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RANDOMISED CONTROLLED TRIAL

Efficacy and safety of *Propionibacterium* extract gel versus glyceryl trinitrate ointment in the treatment of chronic anal fissure: a randomized controlled trial

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Abstract

Aim: Chronic anal fissure (CAF) is an extremely frequent finding in clinical practice. Several topical agents have been proposed for its treatment with the common goal of increasing anodermal blood flow to promote healing. The aim of this study was to compare the efficacy and safety of a *Propionibacterium* extract gel (PeG) and 0.4% glyceryl trinitrate ointment (GTN) in patients with CAF.

Method: Patients were randomly allocated to a PeG or GTN group and medication was administered every 12 h for 40 days. The primary outcome was the success rate, as measured by a decrease in the REALISE scoring system for anal fissure at 10, 20 and 40 days after initiating either treatment. The secondary outcomes recorded at the same time points were healing rate, visual analogue scales for itching and burning, rate of complications and adverse events, patient quality of life and satisfaction, and cost analysis.

Results: A total of 120 patients were enrolled, and 96 patients (PeG, $n=53$; GTN, $n=43$) completed the primary outcomes. A significant decrease over time in the REALISE score was observed in both groups. Adverse events occurred more frequently in the GTN group than in the PeG group, peaking at visit 1 [37 (63.8%) vs. 2 (3.4%), respectively], with headache being the most prevalent. The between-treatment cumulative average costs per patient were significantly higher for GTN than that for PeG at each follow-up visit. There were no other significant differences between the two groups for any of the other outcomes.

Conclusion: While there was no difference in healing rates between the two treatments, PeG was more cost-effective and associated with fewer adverse events.

KEYWORDS
anal fissure, glyceryl trinitrate, headache, healing, *Propionibacterium*

INTRODUCTION

The concept of anal fissure was first introduced by Lockhart-Mummery in 1934 as a linear or oval-shaped tear in the anoderm that can potentially extend from the anal verge to the dentate line [1].

Anal fissures can be categorized as acute or chronic based on their morphology and time of onset, with a 6-week cut-off often used to label anal fissures as chronic. While acute anal fissures typically present as linear lesions with clear margins, chronic anal fissures (CAFs) are typically relatively wider and deeper with granulation tissue at the base and potential exposure of the internal sphincter.

The pathophysiology of CAFs is not yet well understood, with the *primum movens* still being a topic of debate. The ischaemic theory proposed by Schouten et al. in 1996 [2], highlighting the role of a high resting sphincter tone and decreased anodermal blood flow, especially at the posterior midline, is the most widely accepted.

Although several therapeutic strategies have been proposed to correct the pathophysiological alterations underlying CAFs [i.e. fibre or sitz baths [3], topical nifedipine/lidocaine [4] and glyceryl trinitrate (GTN) ointments [5], and botulinum toxin [6]], a partial lateral internal sphincterotomy is still considered the gold standard despite possible detrimental sequelae, such as soiling and some degree of anal incontinence [7, 8]. Conservative medical approaches continue to play an important role in this scenario because of their low cost and safety, with surgery being exclusively recommended after the failure of multiple lines of medical therapy [9].

0.4% GTN ointment is a well-known nitric oxide donor that promotes CAF healing by decreasing resting anal pressure and increasing anodermal blood flow via the stimulation of intracellular cyclic guanosine monophosphate, resulting in a consequent reduction in cytosolic calcium [10]. The success rate is variable, with 28% of patients experiencing transient headaches; this often leads to drug discontinuation and poor compliance with treatment [7].

Propionibacterium extract gel (PeG) is a topical product that protects skin and mucous membranes from external agents [11, 12]. Its film-forming property on the epidermis helps reduce inflammation, itching and pain, while the adjunct of antioxidant ingredients helps promote the healing process [13, 14]. This product is currently available only in Italy for this indication.

This study aimed to compare the efficacy and safety of PeG (Emorsan Rag®) and GTN (Rectogesic®) in patients with CAF.

METHOD

Study design

This was an open-label, randomized parallel-group controlled trial conducted between October 2021 and March 2022 across five high-volume tertiary referral centres for proctological disorders. A power analysis was performed to determine the number of patients enrolled in each arm. The protocol was approved by all local ethics committees in accordance with the Declaration of Helsinki (1996) and the International Conference on Harmonization Good Clinical Practice guidelines. All the patients received full information and provided informed consent for inclusion in the study.

Study population

Consecutive patients diagnosed with CAF in our outpatient clinics and aged 18–75 years were included in this study. Patients with faecal incontinence, other proctological diseases, inflammatory bowel disease, a history of anal surgery or previous or concomitant treatment for anal fissures, a sexually transmitted disease or cancer, who were undergoing immunosuppressive treatment, were pregnant or breastfeeding or had a known allergy to one of the agents contained in the evaluating drugs were excluded. Patients who were unable to return for postoperative follow-up visits or showed an unwillingness to sign the informed consent form were also excluded.

Digital rectal examination (DRE), anoscopy and anorectal manometry were performed at each follow-up visit unless they could not be tolerated by the patient. In cases where it was impossible to perform both a DRE and anoscopy during enrolment (baseline), the CAF site was determined by inspecting the anal region by asking the patient to bear down during defaecation while spreading the glutei. In cases with a suspicious and unusual location, a colonoscopy was performed to rule out other neoplastic or inflammatory disorders.

After enrolment, patients were followed up for 10 (visit 1), 20 (visit 2) and 40 days (visit 3). The duration of the therapy and last follow-up visit were defined based on the results of the study, where no difference was found between 40 and 80 days in terms of healing rate and pain [15].

In addition to an onset more than 6 weeks previously, the presence of at least two of the following features proposed by Scholefield et al. [16]. were considered when diagnosing CAF: a sentinel skin tag, hypertrophic anal papillae, an exposed internal anal sphincter, a fibrotic lateral fissure or a fibrotic anal sphincter.

Outcome measures

A recently developed and validated five-item score, REALISE, was used from baseline to visit 3 to assess pain (score range 0–10), quality of life, duration of pain, intake of analgesics and bleeding. The latter four items were rated on a scale of 1–5 [17].

The degree of epithelialization of the fissure was determined at each visit and stratified into three levels, corresponding to <50% (i.e. nearly no change from baseline), >50% healing and complete healing.

Itching and burning were assessed using two visual analogue scales (VASs) (minimum score = 0, maximum score = 10) at each time point.

The Bristol stool chart (BST), a seven-point scale, was used to evaluate stool shape and consistency [18] from baseline to visit 3.

Three groups were identified: regular (type 3–4 BST), constipation (type 1–2 BST) and diarrhoea (type 5–7 BST).

Quality of life was evaluated at baseline and visit 3 using Short-Form 12 (SF-12), a 12-item subset of SF-36 that includes both physical (PCS) and mental component scores (MCS) [19, 20].

Finally, patient satisfaction was assessed at visit 3 using a five-point Likert scale (1 = unsatisfied, 2 = neutral, 3 = quite satisfied, 4 = very satisfied, 5 = extremely satisfied).

A cost analysis was performed according to the commercial values at the time of enrolment in the study [21].

Patients and investigators (the responsible clinicians were the assessors at each centre) were not blinded to the allocated treatment group.

Treatment plan

Patients were instructed to squeeze out approximately 1.5 mg from an aluminium tube containing GTN and apply it to the distal anal canal and perianal area with a gloved finger every 12 h for 40 days, as described elsewhere [22].

In the PeG group, 3 g of gel (3 cm) was applied twice daily for 40 days to the distal anal canal and perianal area. Both groups were instructed not to use any other topical preparations until study completion.

Patients in both groups were encouraged to prevent passing hard stools and constipation by using laxatives (macrogol twice or three times a day) and a recommended oral dose of ketorolac tromethamine (10 mg every 6 h) on an as-needed basis, not exceeding 40 mg per day.

At each follow-up visit, patients were asked about their willingness to continue treatment and the number of tubes/boxes consumed.

Safety

Safety was evaluated by reporting adverse drug effects (ADEs), adverse events (AEs), serious AEs and toxicity after each topical drug application. Toxicity was defined using the World Health Organization toxicity scale [23]. The AEs were stratified as none, remote, possible, probable or not assessable based on their relationship with the drug.

Sample size and randomization

Assuming a compound symmetry covariance structure, a within-patient autocorrelation of 0.50, a common 20% value for the standard deviation and a 10% noninformative dropout rate, a minimum of 59 patients per arm were required to test an average REALISE score improvement of at least 10% over time under the alternative hypothesis using a repeated measurement design ($1 - \beta = 0.80$, $\alpha = 0.05$). The expected value under the alternative hypothesis was derived from the literature data using a linear interpolation function. The patients were allocated to either group using a blocked randomization scheme with a fixed block size of six (Table S1).

Statistical analyses

The analyses were conducted using SAS 9.4 according to intention to treat principles. Data are presented as per cent or mean and median, along with standard deviation (SD) and interquartile range (IQR). Differences between treatment arms of categorical variables were tested using Fisher's exact test. Within treatment arms, score changes from baseline were estimated at all visits using the least squares means method and tested for multiple comparison. Multivariate analysis of variance was performed to test any possible association between some evaluated outcomes and factors such as age, score at baseline, fissure localization, bowel habit and visit. All tests were two-tailed and considered significant at the 5% level.

RESULTS

The CONSORT diagrams [24] are shown in Figure 1, and the patient characteristics and procedures at the time of enrolment are listed in Table 1. All follow-up visits were completed by 53 and 43 patients in the PeG and GTN groups, respectively. The number of patients included in the analysis of the clinical outcomes at each visit is detailed in Table 2.

Digital rectal examination

At visit 1, DRE was performed in 50 (86.2%) patients in the GTN group and in 51 (86.4%) patients in the PeG group, while at visit 2, 48 (88.9%) GNT patients and 50 (87.7%) PeG patients underwent the same examination. At visit 3, DRE was performed in 53 (100%) PeG patients and in 42 (97.7%) GTN patients. No statistically significant differences between groups were observed at any evaluated timepoint ($p > 0.05$).

The overall proportion of patients who underwent an anoscopy increased over time, with no significant differences between the groups ($p > 0.05$). As regards the PeG arm, anoscopy was performed in 25 (42.4%) patients at visit 1, in 26 (45.6%) at visit 2 and in 37 (69.8%) at visit 3. Concerning the GNT group, 17 (29.3%) patients underwent anoscopy at visit 1, while 24 (44.4%) and 22 (51.2%) were examined at visits 2 and 3, respectively.

None of the patients in either group underwent manometry at visit 1 and only two PeG patients (1.8% of all patients) underwent such examination at visit 2. In total, six patients underwent manometry at visit 3, of whom four (7.6%) were in the PeG group and two (4.7%) were in the GTN group ($p = 0.44$).

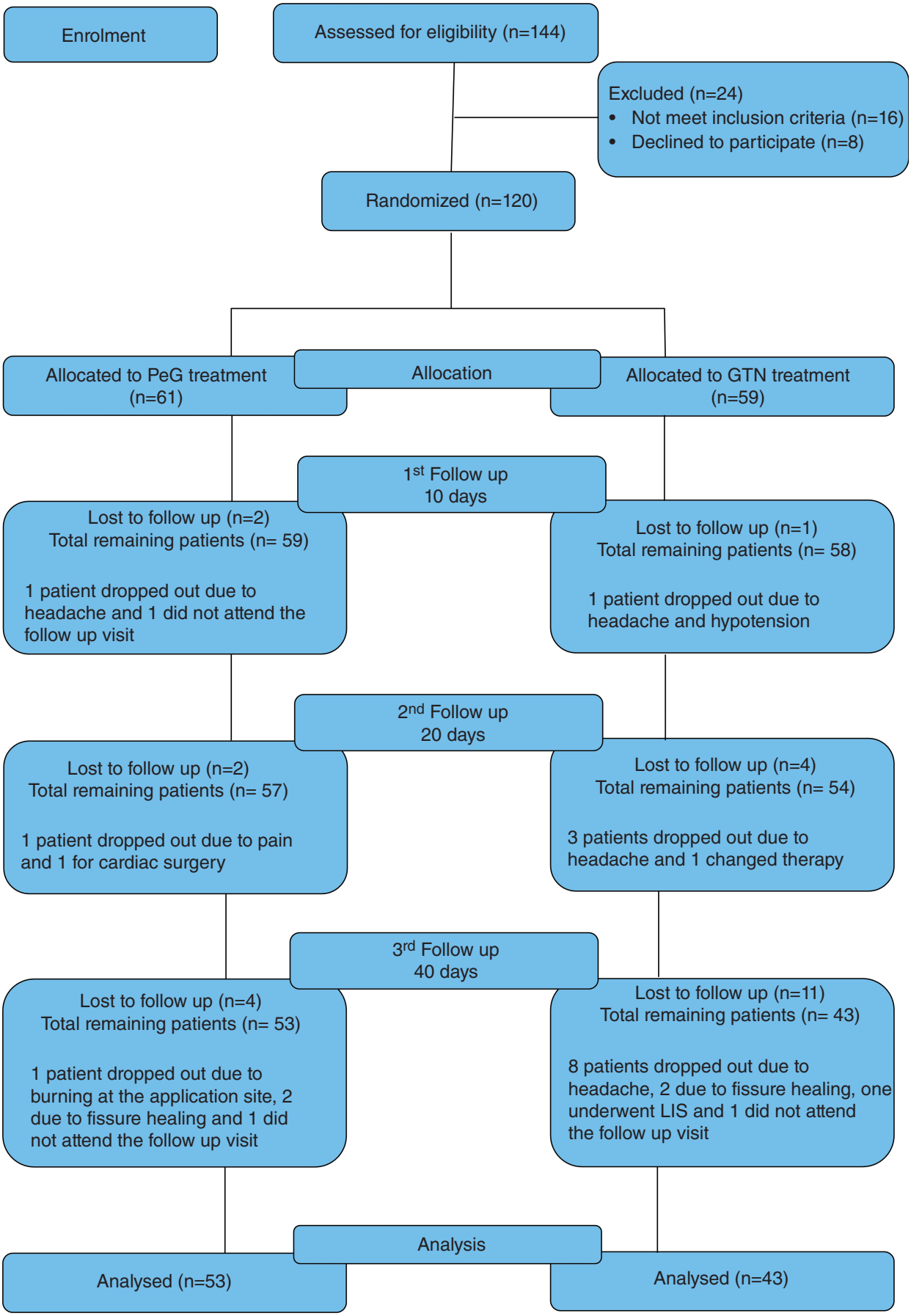

FIGURE 1 CONSORT diagram (GTN, glyceryl trinitrate ointment; LIS, lateral internal sphincterotomy; PeG, propionibacterium extract gel).

TABLE 1 Patient characteristics and diagnostic workup at baseline divided by treatment arm.

Characteristic	Treatment arm	
	PeG ($n=61$)	GTN ($n=59$)
Mean age (years) (SD)	44.0 (15.0)	46.2 (15.0)
Female gender (%)	28 (45.9)	32 (54.2)
Bristol stool chart (%)		
1–2	31 (53.0)	35 (59.3)
3–4	23 (37.7)	22 (37.3)
5–7	7 (11.5)	2 (3.4)
Fissure localization (%)		
Anterior	8 (13.1)	8 (13.6)
Anterior and posterior	1 (1.6)	0
Anterolateral	1 (1.6)	1 1.7)
Posterior	51 (83.6)	50 (84.8)
Obstetric history (%)		
Nulliparous	10 (35.7)	12 (37.5)
Multiparous	18 (64.3)	20 (62.5)
DRE (%)	58 (95.1)	52 (88.1)
Anoscopy (%)	31 (50.8)	23 (39.0)
Manometry (%)	4 (6.6)	1 (1.7)

Abbreviations: DRE, digital rectal examination; GTN, glyceryl trinitrate ointment; PeG, *Propionibacterium* extract gel; SD, standard deviation.

TABLE 2 Number of patients included in the analysis of the clinical outcomes at each visit.

Visit	Clinical outcome	No. of patients		
		Emorsan Rag® (PeG)	Rectogesic® (GTN)	Total
1	DRE	51	50	101
	Anoscopy	25	17	42
	Manometry	0	0	0
	REALISE score	59	58	117
	VAS score	59	58	117
	SF-12	59	58	117
	Epithelialization	59	58	117
2	DRE	50	48	98
	Anoscopy	26	24	50
	Manometry	2	0	2
	REALISE score	57	54	111
	VAS score	57	54	111
	SF-12	57	54	111
	Epithelialization	57	54	111
3	DRE	53	42	95
	Anoscopy	37	22	59
	Manometry	4	2	6
	REALISE score	53	43	96
	VAS score	53	43	96
	SF-12	53	43	96
	Epithelialization	53	43	96

Abbreviations: DRE, digital rectal examination; GTN, glyceryl trinitrate ointment; PeG, *Propionibacterium* extract gel; VAS, visual analogue scale.

Primary outcome

A steady average decrease in the REALISE score over time was observed in both groups (Table 3).

Significant mean decreases of 6.2 and 12.8 points for PeG and 6.2 and 13.7 points for GTN were observed from baseline at visits 1 and 3, respectively. Factors included in the multivariable analysis were not significantly associated with the observed score changes except for the REALISE score at baseline and visit (Table S2).

VAS for burning

A steady average decrease in the VAS burning score over time was observed in both groups (Table 3). Significant mean decreases of 2.5 and 5.2 points for PeG and 2.3 and 5.6 points for the GTN group were obtained from baseline at visits 1 and 3, respectively ($p<0.001$). Factors included in the multivariate analysis were not significantly associated with the observed score changes except for the VAS score at baseline and visit (Table S3).

VAS for itching

A steady average decrease in the VAS itching score over time was observed in both groups (Table 3). Significant mean decreases of 2.4 and 4.3 points for PeG and 2.0 and 4.1 points for the GTN group were obtained from baseline at visits 1 and 3, respectively ($p<0.001$). Factors included in the multivariate analysis were not significantly associated with the observed score changes except for the VAS score at baseline and visit (Table S4).

SF-12: PCS-12 and MCS-12

There was an increase in the PCS-12 score at visit 3 for both groups. Compared with the baseline, significant mean increases of 13.0 points for PeG and 15.4 points for GTN were observed at visit 3 ($p<0.001$).

Similar results were obtained for the MCS-12 score, with significant mean increases of 9.2 points for PeG and 11.2 points for GTN at visit 3 ($p<0.001$). Factors included in the multivariate analysis were not significantly associated with the observed score changes except for the PCS-12 and MCS-12 scores at baseline and visit (Tables S5, S6).

Epithelialization

Complete epithelialization increased from 1.7% and 0% at visit 1 to 5.3% and 7.4% at visit 2 and to 56.6% and 53.5% at visit 3 for the PeG

TABLE 3 Within-treatment differences from baseline (Δ)[a] in the REALISE and VAS scores of both treatment arms.

		PeG			GTN		
Outcome	**Visit**	**Mean (SD)**	**Δ (SE)[a]**	***p*-value[b]**	**Mean (SD)**	**Δ (SE)[a]**	***p*-value[b]**
REALISE	0	18.9 (4.0)	0	–	19.9 (4.8)	0	–
	1	12.4 (4.6)	−6.2 (0.6)	<0.001	13.7 (4.9)	−6.2 (0.6)	<0.001
	2	9.0 (4.2)	−9.4 (0.6)	<0.001	8.9 (5.0)	−10.3 (0.6)	<0.001
	3	5.3 (4.3)	−12.8 (0.6)	<0.001	4.9 (4.3)	−13.7 (0.6)	<0.001
VAS burning	0	6.2 (5.8)	0	–	6.7 (6,8)	0	–
	1	3.7 (3.6)	−2.5 (0.3)	<0.001	4.4 (3,6)	−2.3 (0.30)	<0.001
	2	2.5 (0.4)	−3.7 (0.3)	<0.001	2.6 (0,4)	−4.2 (0.30)	<0.001
	3	1.1 (0.2)	−5.2 (0.3)	<0.001	1.1 (0,2)	−5.6 (0.33)	<0.001
VAS itching	0	4.8 (3,7)	0	–	4.5 (2,7)	0	–
	1	2.4 (1,4)	−2.4 (0.27)	<0.001	2.6 (0,4)	−2.0 (0.27)	<0.001
	2	1.3 (0,2)	−3.4 (0.27)	<0.001	1.4 (0,3)	−3.2 (0.28)	<0.001
	3	0.6 (0,1)	−4.3 (0.27)	<0.001	0.4 (0,1)	−4.1 (0.29)	<0.001

Abbreviations: GTN, glyceryl trinitrate ointment; PeG, *Propionibacterium* extract gel; SD, standard deviation; SE, standard error; VAS, visual analogue scale.

[a]Least Squares Means.

[b]Test for changes versus baseline adjusted for multiple comparisons.

TABLE 4 Frequency distribution of the three evaluated levels of epithelization (≤50%, >50%, complete) divided by treatment arm at all visits.

			Treatment, *n* (%)[a]		
Visit	**Epithelialization**	**All patients (*N* = 120)**	**PeG (*n* = 61)**	**GTN (*n* = 59)**	***p*-value[c]**
1	≤50%	89 (76.1)	45 (76.3)	44 (75.9)	
	>50%	27 (23.1)	13 (22.0)	14 (24.1)	
	Complete	1 (0.9)	1 (1.7)	0	1.00
	Dropout[b]	3 (2.5)	2 (3.3)	1 (1.7)	1.00
2	≤50%	27 (24.3)	11 (19.3)	16 (29.6)	
	>50%	77 (69.4)	43 (75.4)	34 (63.0)	
	Complete	7 (6.3)	3 (5.3)	4 (7.4)	0.34
	Dropout[b]	9 (7.5)	4 (6.6)	5 (8.5)	0.74
3	≤50%	7 (7.3)	3 (3.1)	4 (9.3)	
	>50%	36 (37.5)	20 (37.7)	16 (37.2)	
	Complete	53 (55.2)	30 (56.6)	23 (53.5)	0.85
	Dropout[b]	24 (20.0)	8 (13.1)	16 (27.1)	0.07

Abbreviations: GTN, glyceryl trinitrate ointment; PeG, *Propionibacterium* extract gel.

[a]Per cent on nonmissing values.

[b]Per cent on total number of patients.

[c]Between treatments Fisher's exact test.

and GTN groups, respectively (Table 4, Figure S6). Fisher's exact test was not significant for any comparison between treatments. A significant overall increase in epithelialization of >50% or complete epithelialization was observed at visits 2 and 3 compared with visit 1 (75.7% vs. 23.9%, $p < 0.001$ and 92.7% vs. 23.9%, $p < 0.001$, respectively). However, there were no significant differences between the groups (OR 1.20; 95% CI 0.68–2.11). No significant differences were observed at each time point in the univariable analysis of the distribution of epithelialization between the treatment arms (Table S7). Compared with visit 1, the ORs for the increase in epithelialization (any grade) were 11.8 ($p < 0.001$) and 16.2 at visits 2 and 3, respectively, for PeG and 7.47 ($p < 0.001$) and 71.5 at visits 2 and 3, respectively, for GTN.

Satisfaction

There were no statistically significant differences between the two arms in terms of patient satisfaction ($p = 0.25$) (Table 5). After pooling

TABLE 5 Treatment satisfaction grade at visit 3 by treatment arm.

Satisfaction grade	All patients ($N=120$)	Treatment, *n* (%)[a] PeG ($n=61$)	GTN ($n=59$)	*p*-value[c]
Unsatisfied	5 (5.2)	3 (5.7)	2 (4.7)	
Neutral	7 (7.3)	4 (7.6)	3 (7.0)	
Quite satisfied	7 (7.3)	2 (3.8)	5 (11.6)	
Very satisfied	16 (16.7)	6 (11.3)	10 (23.3)	
Extremely satisfied	61 (63.5)	38 (71.7)	23 (53.5)	0.25
Dropout[b]	24 (20.0)	8 (13.1)	16 (27.1)	0.07

Abbreviations: GTN, glyceryl trinitrate ointment; PeG, *Propionibacterium* extract gel.

[a]Per cent on nonmissing values.

[b]Per cent on total number of patients.

[c]Between treatment Fisher's exact test.

the two most positive satisfaction levels, at visit 3, 44 (83.0%) patients in the PeG group were very or extremely satisfied compared with 33 (76.7%) patients in the GTN group ($p=0.44$). The dropout rate was higher in the GTN group [16 (27.1%) vs. 8 (13.1%) for the PeG group; $p=0.07$].

Adverse events

The frequency distribution for AEs according to treatment arm and visit is shown in Table 6. A significantly greater proportion of AEs of any type at each visit were observed in the GTN group than in the PeG group [visit 1, 37 (63.8%) vs. 2 (3.4%); visit 2, 27 (50.0%) vs. 3 (5.3%); visit 3, 18 (42.9%) vs. 1 (1.9%), respectively; $p<0.001$ for all comparisons]. After pooling all patients, headache was the most prevalent ADE, with a decreasing trend from 29/117 (24.7%) to 23/111 (20.7%) and 12/95 (12.6%) at visits 1, 2 and 3, respectively.

TABLE 6 Frequency distribution of adverse events by treatment arm and visit.

Visit	Adverse event	All patients	Treatment, *n* (%)[a] PeG	GTN	*p*-value[b]
1	Total	($N=39/117$)	($n=2/59$)	($n=37/58$)	<0.001
	Headache	29 (24.8)	1 (1.7)	28 (48.2)	
	Headache/hypotension	3 (2.6)	0	3 (5.2)	
	Headache/lipothymia	2 (1.7)	0	2 (3.4)	
	Headache/dizziness	1 (0.9)	0	1 (1.7)	
	Headache/burning	2 (1.7)	0	2 (3.4)	
	Dizziness	1 (0.9)	0	1 (1.7)	
	Unspecified	1 (0.9)	1 (1.7)	0	
	Dropout	3/117	2/59	1/58	1.00
2	Total	($N=30/111$)	($n=3/57$)	($n=27/54$)	<0.001
	Headache	23 (20.7)	0	23 (42.6)	
	Headache/hypotension	3 (2.7)	0	3 (5.6)	
	Headache/tinnitus	1 (0.9)	0	1 (1.9)	
	Anal pain	1 (0.9)	1 (1.8)	0	
	Itching/burning	1 (0.9)	1 (1.8)	0	
	Oedema/phlogosis	1 (0.9)	1 (1.8)	0	
	Dropout	9/111	4/57	5/54	0.74
3	Total	($N=19/96$)	($n=1/53$)	($n=18/43$)	<0.001
	Headache	12 (12.6)	0	12 (27.9)	
	Headache/hypotension	3 (3.2)	0	3 (7.0)	
	Headache/lipothymia	2 (2.1)	0	2 (4.7)	
	Unspecified	2 (2.1)	1 (1.9)	1 (2.3)	
	Dropout	24/96	8/53	16/43	0.07

Abbreviations: GTN, glyceryl trinitrate ointment; PeG, *Propionibacterium* extract gel.

[a]Adverse events per cent on evaluable patients.

[b]Between treatment Fisher's exact test.

TABLE 7 Treatment boxes and costs summary per patient divided by visit and treatment arm.

	Visit	Treatment no. of patients, mean (IQR)		*p* value	*p* value[c]
		PeG	GTN		
No. of boxes[a]	1	50, 1.0 (1.0–1.0)	46, 1.0 (1.0–1.0)	0.96	1.00
	2	50, 1.7 (1.0–2.0)	45, 1.4 (1.0–2.0)	**0.03**	0.39
	3	38, 2.6 (2.0–3.0)	32, 2.2 (1.0–3.0)	**0.004**	0.06
Cost (EUR)[b]	1	50, 32.6 (32.6–32.6)	46, 73.1 (73.1–73.1)	**<0.001**	**<0.001**
	2	50, 55.4 (32.6–65.2)	45, 105.6 (36.7–73.1)	**<0.001**	**<0.001**
	3	38, 85.4 (65.2–97.8)	32, 161.0 (73.1–219.3)	**<0.001**	**<0.001**

Note: Bold values indicates all *p*-values have been reported for each comparison (both unadjusted and adjusted).

Abbreviations: GTN, glyceryl trinitrate ointment; IQR, interquartile range limits; PeG, *Propionibacterium* extract gel.

[a] Main effects: treatment, $p=0.02$, visit $p<0.001$. Interaction: treatment per time, $p=0.03$.

[b] Main effects: treatment, $p<0.001$, visit $p<0.001$. Interaction: treatment per time, $p=0.001$.

[c] Adjusted for multiple comparisons.

Patients in the GTN group were the most affected, with only one (1.7%) patient in the PeG group experiencing this AE at visit 1.

Treatment boxes and cost analysis

The cumulative average number of treatment boxes and costs per patient are shown in Table 7. Although these increased in both groups, a significant difference was observed between the treatments as time progressed. Both arms started with a mean of 1 box at visit 1, but this increased to a mean of 2.6 and 2.2 for PeG and GTN, respectively, at visit 3 ($p=0.02$). Significant increases with time ($p<0.001$) and an interaction between the number of boxes and time ($p=0.03$) were also observed.

Assuming that prices were fixed at €32.60 and €73.09 per box for PeG and GTN, respectively, the between-treatment cumulative average costs per patient were significantly higher for GTN than those for PeG at each follow-up visit ($p<0.001$). After 40 days of treatment, the estimated average cost per patient was €85.4 versus €161.0, corresponding to an average per patient cost of €2.14 per day versus €4.03 per day for PeG and GTN, respectively.

DISCUSSION

This is the first trial to compare Emorsan Rag® (PeG) and Rectogesic® (GTN) for the treatment of CAF. A statistically significant reduction in the REALISE score was observed at each follow-up visit in both groups. Similar results were obtained for burning, itching and quality of life.

Considering anoscopy to be the least well-tolerated part of the proctological examination, we suggest that the higher (comparison by formal test hypothesis led to a *p*-value of 0.07) proportion of patients undergoing anoscopy at visit 3 shows that PeG had a better efficacy at promoting sphincter relaxation and CAF healing.

More than half of the patients attending the last visit in both groups achieved a complete healing rate (GTN, 55%; PeG, 54%), with 38% and 37% of the patients achieving >50% epithelialization in the PeG and GTN groups, respectively. The overall success rates, including the 24 patients who dropped out, were 49% and 39% for PeG and GTN, respectively ($p=0.27$). These rates are probably underestimates, given that two patients in each group dropped out after CAF healing rather than following an AE.

In the absence of previous studies evaluating the efficacy of Emorsan Rag® in CAF healing, our results are in line with those reporting this outcome with Rectogesic®. Scholefield et al. reported a healing rate of 57% in the GTN group [16] after a double-blind randomized comparative study of 181 patients with CAF that aimed to address the dose–response to three different concentrations of GTN ointment (0.1%, 0.2% and 0.4%) compared with a placebo. Similarly, in a randomized open-label multicentre trial of 154 patients, Gagliardi et al. [15] reported healing rates of 55% at 6 weeks and 53% after 80 days, with reductions of 43% and 46%, respectively, after considering the dropout rate. No further statistically significant differences were found upon extending the treatment period to 6 weeks. While Scholefield et al. [16] reported an overall headache rate of 31% (57/181), Gagliardi et al. [15] reported that 23% (35/154) of patients who completed the follow-up visits experienced headache compared with 44% (15/34) of those who did not.

The results of our study were equivalent in the two arms, except for the rate of AEs, which was higher for the GTN group than for the PeG group at all follow-up visits. The extremely high rate of headache, reaching 48% at visit 1 in this group, caused a high dropout rate, eventually resulting in poor satisfaction [38 (71.7%) vs. 23 (53.5%) in the PeG group].

At visit 1, the number of boxes was one for both groups, and patients in the GTN arm had to face almost twice the costs sustained by patients in the PeG group at each follow-up visit.

In a study comparing the costs of anal fissure treatments, Brisinda et al. highlighted the importance of weighing the cost of

each therapy against the success rate. They demonstrated the greater cost-effectiveness of calcium channel blockers compared with topical nitrates [9].

This is in accordance with the most recent guidelines, which recommend using calcium channel blockers as the first-line treatment for the lowest number of AEs combined with the highest success rate and cost-effectiveness [7, 25]. The same discussion can be applied in the present study where PeG demonstrated a comparable healing rate to GTN, but with significantly fewer AEs and a low cost.

Limitations

This study has some limitations that need to be considered. Given the anticipated potential side-effects of the treatments (especially GTN), the follow-up visits were not blinded. Formal interobserver agreement to establish the degree of epithelialization was not obtained. Anorectal manometry was not performed as a mandatory test in all patients because of symptom severity and the discomfort it would have caused. Therefore, an objective assessment of the decrease in the resting anal pressure was not possible. However, a DRE and anoscopy at each follow-up point could provide an indication of symptomatic improvement with gradual sphincter relaxation and CAF healing.

Finally, the cost analysis can be considered partial because it only included the cost per patient. The most appropriate methodology for cost assessment would have been a health technology assessment study, but the latter was beyond the scope of the present study.

The greatest strength of this randomized controlled trial was the use of a validated scoring system for anal fissures, which provided a comprehensive evaluation of pain, quality of life, analgesic intake and bleeding.

CONCLUSIONS

Although there was no difference in healing rates between the two treatments, PeG was more cost-effective, within the limits of the economic analysis, and associated with fewer adverse events. Future prospective, relatively larger, trials with longer follow-up periods are needed.

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None.

CONFLICT OF INTEREST STATEMENT

All authors declare no personal conflict of interest.

ETHICS STATEMENT

This study was approved by all ethics committees at all study centres and written informed consent was obtained from all patients. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

TRIAL REGISTRATION

NCT05616455.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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