant (1.73 CI95% 1.26-2.20 p<0.001) indicating a significantly greater reduction in A than in B (Table 8; Figures 6-7).

Safety Analysis

No systemic and local adverse events related with topical treatment with CONAN® was gathered.

Discussion

In this clinical study we demonstrated that the use of a topical treatment containing escin, hesperidin and hyaluronic acid decreased the intensity of the symptoms associated with haemorrhoidal disease and anal fissures. CONAN®, showed high efficacy in reducing symptoms as early as two weeks, until their disappearance at 30 days, in the absence of adverse effects. In HD CONAN® it proved to be very effective especially in treating symptoms such as itching and bleeding, showing a statistically significant difference compared to the control group. It has also proved effective in AF, however the sample was probably too small to show a statistically significant difference between the two groups, although in the group of treated patients, the patients reported a partial benefit at the end of the treatment. These results can be attributed to the synergistic action of the ingredients contained in CONAN®, such as the decongesting action of hesperidin, the vasoprotective and venotonic action of escin and the trophic-healing action of hyaluronic acid and are in line with the results described in the literature. In a recent, prospective, randomized, triple-blind, controlled study with a blend of flavonoids containing hesperidin, Giannini I et al. showed that there is an improvement in the symptoms associated with chronic and acute haemorrhoidal disease, with a decrease in pain, bleeding, oedema, itch, number of analgesics taken and number of patients who experienced thrombosis [15].

Adnan Hasanoglu et al. demonstrated that hesperidin via the topical route exert its anti-inflammatory and anti-oedematous action, also accelerating wound healing time [23]. In 2021 Cho JR et al. demonstrated the effectiveness of topical treatment with hyaluronic acid in promoting the healing of perianal wounds with a statistically significant difference compared to the control group with a 80% of healing rate after 11 days of treatment. Resolution was taken as re-epithelisation rate and absence of ulcers, haemorrhagic events and inflammatory processes [24]. Gallelli L et al. demonstrated that patients randomized to receive a topical gel containing escin presented a significant increase in venous wall tone compared to the group treated with placebo after two weeks. The treated patients also reported an increase in the overall scores for symptoms such as pain, burning and itch, after 14 days of treatment [20]. Chiaretti et al reported none patients with discomfort in the application [25]. In conclusions our randomized study showed that the use of CONAN® Proctological Cream was able to significantly and rapidly reduce symptoms severity in patient with grades I-II HD and in AF. CONAN® also had an excellent tolerability profile; we did not record adverse effect and all patients completed the study. This efficacy is given by the synergistic action of its active ingredients, such as escin, hesperidin and hyaluronic acid on the main signs and symptoms of these conditions, thereby proving to be an excellent aid for the conservative treatment in proctological disease to delay or avoid surgery; resulting in an improvement in the clinical management of these patients. However, a long-term follow-up study in a large population is required to confirm these findings.

Funding

This trial was funded by Omikron Italia Srl

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