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Alternative herbal medicine for hemorrhoids, Effect of *Arum maculatum* on the quality of life of patients: A randomized controlled trial

Serafeim Zisis[1], Konstantinos Giannakou[2], Giagkos Lavranos[1], Demetris Lamnisos[1*]

[1]Department of Health Sciences, School of Science, European University of Cyprus, Nicosia, Cyprus.
[2]Cyprus International Institute for Environmental and Public Health, Cyprus University of Technology, Limassol, Cyprus.

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ABSTRACT

Hemorrhoids is a common disorder and a leading cause of rectal bleeding, with unpleasant discomfort and pain for the patient. Medication and surgery are the standard treatments of hemorrhoids. In this study, we are investigating an alternative herbal treatment of hemorrhoids using the *Arum maculatum* L. (Araceae). A randomized controlled trial was conducted with a test treatment period of 2 weeks using a sample of 53 diagnosed patients from Greece to assess the efficacy of *Arum maculatum* in treating symptomatic hemorrhoids. The patients randomly assigned to consume a liquid mixture of *Arum maculatum* or a standard antihemorrhoid cream. The primary outcome was the health-related quality of life measured by the SF-36 health survey at the baseline and 2 weeks after the end of treatment. The mixed ANOVA statistical method was used to compare the groups. Participants in the treatment group had significantly greater improvement in all measures of the SF-36. Particularly the treatment effect for the physical health summary was 5.0 [95% confidence interval (CI): 0.9–9.1] while for the mental health summary was 4.7 (95% CI: 1.3–8.0). This trial shows that treatment with *Arum maculatum* improves the quality of life of patients with hemorrhoids, but further studies are needed to confirm these results.

INTRODUCTION

Hemorrhoid disease (commonly described as simply hemorrhoids) is a common rectal disorder caused by swelling and downward displacement of the anal cushions. The pathophysiology of hemorrhoids includes a degenerative change of the supportive tissue in the anal cushions, vascular hyperplasia, and the overdispersion of the hemorrhoid complex (Lohsiriwat, 2012). Hemorrhoids is the main cause of rectal bleeding with unpleasant symptoms of discomfort and pain for the patient (Riss *et al*., 2012).

Hemorrhoids is one of the most common gastrointestinal disorders seen by general practitioners. It has been estimated that they can occur at any age and can affect both men and women (Agbo, 2011). The exact prevalence of hemorrhoid disease is very difficult to be established because many patients do not seek medical care (Kaidar-Person, 2007). However, the prevalence of hemorrhoid disease is estimated to be between 4.4% and 12.8% in normal adult populations and approximately 40% in patients with symptoms of anal disease (Johanson and Sonnenberg, 1990; Riss *et al*., 2012).

Treatment options for hemorrhoids vary based on the degree and severity of symptoms (Acheson and Scholefield, 2008; Kaidar-Person, 2007). They may be medical (prescribing high fiber diet, antimotility agents, topical analgesics and corticosteroid creams for symptomatic relief, alternative/traditional medicines), nonoperative (sclerotherapy, cryotherapy, rubber band ligation, infrared photocoagulation, etc.) or surgical (Aggarwal *et al*., 2014). According to the World Health Organization (WHO), between 65% and 80% of the populations of developing countries currently use medicinal plants as remedies (WHO, 2011). In traditional and

*Corresponding Author
Demetris Lamnisos, Department of Health Sciences, School of Science, European University of Cyprus, Nicosia, Cyprus.
E-mail: d.lamnisos @ euc.ac.cy

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folk medicine of Greece, Western Balkans, and Turkey, the plant *Arum Maculatum* L. (Araceae) is used as a traditional therapeutic treatment of hemorrhoids (Kültür, 2007; Jarić *et al*., 2015; Kochmarov *et al*., 2015).

The therapeutic effect of *Arum maculatum* tuber in the treatment of various hemorrhoids and in cases of chronic traumatic pain and purulent infections led Kochmarov *et al*.(2015) to make the hypothesis that the plant substance causes constriction of the blood vessel walls and has an anti-inflammatory and an analgesic effect. However, no standardized research on the application of *Arum maculatum* in hemorrhoids treatment has been conducted to date. Therefore, the aim of this study was to conduct a randomized controlled trial (RCT) to assess the efficacy and safety of *Arum maculatum* for treating symptomatic hemorrhoids compared with the conventional conservative treatment.

MATERIALS AND METHODS

Study design

This was a two-arm, randomized, and controlled trial using a parallel design with a 1:1 allocation ratio, and it was conducted at the city of Ptolemaida, North Greece. The study was reviewed and approved by the ethics committee of the European University Cyprus and conformed to the principles of the Declaration of Helsinki (World Medical Association, 2013). The Bioethics Committee/ Scientific Board of the Regional General Hospital approved the local implementation of the study as required by national legislation. All patients had given signed informed consent prior to participation. Patients were randomly assigned either to consume the dried root of *Arum maculatum* after it had been grounded and mixed with milk or to receive a cream-ointment (control group) (Fig. 1).

Participants

The participants were prospectively enrolled either in the treatment group or control group between October 2016 and March 2017. Eligible patients of either gender, aged ≥ 18, with symptoms of hemorrhoid disease were recruited in the study. Exclusion criteria were as follows: a history of liver cirrhosis, pregnant, and lactating women and patients with allergic/atopic conditions. Patients with major communication problems (severe dysarthria, Greek language awareness below B2 CEF) were also excluded from the study because miscommunication made difficult the understanding and application of the instructions.

Interventions

Participants were randomly assigned (1:1) either to consume the dried root of *Arum maculatum* or to receive a cream-ointment (control group). Treatment allocation occurs when the participants met the inclusion criteria and signed the informed consent form. Randomization was at an individual level without restriction (i.e., no blocking) and was made by drawing lots. The treatment group received a liquid mixture of the *Arum maculatum*, while the control group used the pharmaceutical ointment cream with active substances acetonide of fluoroquinolone and lidocaine. The treatment group consumed the dried tuber of *Arum maculatum* after it had been grounded into a fine powder and mixed with milk. The mixture of 3 g of the dried tuber powder and 1 l of milk was being heated to its boiling point (pasteurization). The pasteurization caused in milk destroyed the primary toxic compounds of the plant, the calcium oxalate and cyano glycoside. After the mixture reached the room temperature, it was conserved in a refrigerator. Participants were instructed to drink a glass of this milk mixture (250 ml/day) for 4 days on an empty stomach. At the end of the first week, the same procedure was repeated once again. Participants were also instructed to avoid consuming alcohol during the 2 weeks of treatment.

The investigators had frequently phone calls with participants to solve any issue related to the preparation and application of treatment care and routine care to ensure patient's compliance with treatment. They were also recording in each call and in the last visit symptomatic adverse reactions including gastrointestinal, psychological, circulatory, respiratory and urinary symptoms as well as rash and edema. A complaint officer was also appointed to independently investigate and report any issues raised by participants with regard to either researcher conduct or intervention-related events but nothing was recorded throughout the study period.

In our study, the sample of *Arum maculatum* was purchased from a local market. It has been collected in Ptolemaida, North Greece, in the fall. The root-tuber of the plant is located 10–20 cm below the ground and collected by digging the ground with a scraping tool. After the collection, the tuber was washed, sliced into small pieces, dried in a shady place, and stored in paper boxes. All the patients in the treatment group received the same batch of the plant. The plant material was authenticated by the Herbarium Unit, The Goulandris Natural History Museum Herbarium, where a voucher specimen was deposited (reference# ATH 62437).

Outcomes

The following details were collected at baseline from each patient: information on age, gender, marital status, educational level, occupation, dietary behaviors for the last month (consumption of alcohol, coffee, carbonated beverages, low-fiber foods, high-fat foods, spicy food and processed food with high sugar content), medication, and diagnosis of any other condition.

The primary outcome was the health-related quality of life measured by the Short Form-36 (SF-36) health survey (Ware, 2000) at baseline and 2 weeks after the end of treatment. The SF-36 is the most extensively validated and used health survey instrument for appraising the quality of life and it has been validated in Greek language by Pappa *et al*. (2006). It is a 36-item, patient-reported survey of health, and it yields an eight-scale profile of scores as well as physical and mental health summary measures. It is an instrument that has extensive applications for population health surveys, comparisons of relative burden of diseases, and differentiation of health benefits across groups produced by diverse interventions (Lee and Chi, 2000; Ware, 2000; Ware and Sherbourne, 1992; Garratt *et al*., 2002). The physical and mental health summary measures of the SF-36 were computed following the standardized three-step procedure described by Taft *et al*. (2001) and using the scale means for the general Greek population sample (Pappa *et al*., 2006).

Statistical methods

We reported means and standard deviation for continuous variables while categorical variables are presented as a number of patients (%) and were compared between the intervention and control groups using the χ^2 test. Baseline values of continuous variables

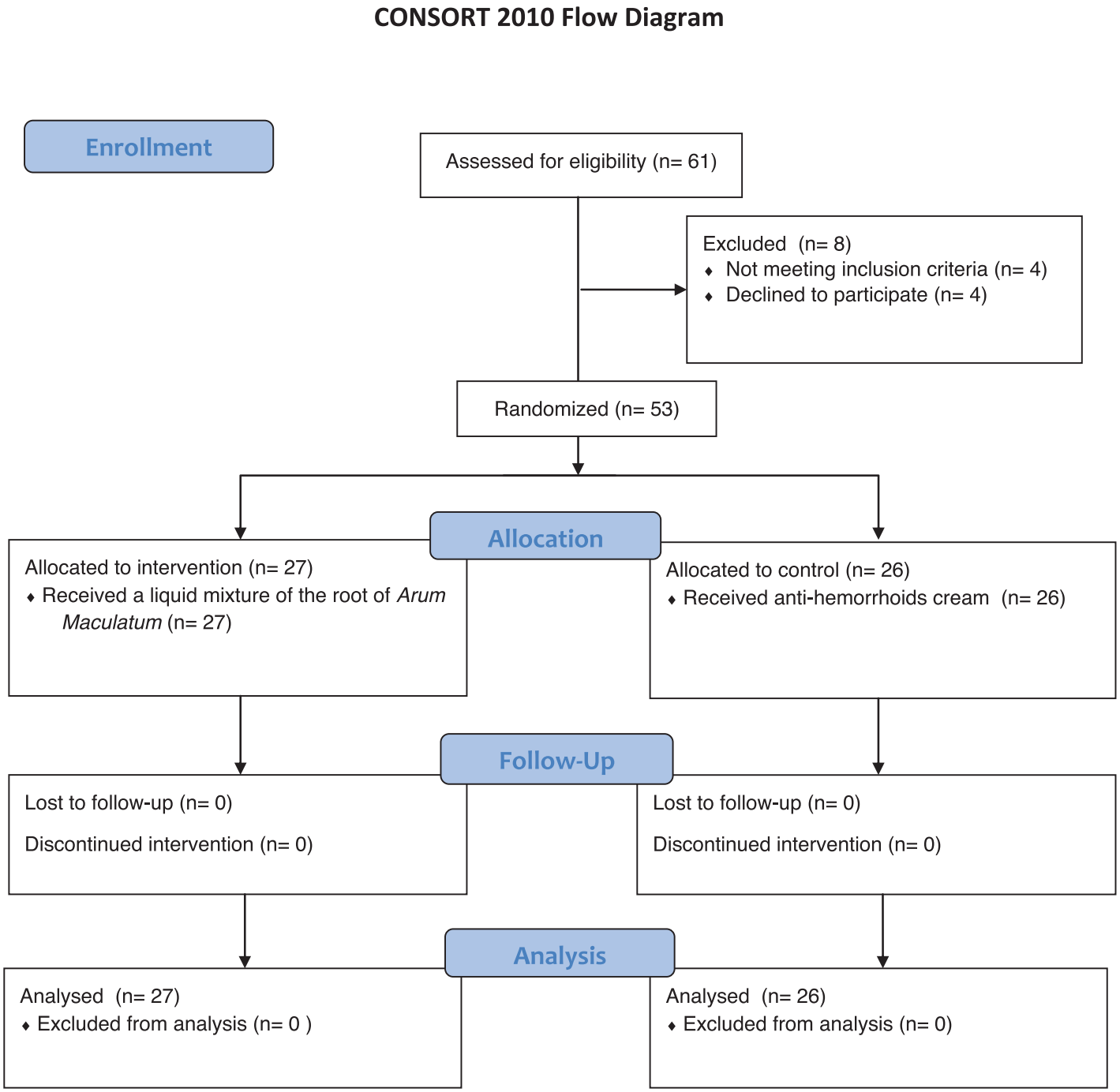

Figure 1. Flowchart of study inclusion, allocation, and follow-up.

were compared between the patients in the treatment and control groups using the independent samples *t*-test. The mixed ANOVA statistical method was used to compare the treatment and control groups with respect to each scale of SF-36 as well as physical and mental health summary measures. In the mixed ANOVA analysis, the time (baseline and 1 month after) was the within patients factor and treatment (treatment-control) was the between patients factor while the dependent variables were the eight scales of SF-36 and the physical and mental health summary measures. All statistical methods were performed using the Predictive Analytics Software Statistics 20 (SPSS Inc, Chicago, IL). Significance test and confidence intervals were calculated at a significance level of 0.05. The study followed CONSORT recommendations for reporting of randomized clinical trials (Schulz *et al*., 2010)

RESULTS

In this study, 53 patients with an average age of 46.5 years (range: 20–74) were enrolled and randomized to the control (n = 26) and intervention group (n = 27). All allocated patients completed the study without any cross match between the two

Table 1. Anthropometric characteristics and baseline measurements of the control and treatment groups (n = 53). Values are numbers of patients (%) unless otherwise indicated. The last column presents the p-values of the statistical tests comparing the baseline measurements between the treatment and control groups.

Variable	Control (n = 26)	Treatment (n = 27)	p-value*
Gender			
Male	18 (69.2)	15 (55.6)	0.31†
Female	8 (30.8)	12 (44.4)	
Age			
20–34	6 (23.1)	2 (7.4)	0.27†
35–49	4 (15.4)	7 (25.9)	
50–64	11 (42.3)	15 (55.6)	
>65	5 (19.2)	3 (11.1)	
Married	19 (76.0)	21 (77.8)	0.88†
Education			
Compulsory (9 years)	8 (30.8)	9 (33.3)	0.62†
Higher Secondary (12 years)	11 (42.3)	14 (51.9)	
Tertiary	7 (26.9)	4 (14.8)	
Occupation			
Unemployed	3 (11.5)	8 (29.6)	0.16†
Employed	12 (46.2)	7 (25.9)	
Retired	11 (42.3)	12 (44.4)	
	Mean (SD)	Mean (SD)	
SF-36 physical health summary	35.6 (9.0)	35.0 (5.9)	0.79+
SF-36 mental health summary	42.3 (6.1)	42.7 (7.4)	0.82+
Domains of SF-36			
General health perception	39.0 (18.9)	43.9 (17.1)	0.33+
Physical functioning	43.9 (29.9)	47.6 (22.8)	0.61+
Role limitation (physical)	26.0 (30.4)	21.3 (29.2)	0.57+
Role limitation (emotional)	32.1 (37.1)	43.2 (35.6)	0.27+
Pain	36.9 (21.6)	26.6 (18.6)	0.07+
Social functioning	39.9 (20.0)	38.4 (19.0)	0.78+
Energy	44.2 (21.0)	43.9 (19.0)	0.95+
Emotional well-being	50.6 (14.7)	52.0 (17.1)	0.75+

†χ^2 test.

+Independent sample t-test.

*p-value < 0.05 indicates a significant difference between the treatment and control groups.

study arms. Figure 1 shows a flow chart that reveals detailed descriptions of the patient's enrollment, randomization, and outcomes. Baseline characteristics (gender, age, marital status, education level, occupation) of the patients in the two groups and baseline measurements of the SF-36 scores are shown in Table 1. There were no significant differences in the baseline measurements between the treatment and control groups (Table 1).

Participants in the treatment group had significantly greater improvement than the routine-care group in all domains of the SF-36 health survey as well as the physical and mental health summary. The treatment effect was statistically significant ($p < 0.05$) for all outcomes indicating significant improvement in the treatment group in comparison to the control group. Particularly there was a statistically significant improvement in the physical health summary [five points greater improvement over control; 95% confidence interval (CI): 0.9–9.2] and the overall mental health summary (4.7 points greater improvement over control; 95% CI: 1.4–8.0). Moreover, there was statistically significant improvement in the treatment group in comparison to the control group in all domains of the SF-36 (the general health perception was 11.3 greater improvement, 95% CI: 2.3–20.3; the physical functioning was 16.4 greater improvement, 95% CI: 2.8–29.9; role limitation due to physical health was 26.9 greater improvement, 95% CI: 6.3–35.5; role limitations due to emotional problems was 23.6 greater improvement, 95% CI: 8.3–39.0; body pain was 10.9 greater improvement, 95% CI: 1.0–20.8; social functioning was 14.2 greater improvement, 95% CI: 3.4–25.0; energy/fatigue was 12.4 greater improvement, 95% CI: 2.3–22.5; and emotional well-being was 13.2 greater improvement, 95% CI: 5.2–21.1) (Table 2).

None patient reported any systematic or local adverse events during the follow-up period in the intervention group or in the control group.

Table 2. Mean (SD) of all domains of the SF-36 health survey as well as the physical and mental health summary. Positive value of treatment effect indicates greater improvement in the treatment group in comparison to the control group. Statistical significance of the treatment effect is indicated by the *p*-value of the mixed ANOVA statistical test.

Variables	Control (n = 25)	Treatment (n = 26)	Treatment effect† (95% CI)	p-value+
SF-36 physical health summary	42.6 (11.0)	53.2 (4.5)	5.0 (0.9, 9.2)	0.02
SF-36 mental health summary	42.7 (8.2)	51.7 (5.8)	4.7 (1.4, 8.0)	0.007
Domains of SF-36¶				
General health perception	45.2 (20.6)	63.0 (15.1)	11.3 (2.3, 20.3)	0.02
Physical functioning	60.8 (32.9)	89.8 (14.6)	16.4 (8.0, 29.9)	0.02
Role limitation (physical)	45.2 (41.2)	91.7 (17.0)	26.9 (6.3, 35.5)	0.006
Role limitation (emotional)	59.0 (41.4)	95.1 (12.1)	23.6 (8.3, 39.0)	0.003
Pain	59.4 (27.6)	91.6 (11.1)	10.9 (1.0, 20.8)	0.03
Social functioning	56.7 (29.4)	86.6 (16.6)	14.2 (3.4, 25.0)	0.01
Energy	49.8 (23.5)	75.0 (14.8)	12.4 (2.3, 22.5)	0.02
Emotional well-being	53.8 (20.6)	78.8 (12.2)	13.2 (5.2, 21.2)	0.002

†Treatment effect from mixed analysis of variance (ANOVA).

+*p*-value of the main effect of treatment.

¶Range of scores = 0–100; higher scores represent a higher level of functioning.

DISCUSSION

Arum maculatum is used in ethnomedicine in Greece, Western Balkans, and Turkey as a traditional therapeutic treatment of hemorrhoids. This study was the first randomized controlled trial that investigated the effect of *Arum maculatum* on the quality of life of patients suffering from hemorrhoids. The treatment group received the folk traditional mixture of the plant, while the control group received a standard antihemorrhoid cream. The SF-36 survey was used to measure the improvement in the health-related quality of life of patients in both groups. In this study, we found that use of a standardized extract of *Arum maculatum* for 2 weeks led to considerable benefit in all domains of the SF-36 health survey as well as physical and mental health summary. The considerable benefit for all outcomes is indicative of true beneficial effect of the herbal formulation. The magnitude of the observed benefit in the mental and physical summary scale was almost five points, while for the eight-domains of SF-36 was greater than 10 points. The greatest benefit was found for the role limitations due to physical health (26.9 points) and the role limitations due to emotional problems (23.6 points).

There are only a few randomized controlled trials in the literature that investigate the efficacy and safety of herbal formulations in the treatment of hemorrhoids in humans (Man *et al*., 2013; Aggarwal *et al*., 2014; Mosavat *et al*., 2015). These RCTs were conducted only in Asia and use different herbs and herbal preparations than the one described in this study. The study of Mosavat *et al*. (2015) was conducted in Iran using the medical plant *Allium ampeloprasum* subsp *iranicum* (leek), while the studies of Man *et al*. (2013) and Aggarwal *et al*. (2014) were carried out in Taiwan and India and used the *Sophora* flower and a mixture of several herbs respectively. Mosavat *et al*. (2015) found that leek cream did not decrease pain after the treatment while it was similarly effective to the antihemorrhoid cream group (control group) in decreasing the grade of bleeding severity and defection discomfort. In addition, although the study of Man *et al*. (2013) demonstrated that the traditional Chinese *Sophora* flower formula is clinically safe, it failed to reveal any distinctive effect on symptoms in comparison to the placebo-control group. The RCT of Aggarwal *et al*. (2014) compared the efficacy of two herbal preparations, Daflon and Roidosanal, and found that both products were equally effective in improving anorectal conditions and associated signs and symptoms of hemorrhoids.

This study has some limitations. The preparation and application of the plant to the treatment group make it impossible to design a blind trial. The outcome of this study was the health-related quality of life that was self-assessed and such measurements are subjective and may be biased. Another important consideration is that hemorrhoid disease is associated with dietary behavior and lifestyle factors that cannot be directly controlled and have unavoidable effects on observed outcomes. The short duration of patient follow-up was another important limitation of this study as a 2-week follow up of patients does not allow the evaluation of following symptomatic relapses of hemorrhoidal diseases and the preventive role of the intervention. Last, the results of this study have to be interpreted with caution as the sample size is small and the sampling frame may not represent the general population.

CONCLUSIONS

The results of this study suggest that short-term use of a mixture of *Arum maculatum* is more effective than standard antihemorrhoid cream in improving the quality of life of patients suffering from hemorrhoid disease. Because this improvement was observed in this study for the first time, further randomized clinical trials with larger sample size and different populations are needed to confirm this finding and determine whether improvements in quality of life remains for larger periods and longer treatment periods. Finally, future studies are needed to assess the phytochemistry and pharmacological properties of *Arum maculatum* in order to determine its biologically active components and their mechanism of action.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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