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ORIGINAL ARTICLE



Comparative efficacy of Glubran and polyvinyl-alcohol particles in the embolization of meningiomas

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Purpose: Preoperative embolization of meningiomas decreases intraoperative bleeding and shortens operation time. However, in meningiomas predominantly vascularized by the internal carotid artery (ICA) or vertebral artery (VA) branches, embolization of external carotid artery feeder branches may lead to a hemodynamic increase in blood supply from the ICA or VA, whereas embolization of ICA or VA feeder branches with particle embolic agents may be associated with complications. This study investigated the safety and efficacy of Glubran, a liquid embolic agent, for the embolization of this type of meningioma compared with polyvinyl-alcohol (PVA) particles. Materials and methods: From January 2006 to June 2015, 157 consecutive patients (98 females; mean age = 48.3 years) who suffered from meningiomas and were preoperatively referred for embolization were retrospectively analyzed. Glubran (n = 40) and PVA (n = 55) were used to devascularize tumors. Sixty-two patients were not embolized because of dangerous anastomosis or other tumor characteristics. Intraoperative blood loss, intraoperative time, degree of angiographic devascularization and embolization-related complications were analyzed. Results: The intraoperative blood loss and operative time were significantly lower in the Glubran-embolized versus non-embolized group. Furthermore, Glubran embolization significantly reduced intraoperative blood loss and operative time for meningiomas that received their primary blood supply from the ICA and/or VA compared with PVA embolization. Conclusions: Preoperative meningioma embolization with Glubran decreases intraoperative blood loss and operative time. Furthermore, embolization with Glubran produces more effective devascularization compared with PVA for meningiomas supplied by the ICA and/or VA. Thus, Glubran may represent a better embolic agent for this meningioma subtype.

KEYWORDS: meningiomas, preoperative embolization, Glubran glue, PVA particles

Introduction

Meningiomas comprise hypervascular tumors that are vascularized by the extracranial and intracranial blood vessels. Surgical excision of meningiomas may potentially lead to significant and, in some cases, catastrophic blood loss. However, preoperative embolization of the feeding vessels facilitates meningioma resection by decreasing intraoperative bleeding and shortening the operative time [1-5]. Many different embolic materials

have been proven to be successful in the embolization of meningiomas. These embolic agents, which may be permanent or temporary, include polyvinyl-alcohol (PVA), microspheres, gelfoam, coil, N-butyl cyanoacrylate (NBCA) and Onyx [6,7]. PVA particles are likely the most common embolic agents [5,6,8,9]. However, PVA particles are associated with potential complications, such as hemorrhage and unintended ischemia [9-11]. Several authors have recently reported that liquid agents, such as NBCA, which are able to penetrate tumor vessels, have more advantages than other particle agents. Studies have also suggested that NBCA has a lower risk of complications compared with particle agents [12-15]. Glubran is composed of the combination of two monomers, NBCA and metacryloxysulpholane (MS) (a monomer manufactured by GEM

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S.r.l., Viareggio, Italy) and has been introduced as a non-absorbable liquid embolic agent.

For meningiomas that are predominantly fed by internal carotid artery (ICA) or vertebral artery (VA) branches, embolization of the feeder branches of the external carotid artery (ECA) may lead to a hemodynamic increase in the blood supply from the ICA or VA, which thereby increases the surgical risk [2,19,20]. However, embolization of the feeder branches of the ICA or VA with particle embolic agents may be associated with complications [9–11]. Therefore, this study aimed to retrospectively investigate 157 consecutive patients diagnosed with meningiomas from January 2006 to June 2015. Furthermore, the safety and efficacy of Glubran in the preoperative embolization of meningiomas were assessed.

Materials and methods

Patients

The database of the Department of Neurosurgery, Zhujiang Hospital, Southern Medical University was systematically reviewed, and 157 patients (98 females and 62 males) who were referred for preoperative embolization of meningiomas from January 2006 to June 2015 were identified. The patients' mean age was 48.3 years (median, 50 years; range: 21–79 years). Demographic information and tumor characteristics, such as tumor location and vascular supply, were recorded. The surgical time, intraoperative blood loss and embolization-related complications were also assessed.

The attending neurosurgeons carefully reviewed the preoperative imaging results and discussed the indications for preoperative embolization prior to the procedure. Preoperative embolization was performed if significant intraoperative bleeding was expected and embolization was considered safe. The patients were divided into three groups according to the embolization agents used: the Glubran group (embolized with Glubran; n = 40), the PVA group (embolized with PVA 300–500 μ m; n = 55) and the non-embolized group (n = 62). The non-embolized group was not embolized for the following reasons. First, the feeding vessels of the meningioma can easily be ligated early in surgery. Second, dangerous extracranial-intracranial anastomoses or supply branches of cranial nerves were present in the target vessels. Third, the vessels were too tortuous or too small for the super selectivity of the microcatheter. Fourth, the patients preferred to undergo only angiography without embolization because of the fear of potential complications.

In most cases, the degree of devascularization was recorded in the operative notes, based on the neuroradiologist's opinion at the time of surgery. In cases without assessment, the extent of devascularization was estimated by the primary author based on a review of the operative reports and pre- and post-operative angiography. The extent of devascularization was assessed by post-embolization angiography and was graded according to three levels: complete level (complete disappearance of the tumor stain), extensive level (tumor devascularization > 60%) and partial level (devascularization <60%). The maximum tumor diameter was determined based on pre-surgical imaging results and was recorded as the largest measurement. Meningiomas were further categorized by the source of their feeding arteries as follows: (1) meningiomas supplied solely by the ECA; (2) meningiomas with a mixed ECA and ICA or VA supply, but with dominant feeders from the ECA; (3) meningiomas with dominant feeders from the ICA or VA and (4) meningiomas with pure ICA or VA.

Furthermore, the extent of resection was graded at three levels: gross total resection, sub-total resection and partial resection. The gross total resection was defined as Simpson grades I or II [16]. However, when the volume of the residual tumor was < 10% of the total tumor volume at operation or postoperative imaging, it was defined as a sub-total resection. A partial resection indicated the total tumor volume was > 10%.

Embolization procedure

Heparin was intravenously injected to achieve an approximate doubling of the activated partial thromboplastin time compared with the baseline level. Embolizations were performed through the transfemoral route under general anesthesia in all patients. Following a diagnostic angiography and the selection of appropriate vessels for embolization, a microcatheter system (Magic 1.5-MP or Magic 1.8-MP, BALT, Montmorency, France or Marathon, ev3, Irvine, CA) was placed in the feeding branches as close to the tumor as possible under road-mapping guidance. Embolization was subsequently performed. The embolization materials included a mixture of PVA 300–500 μ m particles (COOK, Bloomington, IN) and contrast agent Ioversol (Mallinckrodt, Quebec, Canada), an 8%-10% mixture of Glubran (GEM S.r.l., Viareggio, Italy) and lipiodol (Guerbet, Roissy, France). A post-embolization angiogram of the target vessel was immediately performed to examine the extent of tumor devascularization. For most patients, the period between embolization and surgery was approximately 2-4 days. All tumors were removed through a craniotomy; no tumors were removed through endoscopic techniques.

An institutional protocol was not formalized in terms of the indications, timing or technical strategies for preoperative embolization. However, the preoperative

	PVA	Glubran	Non-embolization	Þ
Total number of patients	55	40	62	_
Sex	M25, F30	M13, F27	M23, F39	0.413 ^a
Age (median), years	53	45	49	0.320 ^b
Maximum tumor diameter (mean \pm SD), cm	5.87 ± 1.74	5.55 ± 1.46	5.46 ± 1.58	0.360 ^c
Recurrence of previously operated meningiomas, n (%)	4 (7.3)	2 (5)	4 (6.5)	0.904 ^a
Tumor location, n (%)				0.086 ^a
Convexity	30 (54.5)	17 (42.5)	22 (35.5)	
Parasagittal/falx	9 (16.4)	6 (15.0)	5 (8.1)	
Olfactory groove	2 (3.6)	2 (5.0)	3 (4.8)	
Tuberculum sellae	3 (5.5)	0 (0)	10 (16.1)	
Sphenoidal ridge	1 (1.8)	3 (7.5)	6 (9.7)	
Middle cranial fossa	2 (3.6)	0 (0)	1 (1.6)	
Posterior fossa	3 (5.5)	8 (20.0)	7 (11.3)	
Intraventricular	0 (0)	0 (0)	2 (3.2)	
Cerebellopontine angle	3 (5.5)	1 (2.5)	4 (6.5)	
Meningiomatosis	2 (3.6)	3 (7.5)	2 (3.2)	
WHO grade, n (%)				0.069 ^b
I	39 (70.9)	29 (72.5)	54 (87.1)	
II	16 (29.1)	9 (22.5)	8 (12.9)	
III	0	2 (5.0)	0	

Table 1.	Characteristics	of patients	with	meningiomas.

 $^{a}\chi^{2}$ test; ^bKruskal–Wallis test; ^cone-way analysis of variance (ANOVA).

imaging and cerebral angiogram were carefully reviewed by the neurosurgeons to discuss the indications for preoperative embolization. In an effort to reduce the risks of the combined embolization and resection procedures, the neuroendovascular interventionist and neurosurgical team reached a consensus regarding the choice of embolic agents, the target branches and the degree of embolization.

Data analysis

SPSS statistical package version 20 (IBM, Armonk, NY) was utilized to conduct all statistical analyses, and the data were summarized as descriptive statistics. The analysis utilized an unpaired *t*-test, χ^2 test, Dunnett's *T*3 test, Mann–Whitney test, one-way analysis of variance (ANOVA) or Kruskal–Wallis test as appropriate. Comparison of the means for the three groups was performed with an ANOVA using a Bonferroni *post hoc* analysis. *p* Values < 0.05 were considered statistically significant.

Results

Tumor characteristics

Between January 2006 and June 2015, 157 consecutive patients received cerebral angiograms, which indicated hypervascular tumors. Regarding the selection of embolization material, PVA particles (300–500 μ m) were used in 55 cases, and Glubran was used in 40 cases. The remaining patients did not undergo embolization. The mean maximum tumor diameter was 56 mm (range:

13–101 mm). The meningioma locations included the convexity in 69 patients, parasagittal or falx in 20 patients, olfactory groove in 7 patients, tuberculum sellae in 13 patients, sphenoidal ridge in 10 patients, middle cranial fossa in 3 patients, posterior fossa in 18 patients, intraventricular in 2 patients, a cerebellopontine angle in 8 patients and meningiomatosis in 7 patients. Pathologically, 122 patients (77.7%) were diagnosed as World Health Organization (WHO) grade I, 33 patients (21%) were WHO grade II and 2 patients (1.3%) were WHO grade III. There was no significant difference between the groups regarding age, sex, tumor locations, maximum tumor diameter or WHO grade (Table 1).

Embolization characteristics

Embolization surgeries were performed for 110 feeding vessels. The most prevalent feeding arteries were middle meningeal artery branches in 67 patients (60.9%), followed by anterior cerebral artery branches in 10 patients (9%) and superficial temporal branches in 6 patients (5.5%). In the Glubran group, the feeding vessels that originated in the ICA and/or VA were accessed more frequently (Table 2). In the Glubran group, 87.5% of the patients had received extensive or complete devascularization compared with 69% of the patients in the PVA group (Table 2). The mean interval between embolization and surgery was 4.25 days (median, 3 days). Two (2.3%) of the 84 patients had embolization-related complications. One intraventricular and intratumoral hemorrhage occurred immediately after the embolization of a large flax meningioma through the anterior cerebral

Table 2. Embolization characteristics.

	PVA	Glubran
Feeding vessel branches, n (%)		
Middle meningeal artery	44 (72.1)	23 (46.9)
Superficial temporal artery	6 (9.8)	0
Internal maxillary artery	4 (6.6)	1 (2.0)
Ascending pharyngeal artery	3 (4.9)	2(4.1)
Occipital artery	2 (3.3)	2(4.1)
Posterior meningeal artery	0	2(4.1)
Anterior cerebral artery	0	10 (20.4)
Middle cerebral artery	2 (3.3)	2(4.1)
Posterior cerebral artery	0	5 (10.2)
Superior cerebellar artery	0	1 (2.0)
Ophthalmic artery	0	1 (2.0)
Total	61	49
Extent of devascularization, n (%)		
Complete level	30 (54.5)	15 (37.5)
Extensive level	8 (14.5)	20 (50.0)
Partial level	17 (30.9)	5 (12.5)

artery branch feeding vessels. An emergency surgical removal of the tumor and a ventricular drain were performed. The patient exhibited good clinical outcomes without hemorrhage-related symptoms. The other patient who underwent embolization of both superficial temporal feeding vessels experienced scalp necrosis after surgical resection.

Surgical outcome

As shown in Table 3, there was a significant difference among the three groups in intraoperative blood loss (p = 0.014, Kruskal–Wallis test) and operative time (p = 0.013, Kruskal–Wallis test). The intraoperative blood loss was significantly lower in the Glubranembolized group compared with the non-embolized group (p = 0.010, Mann–Whitney test), which remained significant following a Bonferroni adjustment. However, there was no significant difference between the Glubran-embolized and PVA-embolized groups (p = 0.603, Mann–Whitney test). The intraoperative blood loss was significantly lower in the PVA-embolized group compared with the non-embolized group (p = 0.019, Mann–Whitney test). However, there was no signifi-

Table 3.	Operative	outcomes.
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cant difference between the PVA-embolized and nonembolized groups when adjusted by Bonferroni *post hoc* analysis.

The operative time was significantly lower in the Glubran-embolized group compared with the nonembolized group (p = 0.006, Mann–Whitney test), which remained significant following a Bonferroni adjustment. The operative time was significantly lower in the PVA-embolized group compared with the nonembolized group (p = 0.030, Mann–Whitney test); however, this difference did not remain significant following a Bonferroni adjustment. There was no significant difference between the PVA-embolized and Glubran-embolized groups (p = 0.584, Mann–Whitney test). Furthermore, there was no significant difference in the extent of resection among the groups (p = 0.308, Kruskal–Wallis test, Table 3).

In the subgroup of meningiomas that were predominantly fed by the ICA or VA, the intraoperative blood loss was significantly lower in the Glubran-embolized group (593 ml) compared with the PVA-embolized group (1087 ml; p = 0.012, Dunnett's T3 test, Table 4). Furthermore, in this subgroup of meningiomas, the operative time in the Glubran-embolized group (7 h) was significantly lower than in the PVAembolized group (10 h; p = 0.005, Mann–Whitney Utest, Table 4). The extent of embolization was more completely achieved in the Glubran group (p = 0.046, χ^2 test with Fisher's exact test, Table 4). There was no significant difference between the Glubran-embolized and PVA-embolized groups regarding age, sex, tumor location, maximum tumor diameter or WHO grade in this subgroup of meningiomas.

Discussion

Preoperative embolization of meningiomas facilitates resection by both decreasing intraoperative bleeding and shortening the operative time [1-5]. Embolization has the best risk-benefit profile for large tumors that are primarily supplied by the ECA [2,17]. Embolization also has favorable effects on meningiomas of the skull base and middle cranial fossa [18,19]. However, regarding

	PVA	Glubran	Non-embolization	Þ
Intraoperative blood loss, mean mL Operative time, median h (P25, P75)	698 ± 376 8 (6.5, 10)	657 ± 375 7.5 (7.0, 8.43)	900 ± 520 9.35 (7, 11)	$p = 0.014^{a}$ $p = 0.013^{a}$
Extent of resection				$p = 0.308^{a}$
Gross total resection	39 (70.9)	33 (82.5)	44 (71)	
Sub-total resection	13 (23.6)	7 (17.5)	15 (24.2)	
Partial resection	3 (5.5)	0	3 (4.8)	

^aKruskal–Wallis test.

e . e	•			
	PVA	Glubran	Non-embolization	Þ
Total patients	11	11	15	_
Intraoperative blood loss, mean \pm SD mL	1087 ± 437	593 ± 189	1089 ± 750	$p = 0.035^{a}$ Glubran vs. PVA $p = 0.012^{b}$
Operative time, median h (P25, P75)	10 (8.5, 12.5)	7.0 (6.67, 8.0)	9.2 (6.5, 12.2)	$p = 0.033^{\circ}$ Glubran vs. PVA $p = 0.005^{\circ}$
Extent of embolization				$p = 0.046^{\rm e}$
Partial	8 (72.7)	2 (18.2%)		-
Extensive	2 (18.2)	6 (54.5%)		
Complete	1 (9.1)	3 (27.3)		

Table 4. Subgroup of meningiomas that are predominantly fed by the ICA or VA.

^aBrown–Forsythe test; ^bDunnett's T3 test; ^cKruskal–Wallis test; ^dMann–Whitney U-test; ^e χ^2 test with Fisher's exact test.

meningiomas that are predominantly fed by the ICA or VA, the embolization of ECA feeders may lead to an increased flow via remnant ICA or VA branches, which increases the surgical risk [2,20,21]. Thus, preoperative embolization of this subtype of meningioma remains controversial.

Many different embolic materials have been proven to be successful in the embolization of meningiomas. These embolic agents, which are either permanent or temporary, include PVA, microspheres, gelfoam, coil, NBCA and Onyx [6,7]. PVA particles are the most common embolic agents [5,6,8,9]. Studies have suggested that liquid embolic agents, such as NBCA, may have more operational advantages and efficacy compared with other particle agents [12,14,15]. The advantages of NBCA include fast and deep penetration into the tumor vasculature, permanent occlusion effects, low infusion pressure delivery and radiopacity [7]. Furthermore, NBCA can be administered with various microcatheters and exhibits superior distal navigation compared with PVA particles [14,22]. Glubran is a non-absorbable liquid embolic agent that comprises a combination of two monomers, NBCA and MS (a monomer manufactured by GEM S.r.l., Viareggio, Italy). The safety and efficacy of NBCA have been proven to be equivalent to PVA in the embolization of arteriovenous malformations [23]. However, there are limited reports concerning the preoperative embolization of meningiomas using NBCA or Glubran.

From January 2006 to June 2015, 95 patients were embolized in our institution, with PVA particles $(300-500\mu m)$ in 55 cases and Glubran in 40 cases. The intraoperative blood loss and operative time were significantly lower in the Glubran-embolized group compared with the non-embolized group. For the subgroup of meningiomas that were predominantly fed by the ICA or VA, embolization with Glubran significantly reduced the intraoperative blood loss and operative time compared with embolization with PVA particles. Thus, these novel findings indicate that preoperative embolization of meningiomas with Glubran, as an alternative embolic agent to PVA, is safe and efficacious. Embolization with Glubran produces more effective devascularization of the tumor vascular bed compared with PVA for meningiomas that are predominantly fed by the ICA or VA. As a liquid embolic agent, Glubran is more appropriate for this type of meningioma, which is rarely embolized by particle agents because of the increased surgical risk.

It is critical to assess the potential mechanism of action of Glubran in meningiomas that are predominantly fed by the ICA or VA compared with PVA particles. Glubran simultaneously occludes both the main and distal vessels because of its viscosity as a liquid [7]. This feature is especially useful for meningiomas that receive their blood supply from multiple arterial feeders. In some cases, when administered from the ECA, Glubran penetrates into the compartment that is fed by the pial arteries through the arterial network within the meningioma (Figure 1) with maximum devascularization effects. On the other hand, liquid embolic agents can be injected as close to the meningioma as possible through various microcatheters in contrast to the particle agents [14,22].

PVA has been considered to be inappropriate for embolizing the ICA or VA feeders [21] for several reasons. First, the high coefficient of friction in PVA particles requires a high injection pressure that causes hemorrhage of the weak pial arteries or results in the clumping and aggregation of particles within the microcatheter [7,24]. Second, PVA is a radiolucent particle. Even if it is mixed with contrast medium, it cannot be directly observed in real time during an injection. Thus, there are risks of inadequate reflux or migration of the PVA into the normal cerebral arteries. In most patients, we only administered PVA particles through the ECA branches, which resulted in only partial devascularization.

In our cases, one intraventricular and intratumoral hemorrhage occurred immediately after embolization of a large flax meningioma through the feeding vessels of the anterior cerebral artery branches. Emergent surgical removal of the tumor and a ventricular drain were performed, and the patient exhibited good clinical outcomes without symptoms related to hemorrhage. The hemorrhage-related complication rate of Glubran embolization was 2.5%, and in some series, this rate has been reported as 3%–6% of patients [8,11,25,26]. It



Figure 1. (a, b) Right ICA angiogram indicated that the tumor was fed by small branches of the ICA; however, the feeder vessels were too small for the super selectivity of a microcatheter. (c, d) Right ECA angiogram demonstrated that the tumor was also fed by a branch of the middle meningeal artery (MMA). (e, f) Superselective injection and embolization of the MMA branch. (g–i) Postembolization angiogram indicated that tumor blush disappeared in both the ECA and ICA. It is possible that Glubran penetrated the compartment fed by the ICA through the arterial network within the meningioma.

remains unknown which embolic agent is associated with a higher risk of hemorrhage because the mechanisms of embolization-related hemorrhages are unknown and the data regarding liquid embolization are limited. However, studies have suggested an increased risk of hemorrhage with particle embolization compared with liquid embolization [12,15].

Although the underlying pathophysiology of hemorrhages remains uncertain, there are several hypotheses regarding the potential mechanisms. First, embolic material obstructs the venous outflow, which leads to high transmural intratumoral pressure [11,26]. Second, the remaining fragile collateral vessels are unable to hold the increasing flow following embolization of the main feeding vessels. Third, continuous infusion of the embolic agent is likely to increase intravascular pressure, which results in rupture of the fragile vascular wall. Fourth, it may result from the strenuous manipulation of the catheter and forceful injection [15] and fifth, it may result from tumor necrosis and reperfusion following recanalization [11,12,26]. Wang and colleagues have suggested that liquid embolic agents simultaneously occlude the main and distal vessels, which thereby reduces the risk of bleeding from the collateral vessels [12,14,15].

However, Borg [22] investigated a series of 117 preoperative patients embolized for meningioma and only identified hemorrhagic complications in glue-embolized patients, despite the fact that particles were also used. The authors concluded that the sudden profound



Figure 2. (a, b) Postembolization CT scan demonstrated intraventricular and intratumoral hemorrhage. (c, d) Postsurgical histopathologic examination indicated angioblastic meningioma with pathologic vessels. The vascular lumen was occluded by a thrombus (arrow), and Glubran appeared as an amorphous material (arrow head) (c, d - 100 Hematoxylin and Eosin, H&E).

ischemia induced by glue may increase the hemorrhage risk [22]. Raper and Waldron have suggested that a relatively conservative embolization policy may be a useful strategy to avoid hemorrhage [19,25].

Despite the technical precautions and low-pressure delivery associated with Glubran, hemorrhagic complications still occurred in one of our patients. The pathological diagnosis of the patient was angioblastic subtype meningioma with pathologic vessels (Figure 2). Although the hemorrhage mechanism was unclear, the fragile vessels in angioblastic subtype meningioma may be the potential cause of hemorrhagic complications. Studies have demonstrated that the angioblastic subtype was associated with spontaneous hemorrhage of meningiomas [27,28]. Furthermore, atypical subtypes of meningiomas and large-sized, dense vascular blush and necrotic or cystic component meningiomas have also been associated with hemorrhagic complications [11,26]. Thus, embolization of these meningioma subtypes is likely to have an increased risk of hemorrhage.

The limitations of our study relate to the inherent bias of a retrospective study design and patient selection. Meningiomas that were predominantly fed by ECA branches were likely to be embolized with PVA particles. Meningiomas embolized with Glubran may represent a more substantial challenge as they were often vascularized by intracranial vessels and contained more skull base meningiomas. The non-embolized group may have contained more patients with meningiomas that were difficult to treat via operation, such as meningiomas located in the tuberculum sellae and intraventricular. The distribution of the embolized feeding vessels was different between the Glubran and PVA groups. Importantly, only two meningiomas with feeding from the ICA/VA were treated with PVA embolization through the intracranial feeding vessels. Finally, the limited data in the subgroup of meningiomas that were predominantly vascularized by the ICA or VA may not be sufficiently large to draw definitive conclusions. A larger prospective study is required to determine the choice of embolic agent for the embolization of meningiomas predominantly fed by intracranial vessels, as well as to accurately provide the overall risk-benefit analysis of this procedure.

Conclusion

Preoperative embolization of meningiomas with Glubran decreases intraoperative blood loss and operative time. Furthermore, embolization with Glubran produces more effective devascularization of the tumor vascular bed compared with PVA for hypervascular meningiomas that are primarily vascularized by the ICA or VA.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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