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A pilot study to evaluate a novel localized treatment to stabilize small- to medium-sized infrarenal abdominal aortic aneurysms

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ABSTRACT

Objective: There is no proven therapy to reduce growth rates of small- to medium-sized abdominal aortic aneurysms (AAAs). Ex vivo and animal studies have demonstrated that a novel stabilizing agent, 1,2,3,4,6-pentagalloyl glucose (PGG), delivered locally to the aneurysm sac, can bind to elastin and collagen to re-establish strength and resist enzymatic degradation. We aimed to demonstrate that a one-time administration of PGG solution to the aneurysm wall is safe and potentially effective to slow the growth of small- to medium-sized AAAs.

Methods: Patients with small- to medium-sized infrarenal AAAs (maximum diameter <5.5 cm) were recruited. Via transfemoral access, a 14F or 16F dual-balloon delivery catheter was introduced into the aneurysm sac. A single, 3-minute, localized endoluminal infusion of PGG was delivered via a 'weeping' balloon to the aneurysm wall. Independent core laboratory measurements of maximum aneurysm sac diameter and sac volume measurements based on computed tomography angiography (CTA) were used for assessments at 1, 6, 12, 24, and 36 months. The primary endpoints were technical success and safety (major adverse events at 30 days). The secondary endpoint was growth stabilization, defined as freedom from aneurysm sac enlargement (diameter increase >5 mm per year or volume increase of >10% per year).

Results: Twenty patients (19 male) were enrolled at five centers from May 2019 to June 2022 (mean age, 67.8 years; range, 50-87 years). All procedures were technically successful. The safety profile was consistent with standard interventional procedures. Four patients demonstrated transient elevations of liver enzymes levels that returned to normal by 30 days with no clinical symptoms. Through November 2022, follow-up CTA data is available on the first 11 patients. The average changes in maximum aneurysm diameter from baseline to 6, 12, 24, and 36 months were 0.2 mm, 1.1 mm, 1.2 mm, and 0.8 mm, respectively, and the average changes in volume were 2.0%, 9.6%, 18.1%, and 11.6%, respectively. At 12 months, none of the aneurysms showed growth >5.0 mm, and three had volume growth >10%.

Conclusions: The early results of this first-in-human, small cohort study demonstrated that a single, localized PGG administration to patients with small- to medium-sized infrarenal AAAs is safe. Longer term follow-up on all 20 treated patients is needed to better assess the potential impact on aneurysm growth. (J Vasc Surg 2023;■:1-7.)

Keywords: Medical treatment; Stabilization; Abdominal aortic aneurysms

Abdominal aortic aneurysms (AAAs) represent a significant public health problem. Current surgical or endovascular AAA treatments are reserved for AAAs larger than 5.5 cm in diameter (5.0 cm for women), in symptomatic patients, or in rapidly expanding aneurysms. To date, randomized clinical trials have shown no survival advantage for repair of aneurysms with a diameter less than 5.5 cm.[1] Small AAAs are traditionally monitored with serial ultrasounds or computed tomography (CT) surveillance.

In recent years, the ability for pharmacologic agents to alter the course of AAA growth in patients with small- to medium-sized aneurysms has been investigated.[2]

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In 2017, several studies tested the hypothesis that doxycycline, a tetracycline derivative, could reduce the growth rate of AAAs. However, 2-year data showed no evidence of an effect.[3] Similar negative results have been seen with other systemically administered therapeutics.[4]

BACKGROUND OF PGG AND THE MECHANISM OF ACTION

AAA formation involves pathophysiologic degradation of elastin and collagen, the major structural proteins in the aortic wall. Elastin, in particular, is important to maintain both aortic wall strength and resilience. Elastin is generated up to early adulthood, after which minimal elastin is produced. In the absence of pathologic degradation, elastin is extremely durable with a half-life of about 74 years.[5]

1,2,3,4,6-Pentagalloylglucose (PGG) is the pentagallic acid ester of glucose. It is composed of a single glucose molecule surrounded by 5-galloyl groups (Supplementary Fig, online only). PGG can be found in a number of naturally occurring edible plants.[6]

The five galloyl groups or "arms" sterically saturate the glucose molecule, making it hydrophobic. When PGG is exposed to degraded elastin, the hydrophobic arms bind strongly to the available hydrophobic regions of elastin, forming complexes that help to stabilize the elastin molecular structure.[7] Because the half-life of elastin is long, any stable binding to the molecule is likely to be durable. The binding of PGG to elastin and to collagen may also result in steric hindrance and prevent further enzymatic attack by matrix metalloproteinases. Therefore, PGG, when introduced into an aneurysm wall, has the potential to reinforce the weakened wall, hinder enzymatic degradation, and ultimately prevent or delay growth of aneurysms and subsequent rupture risk.

The stabilizing mechanism of action of PGG was supported by a number of animal experiments. In 2007, a study was performed at Clemson University, where a calcium-chloride-mediated rodent aortic aneurysm was treated periadventitially with PGG vs saline control 28 days after aneurysm induction.[8] At 56 days post induction, the PGG-treated aortas showed a smaller diameter when compared with controls. In a porcine model in 2016, AAA was induced by balloon dilatation and administration of elastase and was randomized to no treatment or intraluminal PGG, which further compared PGG treatment with sham-operated controls.[9] All pigs subjected to elastase infusion developed rapidly expanding AAAs. Aortic growth rates returned to that seen in controls following treatment with PGG.

In 2018, a study was performed on 50-kg pigs in which aortic aneurysms were created by a treatment with calcium chloride, elastase, and collagenase followed by balloon dilatation. Aneurysms were subsequently treated with PGG using a balloon catheter system.[10] A relative improvement on digital subtraction angiographic assessment was observed in the treatment group compared with the control after 10 weeks.

ARTICLE HIGHLIGHTS

- **Type of Research**: Multicenter non-randomized longitudinal study
- **Key Findings**: One-time transarterial local delivery of a novel stabilizing agent 1,2,3,4,6-pentagalloyl glucose (PGG) to 20 patients with small- to medium-sized abdominal aortic aneurysms were 100% successful and safe. Serial computed tomography in 11 patients showed none of the aneurysms grew >5.0 mm, and all but three had volume growth <10% at 12 months.
- **Take Home Message**: PGG delivered via a dual balloon catheter system to the aneurysm wall is safe and potentially effective to slow the growth of small to medium-sized abdominal aortic aneurysms.

With this background, a dual-balloon catheter system with PGG solution (Nectero EAST, Endovascular Aortic Stabilization Treatment [EAST System], Nectero Medical) was designed for local delivery of PGG into the aneurysm sac in humans with small- to medium-sized AAAs with the goal of reducing their rate of growth.

Early preclinical studies performed both in vitro and in vivo demonstrated a dose-dependent effect of PGG on aortic tissue. As concentrations of PGG bathing the tissue were increased from 0.03% to 0.3%, there was an increase in PGG binding to elastin, an increase in aortic tissue strength.[8] Rapid diffusion into aortic tissue was observed that saturation occurred within about 2.5 minutes. A concentration of 0.3% PGG (3 mg/mL) was therefore selected, based on preclinical safety/toxicology data to be delivered in 3 minutes. About 5 to 8 mL of PGG was required to saturate a 5-cm segment of porcine aorta in ex vivo studies, and an initial extrapolated dose volume of 25 mL was chosen for the human study.

After local delivery via the balloon, some residual PGG may enter the systemic circulation and become rapidly diluted by blood flow. PGG is largely bound to plasma proteins in the circulation. PGG concentration peaks at a low level of approximately 2 μg/mL and is not detectable in blood beyond 24 hours. There is low-level uptake in non-target organs, and historically, it has been shown that PGG is metabolized both by liver and kidneys.

STUDY AIM

The aim of this first-in-human study was to evaluate the safety and initial efficacy of the EAST system. The primary endpoints are defined as: (1) successful delivery of PGG with the delivery catheter; and (2) absence of major adverse events (MAEs) within 30 days. Secondary endpoints are freedom from aneurysm sac enlargement

Table I. Patient inclusion/exclusion criteria

Inclusion criteria	Exclusion criteria
• Age 18 years or older • Infrarenal AAA • Neck length ≥15 mm • Neck diameter ≤28 mm • Neck angulation ≤60° • Maximum diameter of 3.5 to 5.5 cm (subsequently changed the upper limit to 5.0 cm) • Overall treatment length <10 cm • Access vessels compatible with the 14F or 16F introducer system • More than 1-year life expectancy	• Ruptured or leaking AAA • Previous aortic repair • Intramural thrombus or wall calcification/plaques that may compromise delivery • Recent myocardial infarction within 6 months • Stroke within 3 months • Active cardiac disease • Connective tissue disease • Poor renal function (serum creatinine level >2.0 mg/dL) • Poor liver function (alanine transaminase or aspartate transaminase at 5 times higher than the normal upper limit • Serum total bilirubin at 2 times higher than the normal upper limit

AAA, Abdominal aortic aneurysm.

(defined as diameter increase of >5 mm per year, or volume increase of >10% per year) compared with baseline at 6, 12, 24, and 36 months.

METHODS

A global pilot study was conducted at five centers. The study was approved by the Research Ethics Committee/Institutional Review Board at each center prior to study initiation. This was a non-randomized study with the initial goal of recruiting 20 subjects with a follow-up of up to 12 months. Due to the strong safety profile seen on the initial eight patients and early signal of efficacy, follow-up was extended out to 36 months.

Patient inclusion and exclusion criteria are shown in Table I. Imaging parameters were based on contrast CT scans performed within 30 days prior to the index procedure.

The EAST procedure. The procedure was performed under general anesthesia with fluoroscopic image guidance. The system consists of a dual-balloon catheter with an aortic occlusion balloon and a porous delivery balloon (Fig). The delivery balloon has multiple laser-cut perforations to allow "weeping" of the PGG solution into the AAA sac. The PGG solution is comprised of a proprietary formulation of PGG, contrast media, and a preservative.

Common femoral artery percutaneous transarterial access was performed as in a typical endovascular procedure. After systemic heparin administration, an angiogram was obtained to delineate the aortic anatomy. A 14F or 16F sheath was inserted over an extra-stiff guidewire, and the catheter was introduced such that the occlusion balloon was positioned in the normal diameter infrarenal neck, and the delivery balloon was placed within the aneurysm sac. The occlusion balloon was inflated with a mixture of iodinated contrast and saline solution in the infrarenal neck to stop antegrade aortic inflow and create a quiescent environment for drug delivery. The blood in the aneurysm sac was displaced by filling the delivery balloon with an estimated volume of PGG solution calculated based on the preoperative three-dimensional CT reconstruction of the aortic lumen. Once the balloon was fully apposed to the aneurysm wall, an additional 25 mL of PGG solution was steadily delivered via the delivery balloon over three minutes using a digital pressure gauge and maintaining pressure between 70 and 100 mmHg. The continual stream of PGG solution ensured the concentration was constant within the aneurysm sac during the delivery period. The delivered amount was designed to be enough to saturate the tissue binding sites, based on preclinical testing. After delivery of the PGG solution, delivery and occlusion balloons were deflated, the catheter was withdrawn, and a final aortogram was obtained. The femoral access site was managed at the discretion of the site investigator using available large-bore closure devices.

Follow-up. Patients were monitored for any systemic, aneurysm, or access-related complications. Additional follow-up assessments were conducted at 1, 6, 12, 24, and 36 months. Serious adverse events were defined according to ISO 14,155 criteria, including death, serious health deterioration, prolonged hospitalization, or medical or surgical interventions. Biochemical parameters measured post-procedure and at 1-month follow-up included a comprehensive metabolic panel, complete blood counts, creatine phosphokinase, and serum lactic acid levels.

Contrast CT scans performed at 1 month following the procedure served as the baseline measurement for uniformity. Subsequent CT angiography (CTA) measurements were taken at each follow-up evaluation at 6, 12, 24, and 36 months. The aneurysm dimensions and volume were analyzed by an independent imaging core-lab (Astute Imaging).

RESULTS

A total of twenty patients were treated in the study through June 2022. Table II summarizes the number of patients treated at each site. The patient baseline demographic information and aneurysm baseline parameters are listed in Table III.

Procedure technical success, defined as successful insertion of the delivery catheter and delivery of PGG, was 100%.

Safety. Patients were monitored in-hospital for 24 hours, and the majority were discharged the next day with minimal complications. One patient was kept in the

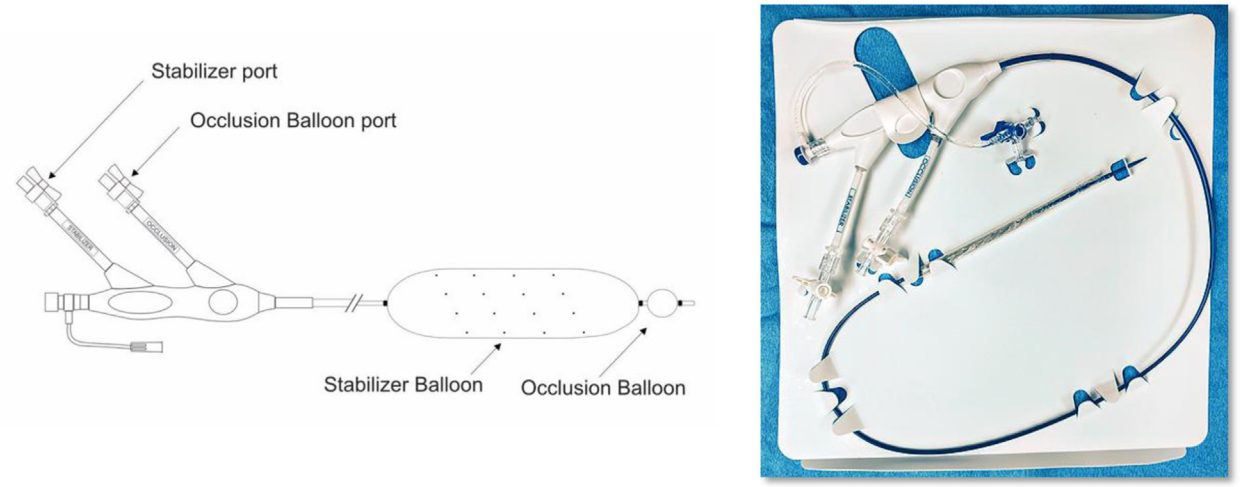

Fig. Endovascular Aortic Stabilization Treatment (EAST) delivery catheter.

hospital until postoperative day 11 for asymptomatic elevation of hepatic transaminase enzymes. Thirty-day safety data is available on all 20 patients. In total, there were seven events; four patients had transient liver function derangements (one significant, with alanine transaminase and aspartate transaminase peaking at 794 U/L and 633 U/L at day 3), one had mild and transient elevation in serum creatinine, one had a femoral artery access site infection, one had ankle cellulitis, and one had postoperative fever. The four subjects with elevated liver function tests, adjudicated as likely related to the administration of PGG, were transient and returned to normal levels at 30-day follow-up. One patient who presented with atheromatous embolization was asymptomatic with a slight discoloration in one toe that resolved without medical intervention within 24 hours. All other biochemical parameters post procedure and at 1-month follow-up were not impacted by treatment.

Aneurysm diameter and volume. Follow-up CTA data to 6 months and beyond is available for the first eleven patients; 6 months (n = 10, CTA was unavailable for 1 patient due to COVID-19 delay), 12 months (n = 7, one patient died of COVID-19), 24 months (n = 4), and 36 months (n = 2). At 6-, 12-, 24- and 36-month follow-up, the average changes in maximum aneurysm diameter as compared with baseline were 0.2 mm, 1.1 mm, 1.2 mm, and 0.8 mm, and the average % changes in sac volume were 2.0%, 9.6%, 18.1%, and 11.6%, respectively. At 12 months, two aneurysms showed a reduction in diameter, four grew ≤2 mm, and one demonstrated 5.0 mm growth. On volume measurements, one aneurysm had a reduction in volume, three had growth <10%, and three exhibited growth >10% volume at 12 months.

For those patients for whom at least 6-month follow-up CTA data is available, the baseline maximum sac diameters and sac volumes along with available data on changes from baseline at various timepoints are summarized in Tables IV and V. The only female patient in the study had a 47.5 mm diameter AAA at baseline. Follow-up CTA at 1 year showed a 2.0 mm growth to 49.5 mm, at which point the patient opted for open repair.

Thrombus. Aneurysms treated included those with different degrees of intra-sac thrombus. The extent of thrombus did not appear to impact the potential treatment effect; baseline thrombus volumes ranged from 22.7 to 48.8 mL. Conversely, treatment with PGG did not appear to impact subsequent sac thrombus volume; at 12 months, the average change in thrombus volume was 15.1%, which ranged from a decrease of 19.0% to an increase of 38.9%.

DISCUSSION

For decades, it has been known that pentagalloyl glucose (PGG) binds to extracellular matrix proteins including elastin and collagen.[11] Researchers began to evaluate the impact of this molecule on diseases associated with degradation of the extracellular matrix. AAAs, regardless of etiology, all involve pathologic degradation of elastin resulting in weakening and bulging of the aortic wall. PGG has been shown to be effective in limiting aortic elastin degradation, stabilizing the extracellular matrix, and reducing the growth rate of AAAs in a wide variety of both small and large animal models of AAAs.[8,9,10,12,13] These results have laid the groundwork for evaluation of PGG in human clinical studies. In preclinical animal studies in rats and swine, systemic administration of PGG could result in transient adverse renal and hepatic effects at high doses, but not in local delivery. This supported the use of a dual balloon catheter for local delivery of the stabilizing agent. The pilot safety study described herein represents the first clinical use of

Table II. Patient enrollment per site

Country	Site	Patients treated
Hong Kong	Queen Mary Hospital	6
Colombia	Hóspital Pablo Tobon Uribe	4
Colombia	Clínica Cardio VID	2
New Zealand	Auckland City Hospital	3
Latvia	Pauls Stradins Clinical University Hospital	5
	Total	20

Table III. Patient baseline demographic data

Age, years	67.8 (8.8), 50-87
Male sex	95.0
Body mass index, kg/m^2	27.3 (3.8)
History of smoking	65.0
Systolic blood pressure, mmHg	137.8 (22.9)
Diastolic blood pressure, mmHg	83.2 (13.7)
Stroke	5.0
Chronic kidney disease	5.0
Hypertension	50.0
Diabetes mellitus	15.0
Peripheral artery disease	35.0
Heart disease	30.0
Cancer	10.0
Hyperlipidemia	60.0
Aneurysm baseline diameter, mm	43.9 (4.8)
Aneurysm baseline volume, cm^3	64.3 (22.6)

Data are presented as number (%) or mean (standard deviation).

PGG as a potential therapy to treat small- to medium-sized AAAs.

These same studies evaluated tissue uptake and again found higher concentrations of drug in non-target organs and lower concentrations of drug in the aorta when the drug was given systemically as opposed to localized delivery. So, on the basis of reduced systemic toxicity and increased drug delivery to target aorta, a localized delivery to the aorta appears to be a better option.

Over the past decade, there has been increased interest in slowing the growth rate of AAAs, with the aim to potentially delay or avoid invasive procedures such as endovascular or open surgical repair. Powell suggested that a realistic therapeutic goal for nonoperative treatment would be to reduce the expansion rate of a 4.0 cm AAA from 2.6 mm per year to 1.3 mm per year so that the time taken for the AAA to exceed the 5.5 cm threshold for intervention would be increased from 5 to 10 years.[14] Postponing the need for endovascular aneurysm repair or open surgical repair for 10 years will mean that many of these patients will never have to undergo the procedure in their lifetime. Thompson et al further stated that, although an annual growth rate of at least 2 mm is significantly associated with clinical events, aneurysms with growth rates of less than 1.5 mm appear to be of little clinical relevance.[15] Of the seven patients with 12-month follow-up CTA, only two had grown >1.5 mm. Although encouraging, determination of efficacy awaits confirmation in a randomized clinical trial.

Aneurysm sac volume growth rate was, on average, less than 10% per year in patients for which follow-up measurements were available. Although measurement of changes in aneurysm volume may provide potentially a more accurate assessment of growth, evaluation of changes in maximum aneurysm diameter remain the primary index for decision-making in clinical practice.[16]

The predominant complication seen was transient increase in liver enzymes. These increases were moderate in three patients and significant in one. Patients with increased liver enzymes were asymptomatic, and values returned to normal within 30 days following the procedure. Systemic PGG is metabolized, in part, by the liver.[17] Comparatively, other compounds such as acetaminophen[18] and statins[19] that are metabolized or degraded in the liver have been shown to result in transient elevations in alanine transaminase and aspartate transaminase. Elevated hepatic transaminases are typically transient, particularly when therapy is not given on a continual basis. Research into use of PGG as a nutraceutical has shown the potential for dose-dependent inhibition of liver mitochondrial enzymes.[20] At low doses, this inhibition has minimal impact on mitochondrial respiration. Although the doses used in this AAA treatment are well below the systemic doses needed to depress mitochondrial respiration, in sensitive patients, this effect could contribute to transient changes in liver enzymes. At doses of PGG above 30 μM, mitochondrial respiration may be significantly impaired. Of note, 30 μM is roughly 10-fold higher than the concentration of full-strength PGG solution that is rapidly diluted into the central circulation prior to any uptake by the liver. The aneurysms from those patients with elevated liver enzymes remained quite stable, similar to all other patients with the exception of patient #5. The elevation in liver

Table IV. Change in maximum aneurysm diameter

		Change in maximum sac diameter from baseline, mm			
Patient	Baseline, mm	6 months	12 months	24 months	36 months
01	48.0	−0.4	−1.1	−1.5	−0.7
02	50.8	0.2	−0.8	0.7	2.2
03	51.5	0.0	0.5	2.5	
04	43.5	−0.3	0.5	3.0	
05	50.0	2.0	5.0		
06	44.5	–[a]	1.5		
07 (Female)	47.5	0.0	2.0	–[b]	–
08	48.5	0.8	–[c]	–	–
09	46.9	−0.4			
10	37.4	0.1			
11	47.0	0.0			
Number of patients	11	10	7	4	2
Average change in sac diameter (mm)		0.2	1.1	1.2	0.8

[a]Patient missed follow-up due to COVID-19.
[b]Patient converted to open repair
[c]Patient died of COVID-19.

Table V. Change in aneurysm sac volume

		Change in sac volume from baseline, %			
Patient	Baseline, mL	6 months	12 months	24 months	36 months
01	56.4	−3.2	4.1	10.8	9.6
02	89.8	0	−4.3	11.1	13.6
03	121.0	6.0	12.6	27.3	
04	78.5	−0.6	8.9	23.3	
05	89.1	4.4	19.8		
06	51.4	–[a]	16.1		
07 (Female)	84.2	2.9	9.7	–[b]	–
08	100.8	1.8	–[c]	–	–
09	58.0	6.2			
10	33.6	−4.5			
11	60.2	7.1			
No. patients	11	10	7	4	2
Average change in sac volume, %		2.0	9.6	18.1	11.6

[a]Patient missed follow-up due to COVID-19.
[b]Patient converted to open repair.
[c]Patient died of COVID-19.

enzymes is not likely linked to either efficacy or the amount of drug that enters the systemic circulation. It is more likely related to patient-specific sensitivity to liver enzyme induction.

Similar to other small aneurysm trials, the current study is designed to evaluate the impact of PGG on aneurysms between 3.5 and 5.5 cm (the upper limit was subsequently amended to 5.0 cm). Most of the patients treated had aneurysms on the upper end of this range. At this early stage of evaluation, there has been no indication of a differential treatment effect within this range of diameters. The beneficial effect of PGG on stabilizing the aortic wall is expected to be more profound in even smaller AAAs where elastin is both more abundant and more organized.

The present study included patients with a range of thrombus burden. Bench studies have shown that thrombus does not constitute a significant barrier to drug delivery, and PGG diffused quickly throughout aortic tissue. Aortic aneurysm tissue harvested from the

patient who underwent open conversion showed levels of PGG in the wall approximately 70% of the target concentration at 1 year, despite a thrombus burden of 42% in this patient.

These early results showed that the EAST procedure is safe with a potential to influence small- to medium-sized aneurysm growth. Nonetheless, this is still an invasive procedure involving anesthesia, introduction of a transfemoral sheath, infusion of heparin and iodinated contrast, and brief aortic occlusion. The advantages of local pharmacological intervention are the ability to deliver treatment directly to the target region while leaving no permanent implant behind and keeping all surgical and endovascular treatment options open if required in the future.

CONCLUSION

This first-in-humans study utilizing the Nectero EAST System for the localized delivery of PGG resulted in 100% procedural success. The 30-day primary safety data on the 20 PGG-treated patients indicated that the procedure was safe. Efficacy data on the initial 11 patients support going forward with further studies. Longer-term follow-up on all 20 treated patients is needed to better assess the potential impact on aneurysm growth. A larger-scale, randomized trial comparing treatment with the EAST System with current standard of care (active surveillance) is planned to confirm the ability of PGG to reduce the growth rate in patients with small- to medium-sized AAA.

AUTHOR CONTRIBUTIONS

Conception and design: SC, VR
Analysis and interpretation: SC, ME, VR
Data collection: SC, SE, JM, AHH, AAH, DK
Writing the article: SC
Critical revision of the article: SC, ME, SE, JM, AHH, AAH, DK, VR
Final approval of the article: SC, ME, SE, JM, AHH, AAH, DK, VR
Statistical analysis: SC
Obtained funding: Not applicable
Overall responsibility: SC

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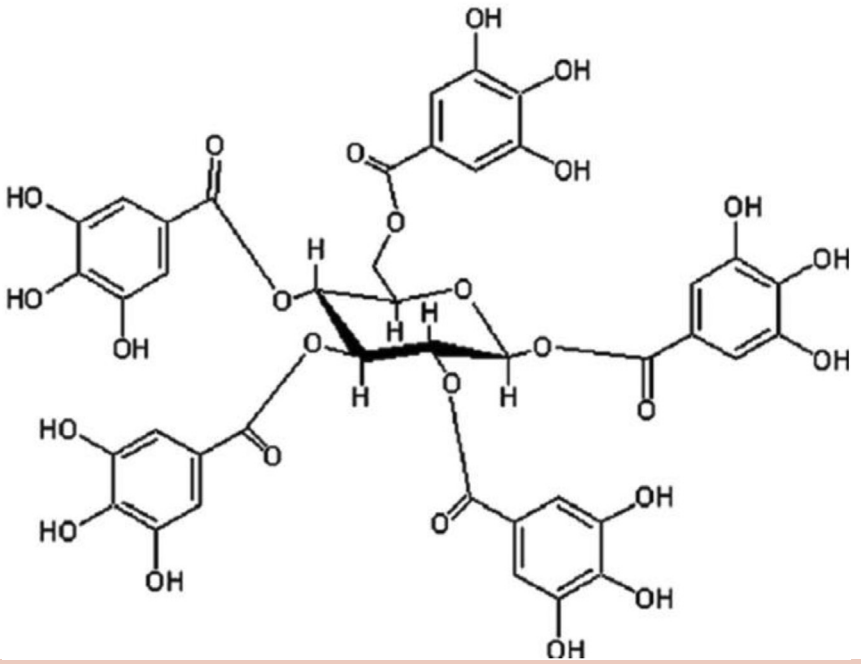

Supplementary Fig (online only). Pentagalloylglucose (PGG) molecule.