Annals of Phytomedicine 4(2): 49-51, 2015

Journal homepage: www.ukaazpublications.com

ANNALS OF PHYTOMEDICINE
An International Journal

ISSN: 2393-9885

Sacran, a new sulfated glycosaminoglycan-like polysaccharide from river alga *Aphanothece sacrum* (Suringar) Okada alleviates hemorrhoid syndrome: Case report

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Received July 1, 2015: Revised July 20, 2015: Accepted July 25, 2015: Published online December 30, 2015

Abstract

Hemorrhoids are a common inflammatory anorectal disorderthat affects millions of people worldwide. Its etiology is multifactorial, including chronic constipation, prolonged strain, thus suggesting the role of lifestyle, diet and occupation in the development of the disease. We report on cases of patients with hemorrhoids who took part in a preliminary study.In total, there 13 participants, including 7 patients treated with the anorectal application of 1%sacran and 6 others treated with Rectosol suppository administered twice daily for at least 2 weeks. Clinical severity of hemorrhoid symptoms was evaluated at baseline and 2 weeks later with the use of a prepared and validated questionnaire.The results showed that anorectal application of 1% sacran could relieve hemorrhoid syndrome as efficiently as Rectosol, with a better effect on constipation and pruritus (itch) ($p<0.01$) than Rectosol. Findings from this preliminary clinical trial suggest that sacran has a potential to improve symptoms of hemorrhoidal disease.

Key words: *Aphanothece sacrum*, glycosaminoglycan, hemorrhoidal disease, sacran

1. Introduction

Hemorrhoids, a common inflammatory anorectal disorder that involves hemorrhoid plexus, are a symptomatic enlargement and distal displacement of the normal anal cushons that affects millions of people worldwide (Lohsiriwat, 2012). Patients with hemorrhoid syndrome often consult a physician only after the disease symptoms get unbearable. The etiology of hemorrhoids is multifactorial and includes chronic constipation, prolonged strain (Lohsiriwat, 2012; Loder *et al*., 1994; Kayhan *et al*., 2008), suggesting the role of lifestyle, diet and occupation in the development of the disease.

A variety of substances are currently in use for the treatment of hemorrhoids such as anti-inflammatory (corticosteroids), anesthetic (xylocaine), venoconstrictive (diosmin) agents (Kayhan *et al*., 2008) and plant-based products. Other treatment procedures include injection sclerotherapy, rubber band ligation (RBL), cryotherapy, infrared photocoagulation, laser therapy and hemorrhoidectomy (surgery) (Dennison *et al*., 1996). In the Democratic Republic of the Congo (DRC), there is still an important fraction of population that utilizes ethnomedicine remedies (mostly plant-based products) for chronic diseases such as hemorrhoids (Ilumbe, 2014).

Sacran is a new bioactive sulfated glycosaminoglycan isolated from *Aphanothe cesacrum* (Suringar) Okada, a river alga currently mass-cultivated in the western Japanese region of Kyushu. Previous studies have shown that sacran improves the skin barrier and exerts anti-inflammatory effects on skin allergic disorders (Okajima *et al*., 2009; Ngatu *et al*., 2012). In addition, findings from a recent research suggest that sacran could be useful in drug delivery for topically administered medications (Motoyama, 2014). Recently, we have gathered a number cases of hemorrhoid patients whose conditions have been improved after 3 to 5 days of anal application of sacran solution (Ngatu, 2014; unpublished). In the present preliminary clinical study, we evaluated the clinical benefice of sacran on hemorrhoid syndrome in African patients in comparison with Rectosol® suppository, one of widely used anti-hemorrhoid agents in Kinshasa.

2. Materials and Methods

2.1 Study design and patients

A pilot preliminary patient-blinded controlled clinical trial (non-randomized) was implemented from October through December 2013 in which a consecutive sample of 15 male adult Congolese

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patients, mainly office workers and mechanics, from the western district of Tshangu in Kinshasa, Democratic Republic of the Congo, participated.

2.2 Sacran extraction and chemical structure

Sacran was extracted by the alkaline dissolution of acid-washed biomaterials of Aphanothece sacrum as previously described (Ngatu *et al*., 2012), and an aqueous solution of 1%sacran was prepared and used in this preliminary study. The Figure 1 below showsthe main chemical structure and composition of sacran chains.

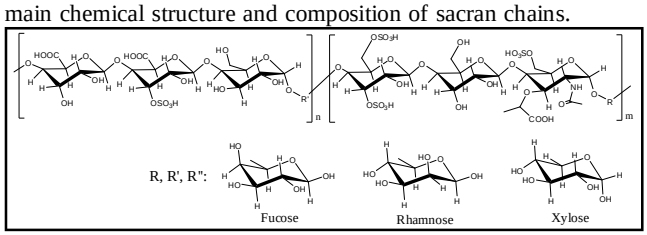

Figure 1 : Main structure of sacran chains with the sequences in monosaccharide triads and glycoside linkages

2.3 Enrollment and clinical evaluation of disease severity

Entry criteria were as follows: voluntary participation upon submission of a written and signed informed consent form, having a documented diagnosis of internal and/or external hemorrhoids and confirmation by the investigator after a clinical examination, not using a concurrent medication at the time of enrollment and duration the follow-up period. The grading of hemorrhoidal disease was performed using four gades (grade 1, 2, 3 and 4) as described previously (Banov *et al*., 1985). Patients were requested to fill-in a self-evaluation form (French version), at baseline and on eighth and fourteenth (7 days of interval).

The patient's form had a list of common hemorrhoid symptoms (anal pain, anal bleeding, constipation, itch, swelling or lump andprolapse); a 4-scale severity was considered for each individual symptom: 0, absence; 1, mild; 2, moderate and 4, severe. The hemorrhoid syndrome severity based on symptoms severity score according to patient's self-evaluation was the outcome variable of this study. Of the 15 patients enrolled, two (1 from sacran group and another one from *Rectosol*® group) were excluded as they did not show up during periodical evaluations; thus, the final sample size was 13 (7sacran-treated patients and 6 controls or *Rectosol* patients).

2.4 Treatments

In this trial, 1% sacran aqueous solution was used as treatment, applied in and out of anus; whereas 2.5% *Rectosol* ® suppository was the control anti-hemorrhoid agent. *Rectosol*® is one of the most commonly used anti-hemorrhoid drugs in Kinshasa and it mainly contain s*hydrocortisone*as principal active molecule. The treatment was administered twice daily; sacran aqueous solution was administered through anorectal application. Participation was voluntary and only patients who were not under other anti-hemorrhoid medication were recruited, and a combination of two agents was not allowed.

2.5 Ethical consideration and data analysis

For this preliminary study, ethical approval was obtained from the academic research ethics review board of the Department of Health Sciences of the Institut Superieur Technique Songwa (I.S.T.S.), Kinshasa, Democratic Republic of the Congo. In addition, signed informed consent form was provided by each of the participants prior to responding to interview questionnaire.Data are expressed as total severity score; for each treatment arm; the total severity score at baseline (start of treatment) and two weeks later were compared using Fisher's exact test. Stata software version 11.0 (Stata corp., TX, USA) was used for data analysis.

3. Results and Discussion

3.1 Demographic, occupational characteristics and baseline disease severity of the patients

Table 1 shows the demographic, occupational characteristics and disease severity grade according the investigator. Of the 13 patients, 11 were males whereas the remaining two others were females. The mean age of the patients was 34.9 +/- 13.5, with the oldest aged 71 years and 22 for the youngest.There were six patients with severe hemorrhoid syndrome (severity level 3), including five patients in the sacran group. Six patients were office workers involved in computer work and four were mechanics. In terms of clinical classification in grades, the majority of patients were of grade II hemorrhoid disease (internal hemorrhoid, prolapse during defecation with spontaneous reduction) (Banov *et al*., 1985). One patients was a retired soldier and two were employed at the time of this study (Table 1).

Table 1: Characteristics of the patients

Patient's code	Gender	Age (y.)	Marital status	Occupation	Disease severity (1–3)	Treatment group
KO1	M	71	M	Retired	3	Sacran
MA12	M	30	S	Office work	1	Rectosol
MA3	M	43	M	Mechanic	2	Sacran
SU4	M	22	S	Mechanic	3	Sacran
DO5	M	28	S	Mechanic	1	Rectosol
ME11	F	47	S	Office work	1	Sacran
EO7	M	28	M	Unemployed	3	Rectosol
LO8	M	22	S	Office work	1	Rectosol
LO9	M	37	M	Unemployed	3	Sacran
IS10	M	27	S	Office work	3	Sacran
MA6	F	30	M	Office work	2	Rectosol
KO2	M	43	S	Mechanic	3	Sacran
EO13	M	26	S	Office work	1	Rectosol

Foot notes: M = male or married; F= female; S = single; y = years

3.2 Effects of sacran and rectosol on hemorrhoid syndrome according patients' self-evaluation of symptoms severity

Figure 1 shows the trend of total severity score of hemorrhoid syndrome. After a 2-week period of treatment, patients treated with 1% sacran saw their symptoms relieved quite earlier as compared with those in Rectosol group; however, the difference was not significant ($p>0.05$). When each of treatment group was considered separately for the severity score at baseline and 2 weeks later, both Rectosol and Sacran could significantly reduce the total

severity score of hemorrhoid syndrome (100% and 26%; 100% and 16% for Rectosol and Sacran, respectively; $p<0.001$) (Figure 2).

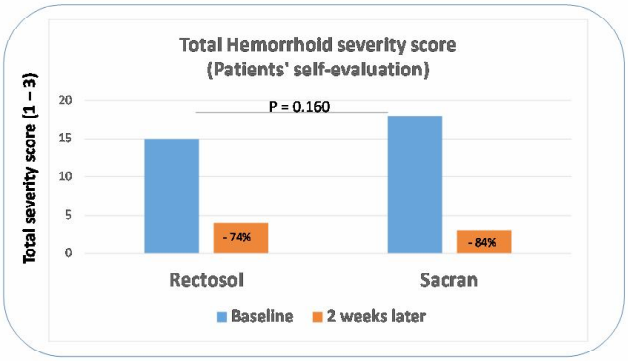

Figure 2: Trend of total severity of hemorrhoid syndrome among Sacran and Rectosol-treated patients

3.3 Effects of sacran on the severity of constipation, anal bleeding, anal pain and itch

Regarding common hemorrhoid symptoms, most patients in sacran group had constipation, anal bleeding and itch; whereas a higher number of Rectosol patients had anal pain. sacran markedly relieved constipation and itch as compared with Rectosol ($p<0.01$). On the other hand, both sacran and Rectosol had similar beneficial effects on anal pain and anal bleeding ($p>0.05$). When considering the symptom severity score at baseline and 2 weeks later for each treatment group separately, both sacran and Rectosol significantly reduced the severity of constipation, anal bleeding, anal pain and itch ($p<0.01$).Though an improvement was observed in both treatment groups, no significant change was observed when comparing the total severity score for lumps or swelling ($p>0.05$) after 2 weeks of treatment (not shown).

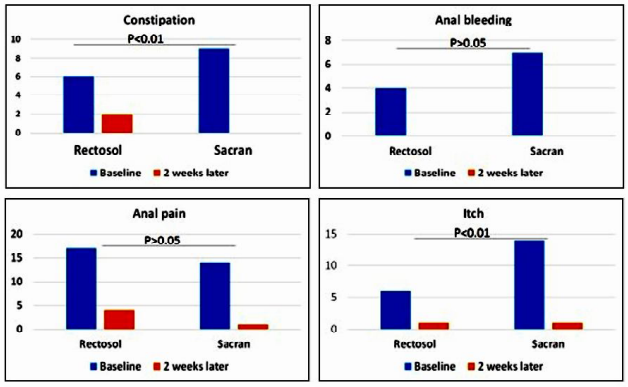

Figure 3: Trend of total severity score for constipation, anal bleeding, anal pain and itch

The present preliminary clinical study investigated the beneficial therapeutic effects of sacran, a sulfated glycosaminoglycan with anti-inflammatory effects, in a small sample of patients with mild to severe hemorrhoid syndrome. The results showed that anorectal application of 1% sacran could relieve hemorrhoid syndrome as efficiently as Rectosol, with a better effect on constipation and pruritus (itch) than Rectosol. Constipation is considered as one of the etiologic factors as well as a common symptom of hemorrhoid disease (Abramowitz *et al*., 2001); its relief by sacran suggests that this new natural product (sacran) could improve bowel function. A part from its anti-inflammatory effects, sacran has a good coating effect (Ngatu *et al*., 2012), which may explain the relief of anal bleeding in patients. The principal limitation of this study is the small sample size (13 patients) and the fact that the main outcome measurement derives from patients' self-evaluation of disease severity, which may differ from patient to patient. Nonetheless, the present case report shows the potential of sacran to improve hemorrhoid syndrome. Another study with a larger sample size should be envisaged to determine.

Acknowledgments

The authors thank Ir Jules MbalaNzobadila and Mr Kei Tanaka who supported this study.

Conflict of interest

We declare that we have no conflict of interest.

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