



Topical Treatment with Bergamot Flavonoid-Based Gel in Post-Surgical Wounds after Hemorrhoidectomy: Preliminary Results

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Received 13 December 2021;

Accepted 26 December 2021;

Published 01 January 2022

Abstract

Background: Haemorrhoidal Disease (HD) is a very diffuse anorectal condition that involves a large part of the population, both male and female of every age. Among the several procedures proposed to treat HD, conventional excisional surgery remains one of the most performed, it is characterized by important post-operative pain whose historical knowledge often scare the patients. The pain is mainly related to the anal wounds and the healing speed surely influence the post-operative course. The aim of this study was to evaluate the effect of using Benebeo Gel® on post-operative wound healing after open haemorrhoidectomy. **Methods and Results:** This was an observational prospective study conducted in the Proctological and Pelvic Floor Clinical Centre (PPFCC) of the University Hospital of Pisa. From April 2019 to January 2020 all the 175 patients aged between 18 and 75 undergone to open hemorrhoidectomy were enrolled. The post-operative follow-up was scheduled as follows: 7 day, 15 day, 22 days and 30 days after surgery. The primary end point was: time taken to get complete wound healing with a re-epithelized tissue. Secondary endpoints were: evaluate post-operative pain using VAS scale, bleeding, discharge and overall patients satisfaction about the procedure and the topical gel. All the patients were instructed to take topical gel by using the cannula provided with the product put it into the finger phalanx and then upon injured area twice a day (once in the morning after defecation and once before sleeping) for 25 days after. The administration of the product begins in 4th post-operative day. The mean post-operative pain at 7 days was 6 ± 2 , at 15 days 4 ± 1 at 22 day 3 and at 30 days was 2 ± 1 . The mean time to get complete wound healing was 23 ± 4 days. **Conclusions:** He present study aimed to evaluate the efficacy of a new topical gel mainly composed by bergamot-derived flavonoids and hyaluronic acid in patients treated with excisional hemorrhoidectomy. The results after 2 weeks of treatment seems to be promising with a very good clinical outcome and patient satisfaction within 1 month.

Keywords: hemorrhoidectomy, flavonoids, bergamotts, surgical wounds

Introduction

Haemorrhoidal Disease (HD) is a very diffuse anorectal condition that involves a large part of the population, both male and female of every age ^[1].

The age mainly involved ranges between 45 and 65 years old with a peak at 45 and 55 years ^[2]. HD affects millions of

people around the world revealing to be a major medical and socioeconomic problem ^[3].

Topical and systemic medical treatment are recommended as first line treatment, but in case of failure or very symptomatic high-graded prolapse, surgery remains the main option ^[4].

Among the several procedures proposed to treat HD, conventional excisional surgery remains one of the most performed

[5]. Although hemorrhoidectomy may be performed also using energy devices [6-8] trying to reduce post-operative bleeding and pain, it is characterized by important post-operative pain [7] whose historical knowledge often scare the patients. The pain is mainly related to the anal wounds and the healing speed surely influence the post-operative course.

Benebeo Gel® is an anal ointment made of Bergamot Polyphenolic Fraction, Pantenol, Sodio ialuronato and Gomma xantana indicated for anal and perianal inflammation. It stimulates and protects tissues repairing showing to have also a vasoprotective effect [9].

The aim of this study was to evaluate the effect of using Benebeo Gel® on post-operative wound healing after open haemorrhoidectomy.

Material and methods

This was an observational prospective study conducted in the Proctological and Pelvic Floor Clinical Centre (PPFCC) of the University Hospital of Pisa. From April 2019 to January 2020 all the patients aged between 18 and 75 undergone to open hemorrhoidectomy were enrolled. The exclusion criteria were: concomitant anal disease or previous proctologic surgery which could influence the study, inflammatory bowel disease, previous local radiotherapy, HIV infection or neoplastic disease, pregnancy or breast feeding, oral anticoagulant therapy for any reason and poor general conditions which made the patient unable to understand the purpose and the aim of the study.

All the patients were preoperatively screened according the current guidelines evaluating also the bowel function. Digital exploration, anoscopy were always performed and transanal 3D 360° ultrasound and colonoscopy when required.

The procedures were performed both with electroscalpel and energy devices as the combination of ultrasound and bipolar energy.

The post-operative course was managed with a combination of paracetamol 1 gr and ketorolac 30 mg for 5 days and after as rescue therapy, in association with oral administration of diosmine 500 mg 3 times per day for 30 days to prevent post-operative haemorrhoidal acute complications.

The post-operative follow-up was scheduled as follows: 7 day, 15 day, 22 days and 30 days after surgery.

The primary end point was: time taken to get complete wound healing with a re-epithelized tissue.

Secondary endpoints were: evaluate post-operative pain using VAS scale, bleeding, discharge and overall patients satisfaction about the procedure and the topical gel.

Topical product and its application

Benebeo Gel® is a bergamot-derived gel whose pharmacological functions are: vasoprotective, reducing the permeability and the fragility of the endothelial layer, antioxidant, by reducing the cyclooxygenase type II production, anti-inflammatory, reducing the pro-inflammatory cytokines activation by inhibiting myeloperoxidases and so the nuclear translocation of NF-KB. A recent study conducted by a research group of the University of Cosenza UNICAL, Pharmacy and Nutraceutica Department, suggested that the antiinflammatory function of Benebeo Gel® is due to reduction of the intracellular free radicals, in particular of the COX-2, and to the inhibition of prostaglandins and leukotriene [10].

All the patients were instructed to take topical gel by using the cannula provided with the product put it into the finger phalanx and then upon injured area twice a day (once in the morning after defecation and once before sleeping) for 25 days after. The administration of the product begins in 4th post-operative day.

Results

In the study period, 175 (100 M, 75 F) patients were enrolled. The mean age was 47 years (range 18-75). Patients characteristics were reported in Table 1.

The mean post-operative pain at 7 days was 6±2, at 15 days 4±1 at 22 day 3 and at 30 days was 2±1. The mean time to get complete wound healing was 23±4 days. There were no cases of post-operative bleeding. All the patients referred a discharge resolution within 30 days with a significant reduction perceived within 15 days.

It was not found any difference in safety and efficacy between patients undergone two or three piles excision or between the two groups treated with or without energy devices.

All the patients were satisfied about the topical gel with a mean rate of 9/10 while the mean satisfaction about the procedure and healing was 7/10. (Figure 1) (Figure 2)

Table 1: Patients' characteristics

Patients		
Age mean (range)		47 (18-75)
Gender		175
Male		100
Female		75
Bowel		
Regular		95
Constipation		46
Diarrhea		34
Goligher grade		
II		7
III		65
IV		103
Piles treated		
3 piles		78
2 piles		49
2 piles + mucopexy		36
3 piles + mucopexy		12



Figure 1: A) Wound after 7 days; B) Wound after 15 days; C) Wound after 22 days



Figure 2: D) Wound after 30 days

Discussion

HD is a growing health condition affecting millions of people around the world [11]. The actual aim is to mitigate post-operative symptoms in those patients in which the preoperative anatomical condition required to perform an excisional haemorrhoidectomy according Milligan-Morgan (MM) [12].

In the MM technique, the wounds are left open for healing by a secondary mechanism and, until it is completely re-epithelialized requiring almost 3-5 weeks, patients usually experience pain and intense discomfort that improve over the weeks. [13]. However, post-operative pain still remains one of the main problem which may affect patients' quality of life [14] and frequently induce the patients to postpone the procedure. Moreover, pain in association with bleeding and anal stricture represents the most frequent complications after MM, which may require re-intervention in the short or long term [15].

Over the years, proctologists have considered many medical and surgical options to reduce the post-operative pain, up to perform an internal lateral sphincterotomy [7].

In this context, plant extracts and oils became always more relevant and present in the current medical clinical practice. Among the wide group of natural products, it was shown that bioactives compound derived from bergamot have relevant anti-inflammatory and vasoprotective properties, helping and supporting haemorrhoidal tissue [9].

Hyaluronic acid, which is present in most of human tissues, contributes to maintain hydration, turgidity and viscosity. It has been involved in several processes as tissue regeneration and matrix organization. It has been observed that local administration is effective helping wounds healing due to the barrier effect protecting the injured epithelium [16,17].

Besides, a recente paper [18] clearly showed that in high-graded HD there are higher levels of matrix metalloproteinases (MMPs), which regulate extracellular structural proteins and tissue remodeling, and Neutrophil gelatinase-associated lipocalin (NGAL), which is involved in the regulation of MMP activity; NGAL is commonly known as a marker of neutrophil activation which can be induced by several cytokines and growth factors. It is common opinion for a long time that degradation of the extracellular matrix is involved in the etiopathogenesis of HD [19].

Benebeo Gel®, by reducing the pro-inflammatory cytokines activation and lowering the intracellular free radicals, prevents the extracellular matrix degradation. It could help in reducing the post-operative aedema and pain, in order to have a faster post-operative recovery.

The present study aimed to evaluate the efficacy of a new topical gel mainly composed by bergamot-derived flavonoids and hyaluronic acid in patients treated with excisional hemorrhoidectomy. The results after 2 weeks of treatment seems to be promising with a very good clinical outcome and patient satisfaction within 1 month. The investigational product showed a good profile of tolerability, safety and efficacy without any major adverse events associated with the use of the new product.

Hence, the treatment of post-hemorrhoidectomy wound with bergamot-derived gel should be recommended to get a quick healing with subsequent pain reduction and faster return to normal activity.

Ethics approval and consent to participate

Regional Ethics Committee for clinical trials of the Tuscany region. Prot. N ° 22207 Pisa 15/04/2019

List of abbreviations

Milligan-Morgan (MM)
Haemorrhoidal Disease (HD)
Matrix metalloproteinases (MMPs)
Neutrophil gelatinase-associated lipocalin (NGAL)

Conflicts of Interest

There is no conflict of interest regarding the publication of this paper.”

Funding Statement

None

Author Contributions

Conceptualization, D.C. and G.N.; writing-original draft preparation, D.C. and A.S.; Methodology and Validation, L.O. Writing-Review and Editing, A.C. and M.S.S.; Supervision, G.N. All authors have read and agreed to the published version of the manuscript

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