

Addition of Chitosan May Improve the Treatment Efficacy of Triple Bandage and Compression in the Treatment of Venous Leg Ulcers

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ABSTRACT

Introduction: Venous leg ulcers are an important problem in public health due to their high prevalence and treatment cost. The gold standard therapy is the compression bandage. Addition of different substances to the compression therapy in order to accelerate ulcer healing has been attempted but none of them has yielded optimal results.

Objective: To describe the treatment efficacy of venous leg ulcers treated with triple compression bandage and chitosan gel.

Methods: A longitudinal and descriptive study was conducted in a sample of 16 patients with 26 venous leg ulcers that were treated with triple compression bandage plus a chitosan gel every seven days during nine weeks. Ulcer surface was measured during each treatment step.

Results: At the end of the treatment period, 89 percent reduction of the ulcer area was found when compared to the initial area at the beginning of the study. This value represents a reduction rate of 1.8 cm²/week.

Discussion: The results obtained in ulcer healing were higher than those previously reported when the compression bandage treatment of venous leg ulcers was performed alone. The observed difference might be due to the effect of the chitosan gel.

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INTRODUCTION

Venous leg ulcers are an important public health problem due to their high prevalence that ranges between 0.06–0.25 percent,¹ to the lowering of the quality of life of affected patients and to the high cost of treatment. In fact, treatment of the disease involves 1–2 percent of the health budgets in Europe.¹ It is estimated that the annual cost of this pathology in the United States (U.S.) varies between 1.9 and 2.5 dollar billions.² In general, about 80 percent of leg ulcers are secondary to venous insufficiency, whereas other 10–20 percent are due to arterial insufficiency, diabetes mellitus or neuropathic damage.¹

The gold standard treatment for venous leg ulcers is the use of compression with double, triple or quadruple bandages providing a pressure of 40–50 mm Hg being changed every week. According to published systematic reviews,^{4,5} no differences have been found between the number of the bandage layers used and healing, as long as they include one elastic layer. It is estimated that 60 percent of the patients will show complete healing after 12 weeks of treatment and that 80 percent of them will achieve complete healing after 24 weeks of treatment.⁵

In spite of the attempts to improve the efficacy of the compression bandage by adding substances that might stimulate the process of healing (e.g., alginates, films, foams, hydrogels hydrocolloids,

etc.), no addition has shown positive effects as reported in various published systematic reviews and meta-analyses.^{4–6}

Chitosan is a polysaccharide isolated from chitin present in the exoskeleton of *Pleuroncodes monodon* (red shrimp), a crustacean species inhabiting the coast of Peru and Chile, South America. This polysaccharide (poly-β-1,4-glucosamine) is the des-acetylated form of chitin.

An efficient stimulating effect on the repairing of epidermis by chitosan has been shown in animals.^{7–9} In addition, the use of chitosan in the treatment of type A and AB burns in humans has been recently reported, showing acceleration and better quality of healing.^{10,11} Chitosan stimulates migration and activation of macrophages into the wound area. There, macrophages synthesize the growth factors IL-1 and TGF-β, stimulate fibroblasts proliferation and synthesis of I, II and IV collagens.^{12,13}

Chitosan also stimulate angiogenesis, inhibits expression of metalloproteinase 2 by fibroblasts¹⁴ and exhibits antibiotic effect upon a wide variety of microorganisms including *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.¹⁰ Lastly, chitosan has been shown to exhibit analgesic, antipruritic and haemostatic effects.⁸

No publications reporting the adjuvant use of chitosan in venous ulcer in the presence of compression have been published.

TABLE 1.

Area of Leg Ulcer (cm ²) of 26 Ulcers Treated With Compression Bandage and Chitosan Gel During Nine Weeks										
ULCER N°	Area (cm ²) Week 0	Area (cm ²) Week 1	Area (cm ²) Week 2	Area (cm ²) Week 3	Area (cm ²) Week 4	Area (cm ²) Week 5	Area (cm ²) Week 6	Area (cm ²) Week 7	Area (cm ²) Week 8	Area (cm ²) Week 9
1	4,26	2,29	1,75	1,47	1,3	0,95	0,59	0,31	0	
2	1	0,35	0,02	0						
3	13,8	11	9,5	8,53	5,5	3,14	1,64	2,25	0	
4	1,34	1,48	3,41	6,84	7,45	4,04	4,96	3,88	3,3	3,71
5	14,1	13,5	11,2	10,01	8,31	7,07	5,89	4,19	3,93	3,48
6	22,15	20,5	16,8	14,5	14,5	12,5	11,11	9,58	8,55	7,71
7	14,05	2,28	0,97	0						
8	91	77,2	62,4	37,5	27,5	21,12	15,3	8,73	5	0
9	11,2	6,25	0,82	0,21	0					
10	1,68	0,62	0,28	0,18	0					
11	12	9,58	9,47	6,89	2,94	6,16	5,25	4,1	2	0
12	0,24	0,09	0							
13	0,21	0,11	0,045	0						
14	1,01	0,66	0,45	0,41	0,11	0				
15	2,47	2,4	1,55	1,13	0,19	1,51	0,31	0		
16	49,6	43,7	35,8	29,6	22	36,5	27,4	19,4	17,2	14,5
17	7,57	4	3,8	2,57	1,9	1,5	0,64	0		
18	20	16,3	17	12,6	15,3	11,8	13,4	12,5	15,3	8,64
19	13,75	7,83	5,58	4,33	0,91	0				
20	8,57	7,07	3,5	3,4	3,21	2,21	0			
21	1,53	1,61	1,23	0,53	0,46	0,23	0			
22	0,84	0,38	0,3	0						
23	7,53	5,92	4,46	3,53	2,61	2,3	2,15	1,3	0,61	0,15
24	5,53	3,61	2,23	1,46	0,76	0,53	0			
25	4,3	3,69	3,38	1,38	0,38	0,15	0			
26	42	29,2	21,1	12,2	5,6	0				
Total	352	272	217	159	121	111	89	66	56	38

Objectives

In this study, a group of patients with leg venous ulcers treated with compression bandage and a chitosan gel was followed up in order to evaluate the frequency of patients with complete healing and the speed of the wound healing with the treatment.

MATERIALS AND METHODS

The study was performed using a longitudinal and descriptive (follow up cases) design in order to obtain basal evidence for the formulation of hypothesis to be used in future trials.

The study group was constituted by patients older than 18 years, of both sexes that attended the Ambulatory Health Centres of the Uni-

versidad Católica de Chile with the diagnosis of venous leg ulcer. Twenty patients were recruited between August 2008 and March 2009. Diagnosis of venous leg ulcer was confirmed by the researchers through anamnesis, clinical examination including ulcer study, presence of pedal and posterior tibial pulses and measurement of the ankle/arm index. The exclusion criteria were pregnancy or maternal lactation, history of arterial insufficiency (excluded after clinical evaluation and in the presence of ankle/arm index >0.8) and ulcer with origin other than venous insufficiency, since those require a treatment different from compression bandage.

The following parameters were measured in the study: (1) proportion of healed area after nine weeks, (2) proportion of

completely healed ulcers after nine weeks and (3) average of ulcer healing rate. The healing rate of each patient was considered to be the ratio between the healed area and the number of weeks required for the complete healing or until nine weeks of treatment.

In addition, the following parameters were determined: age, sex, body mass index (BMI), time with venous insufficiency, time with non-healed ulcer, history of diabetes mellitus (DM), arterial hypertension (AHT), use of anticoagulant therapy (ACT) and aspirin, and presence of infection at the initiation of the study.

A procedure protocol was designed to perform evaluations. This included: (1) individual interview with the physician in order to look for defined secondary variables; (2) Before starting the treatment, samples from the ulcer being submitted to the laboratory for bacterial culture and antibiogram. In those cases with laboratory proved infection, antibiotic treatment was initiated and then the protocol was again followed; (3) Weekly treatments conducted by qualified nurses; (4) Weekly photographs of the ulcer obtained during patient examination and recording the ulcer area with a pencil upon transparent paper. The ulcer area was calculated using the Professional Adobe Acrobat 6.0 program.

The weekly treatments included ulcer cleansing with sterile saline, skin débridement and application of an emollient substance (fluid paraffin) on the leg area where bandage was to be applied, maintaining the ulcer free, and chitosan application (Biopiel®) over the ulcer. Then a triple compression bandage with one elastic layer in the middle was applied, from the base of the great toes up to the lower part of the knee, according to the triple compression bandage standardized technique (Dynaflex®).

The study was conducted according to the ethical principles of the Declaration of Helsinki and of the Clinical Good Practices. The study protocol was revised and approved by the Ethical Committee of the Faculty of Medicine of the Universidad Católica de Chile. An approved consent document was signed by every patient before being included in the study.

RESULTS

Twenty patients were recruited, with a total of 30 venous leg ulcers. Within the two first weeks of treatment, the voluntary withdrawal of four patients (two men and two women) was produced with the reason of the pain produced by the compression bandage, these were not included in the analysis. In total, 16 patients were followed up during nine weeks with a total of 26 ulcers among all patients. The initial average ulcer surface was 352 cm.²

Nine women and seven men, with an average age of 59.3 years and a range of 49–80 years were treated. The patients

FIGURE 1. a) Ulcer N° 7, three years of evolution and 14 cm² at week 0; **b)** Ulcer N°7 completely healed at week 3.

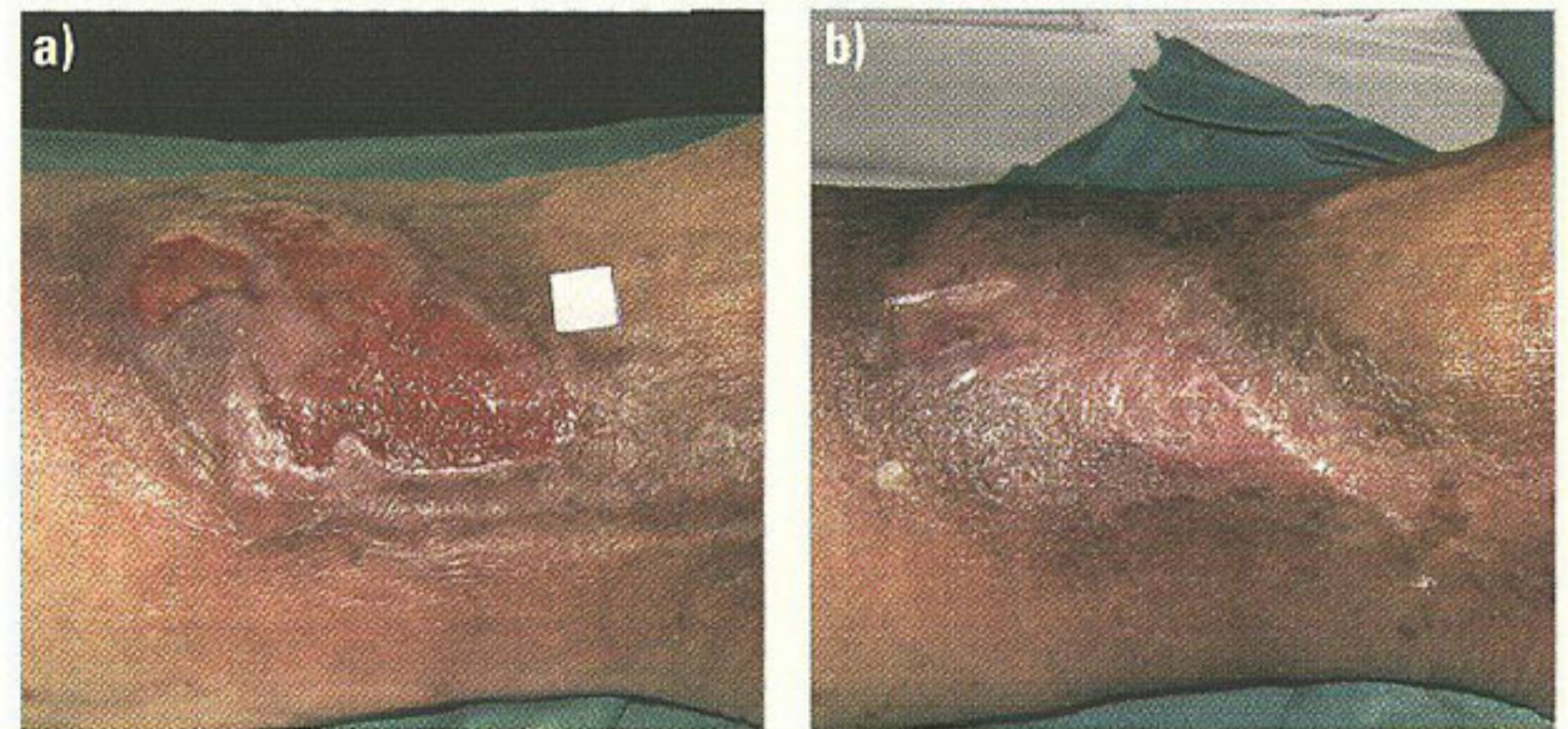


FIGURE 2. a) Ulcer N° 8 of 91 cm² at week 0. The patient had this ulcer for twenty years, was invalid and bedridden; **b)** Ulcer N° 8 completely healed at week 9, with excellent improvement in the quality of life with recovery of activity.

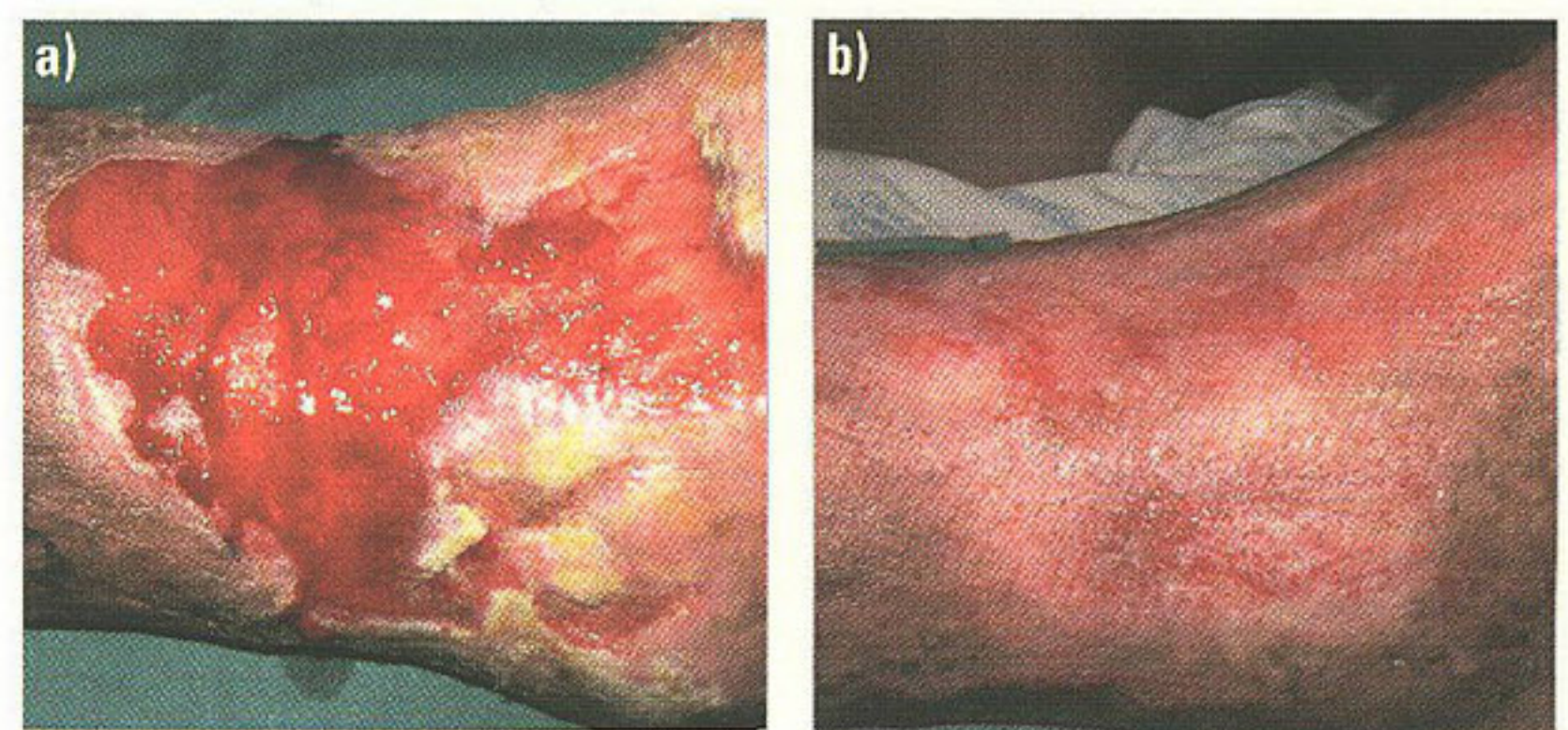
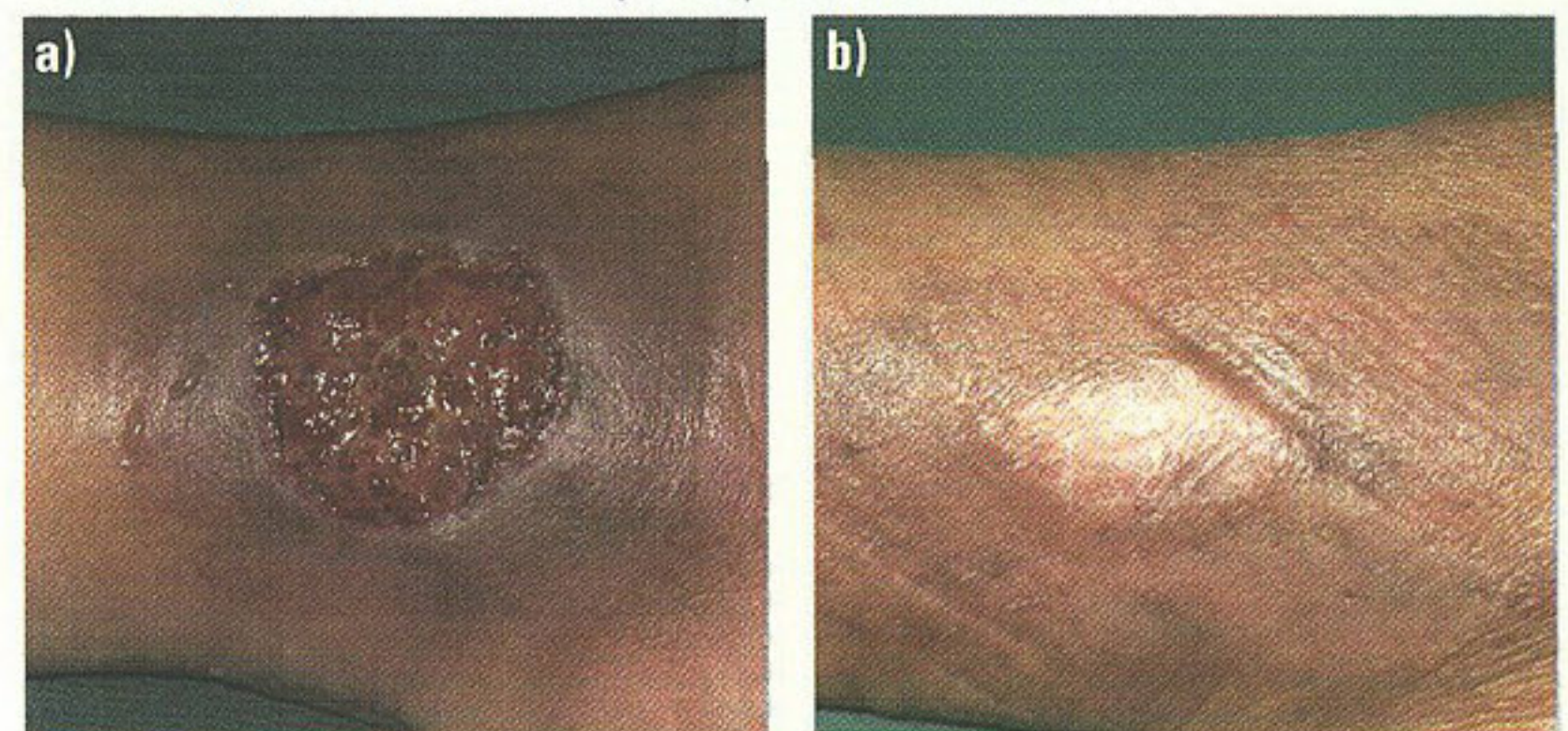


FIGURE 3. a) Ulcer N° 19, two years of evolution and 13,75 cm² at week 0; **b)** Ulcer N° 19 completely healed at week 5.



had a prolonged history of venous leg ulcer, with an average of 19 years. The average period of ulcer evolution had been six years. Other important data of the patients were: media of BMI of 29.4, 31.2 percent of patients with DM2, 43.8 percent of patients were hypertensive, 12.5 percent used TACO and 25 percent consumed aspirin.

Out of the 26 ulcers being treated, 20 of them (77%) were completely healed after nine weeks of treatment or before. Five of the other six ulcers were considerably reduced, in comparison to the initial size, and only one evolved with an increase of the affected area (Table 1). The total initial ulcer area was 352 cm²

and the total surface area after nine weeks of treatment was 34 cm², with 89 percent reduction in the ulcer area in the period (Figures 1–3). The mean rate of speed of reduction of the surface area was 1.8 cm²/week/ulcer.

At the starting of the study, 62.5 percent of the patients had infection as proved by the bacterial culture. These infections were successfully treated with the appropriate antibiotic during 10 days, and then ulcer treatment was initiated. No clinical infections were produced during the nine weeks of venous ulcer treatment.

DISCUSSION

Various studies show that between 50–60 percent of ulcers treated with compression bandage heal between three to four months of treatment.^{4,5} Although the current study does not compare with those, it is interesting that 77 percent of the ulcers were cured at the ninth week of treatment, thus representing a rate of healing 20–30 percent higher than that published in the literature when compression bandage has been used alone during longer periods of treatment.

On the other hand, Nelson et al.¹⁵ performed a study that included 387 patients with venous ulcers, randomized into two groups. One group was treated with quadruple compression bandage and a control group was treated with straight bandage. It was reported that 46.3 percent of treated ulcer with quadruple compression bandage were completely healed after 12 weeks of treatment.

In the current study, the healed ulcer area was 89 percent after nine weeks of treatment. In other few studies the percentage of healed area has been measured. Among them, Blecken et al.¹⁶ showed that, in the group of patients treated with quadruple bandage with an elastic layer, 62 percent of the affected area healed after 12 weeks of treatment. In that trial, the authors' patients with systemic conditions were excluded, whereas in the current study, 31 percent of the patients were diabetic.

These findings lead the authors to suggest that the higher proportion of healed ulcers in this current study is probably due to the action of chitosan. However, the number of patients included (n=16) and the absence of a control group do not allow the results to be generalized into the general population. Therefore, the formulated hypothesis can neither be validated nor rejected. The authors believe that further randomized and controlled studies with chitosan must be conducted in the treatment of venous ulcers.

CONCLUSION

On the basis of the results obtained in this study, according to the proportion of healed ulcers at nine weeks of treatment and the healing speed, the authors might conclude that addition of chitosan might improve the treatment efficacy of triple bandage

and compression in the treatment of leg venous ulcers. This is why it seems important the conduct of future research to reject or verify the hypothesis.

DISCLOSURES

The authors have no relevant conflicts of interest to disclose.

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