Case series

Endovascular treatment for vaccine-induced cerebral venous sinus thrombosis and thrombocytopenia following ChAdOx1 nCoV-19 vaccination: a report of three cases

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ABSTRACT

Background Vaccine-induced thrombosis and thrombocytopenia (VITT) is a rare complication following ChAdOx1 nCoV-19 vaccination. Cerebral venous sinus thrombosis (CVST) is overrepresented in VITT and is often associated with multifocal venous thromboses, concomitant hemorrhage and poor outcomes. Hitherto, endovascular treatments have not been reviewed in VITT-related CVST.

Methods Patient records from a tertiary neurosciences center were reviewed to identify patients who had endovascular treatment for CVST in VITT.

Results Patient records from 1 January 2021 to 20 July 2021 identified three patients who underwent endovascular treatment for CVST in the context of VITT. All were female and the median age was 52 years. The location of the CVST was highly variable. Two-thirds of the patients had multifocal dural sinus thromboses (sigmoid, transverse, straight and superior sagittal) as well as internal jugular vein thromboses. Intracerebral hemorrhage occurred in all patients; subarachnoid blood was noted in two of them, and intraparenchymal hemorrhage occurred in all. There was one periprocedural parenchymal extravasation which abated on temporary cessation of anticoagulation. Outcome data revealed a 90-day modified Rankin Scale (mRS) score of 2 in all cases.

Conclusions We demonstrate that endovascular treatment for VITT-associated CVST is feasible and can be safe in cases that deteriorate despite medical therapy. Extensive clot burden, concomitant hemorrhage, rapid clinical progression and persistent rises in intracranial pressure should initiate multidisciplinary team discussion for endovascular treatment in appropriate cases.

INTRODUCTION

Over 4 billion vaccine doses have been administered in the global response to the COVID-19 pandemic,[1] with more needed. Although COVID-19 vaccines are generally safe, vaccine-induced thrombosis and thrombocytopenia (VITT) has emerged as a rare but important complication of adenovirus vector products (AstraZeneca ChAdOx1 and Johnson & Johnson Ad26.COV2.S vaccines).[2–6] Cerebral venous sinus thrombosis (CVST) is overrepresented in VITT[7] with poor outcomes despite best medical and surgical management[5] including death described following decompressive craniectomy.[8] Endovascular treatment (EVT) as established in conventional CVST[9] has a role, but its utility in VITT has hitherto not been reviewed.

VITT has been reported in 1 in 125 000 to 1 in 250 000 of vaccinated cases.[10–12] Patients present with symptomatic thrombosis 5 to 30 days post-vaccination. The most common sites for thrombosis are the cerebral veins and sinuses, but pulmonary embolism and splanchnic vein thrombosis have also been reported.[10] Vaccine DNA may interact with nuclear histone proteins and platelet factor 4 (PF4) to induce PF4 autoimmunity.[13] PF4 autoimmunity leads to thrombocytopenia and thrombosis through immune complex-mediated platelet activation.[14]

The World Health Organization (WHO) recommend non-heparin-based anticoagulation and intravenous immunoglobulin (IVIg) for the management of VITT.[15] They advise against platelet transfusions unless emergency surgery must take place despite thrombocytopenia. No recommendations are provided for EVT or cranial decompression surgery.

In VITT, CVST carries a poorer prognosis than usual. Two-thirds of patients with conventional CVST are left with no significant disability[16] whereas almost half (47%) of patients with VITT die or are dependent.[17] Reports received by the Medicines and Healthcare products Regulatory Agency (MHRA) (from 1 March 2021 to 26 May 2021) identified an overall mortality estimate from VITT CVST of 18% following ChAdOx1 nCoV-19 vaccination.[18] Furthermore, decompressive craniectomy is associated with a higher risk of death in VITT (54%) than in conventional CVST (16%).[19] EVT thus may be of benefit, as an adjunctive therapy. Such treatment may stabilize the clot burden with a view to avoiding high-risk decompressive surgery. The aim of this study was to describe our experience of CVST in VITT with a focus on treatment decision-making, safety and outcomes with EVT in this scenario.

METHODS
Consent

Written procedural consent from patients in our case series was obtained from patients or a healthcare proxy.

Table 1 Factors pertinent to the endovascular interventional decision-making process and associated treatment outcome.

Factor	Case 1	Case 2	Case 3
Age (years)	20s	50s	50s
Gender	Female	Female	Female
Focal neurological deficit	Left hemiparesis	Expressive dysphasia, right hemiparesis and neglect	Collapse, left hemiparesis
CVST location	Superior sagittal sinus (central third)	Left jugular bulb, sigmoid, transverse, straight sinus	Right sigmoid sinus and upstream right internal jugular vein, superior sagittal and right transverse sinuses
Additional intracerebral hemorrhage	SAH over vertex; hemorrhagic transformation in the deep white matter of the frontal lobes	Left temporal hemorrhage with intraventricular extension	Right frontal lobe hemorrhage with associated SAH
Time from admission to EVT (days)	2	3	1
Type of EVT	Mechanical thrombectomy	Mechanical thrombectomy	Mechanical thrombectomy
Outcome of EVT	Partial recanalization	Complete recanalization	Partial recanalization
ICP monitoring required	Yes	No	No
Admission length	42 days	18 days; 2 weeks further inpatient rehabilitation	23 days; 2 weeks further inpatient rehabilitation
mRS prior to admission	0	0	0
mRS at 30-day follow-up (or closest available)	4	3	3
mRS at 90-day follow-up	2	2	2

CVST, cerebral venous sinus thrombosis; EVT, endovascular treatment; ICP, intracranial pressure; mRS, modified Rankin Scale score; SAH, subarachnoid hemorrhage.

Case series
Patient records from our tertiary neurosciences center, which serves a population of 2.3 million adults, were reviewed to identify patients who had EVT for CVST in VITT.

Clinical follow-up
All cases were contacted at 90 days post-treatment by telephone and assessed by neurologists trained in applying the modified Rankin scoring chart.

RESULTS
Three cases were identified from patient records in our center and are reviewed chronologically here. Factors pertinent to the endovascular interventional decision-making process and associated treatment outcomes are compared in table 1.

Case series
Case 1
A woman in her 20s presented with acute left-sided weakness and a 4-day history of new severe headache. She received a first dose of the ChAdOx1 nCoV-19 vaccine in the preceding 8 days. Thrombocytopenia (85×10^9 platelets/L) raised the possibility of VITT. Computed tomography of the head (CT-head) showed fronto-parietal parasagittal cortical and white matter edema and subarachnoid hemorrhage (SAH), and a CT-venogram demonstrated occlusion of the anterior two-thirds of the superior sagittal sinus (SSS). A low molecular weight heparin infusion was initiated in line with local protocols. A generalized tonic–clonic seizure prompted tracheal intubation and transfer
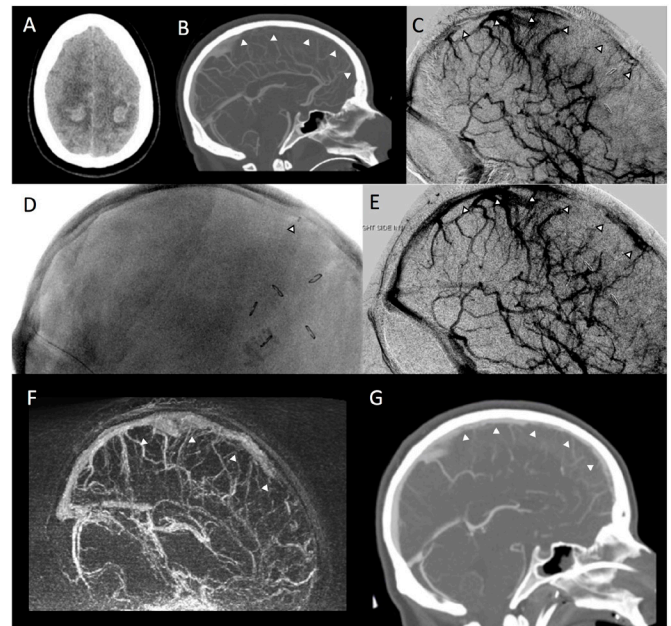

Figure 1 Case 1. Non-contrast axial computed tomography (CT) imaging demonstrating bilateral paracentral parenchymal hemorrhage and edema (A). Sagittal CT venography demonstrating occlusion of the anterior two-thirds of the superior sagittal sinus (SSS) (B, arrowheads). Lateral projection venous phase angiography following right internal carotid artery (ICA) injection showing occlusion of the anterior two-thirds of the SSS (C, arrowheads). Lateral fluoroscopic image showing positioning of the JET7 aspiration catheter (Penumbra) in the SSS (D, arrowhead). Lateral projection venous phase angiography following right ICA injection demonstrating partial recanalization of the middle third of the SSS (E, arrowheads). Completion subtraction Dyna CT venography demonstrating partial recanalization of the SSS (F, arrowheads). Follow-up CT venographic imaging on day 9 of admission showed a patent SSS (G, arrowheads).

to the Neuroscience Intensive Care Unit. A further CT-head demonstrated new bilateral paramedian frontal lobe hemorrhages (Figure 1A) and repeat CT venography showed stable but persistent SSS occlusion (Figure 1B). Following concern for a diagnosis of VITT, heparin was stopped and 1 g/kg IVIg and an argatroban infusion was started. Later anti-PF4 antibodies returned positive.

Repeat CT-head demonstrated progression of white matter edema. A Codman intracranial pressure (ICP) monitor revealed sustained high ICP (>25 mmHg). A multidisciplinary team decision was made to proceed to EVT in order to recanalize the middle third of the SSS and reduce venous hypertension in the hope of avoiding the need for surgical decompression which would require therapeutic anticoagulation to be interrupted. The benefit of bifrontal craniectomy was also uncertain, potentially limited by the extensive nature of the edema and cerebral swelling extending from the frontal to parietal regions bilaterally.

Initial angiography confirmed SSS occlusion (figure 1C). Right common femoral arterial (CFA) and venous access were used and a right common carotid artery (CCA) 4F control catheter was left on continuous saline flush. Intermittent CCA contrast injections were performed to acquire venous road maps and to assess for any change in venous drainage. Heparin was avoided in all flushes but argatroban was given intravenously. A 6F NeuronMax (Penumbra) sheath was positioned in the left internal jugular vein and a JET7 (Penumbra) aspiration catheter
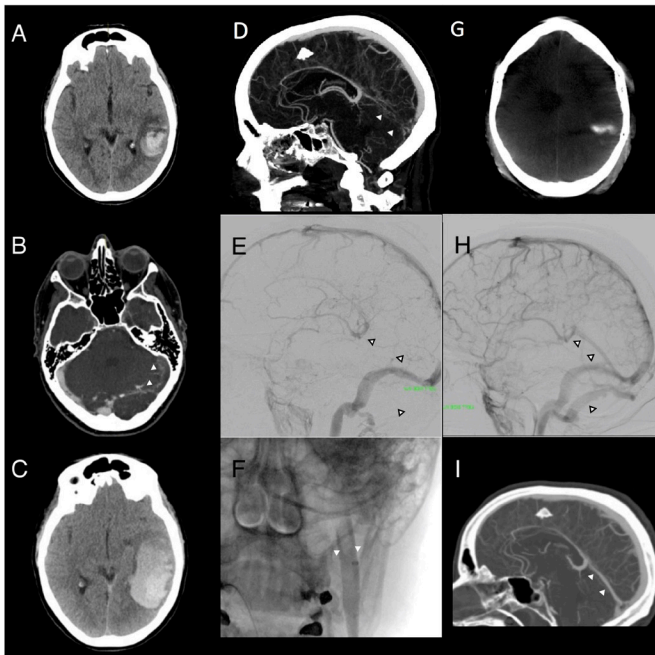
Figure 2 Case 2. Initial axial non-contrast computed tomography (CT) head (A) and axial CT venogram (B) demonstrating parenchymal hemorrhage and edema in the left temporal lobe and left transverse and sigmoid sinus occlusion (arrowheads), respectively. Repeat axial CT imaging 24 hours later (C) demonstrating left temporal hematoma expansion. Repeat sagittal CT venography demonstrating progression with occlusion of the straight sinus (D, arrowheads). Left internal carotid artery (ICA) angiography in the venous phase demonstrating occlusion of the left transverse and sigmoid sinus and straight sinus (E, arrowheads). Frontal venography demonstrating a large left jugular bulb thrombus protruding into the left internal jugular vein (F, arrowheads). Axial on-table Dyna CT demonstrating a small contrast extravasation at the superior aspect of the hematoma (G). Left ICA angiography in the venous phase post-thrombectomy demonstrating recanalization (H, arrowheads). Sagittal CT venography preformed after endovascular traeatment on day 4 of admission demonstrating patency of the straight sinus (I, arrowheads).

navigated to the SSS over a Synchro 2 (Stryker) microwire and Velocity (Penumbra) microcatheter. Aspiration thrombectomy was performed (Penumbra Engine). There was clot evident in the aspiration canister and repeat angiography and Dyna CT-venography demonstrated partial recanalization of the middle third of the SSS (figure 1E,F). Follow-up CT-venography after a period of anticoagulation showed complete SSS recanalization at day 9 (figure 1).

Ongoing care included a tracheostomy on day 20 and the patient was discharged for rehabilitation on day 27. Follow-up modified Rankin Scale (mRS) score was 2 at 90 days.

Case 2

A woman in her 50s presented to her local hospital with a progressive 5-day history of headache, disorientation, photophobia and word-finding difficulties. She received the ChAdOx1 nCoV-19 vaccination 13 days prior. CT-head revealed a left temporoparietal hemorrhage and edema (figure 2A). Platelet count was 23 $\times 10^9$/L and later anti-PF4 antibodies returned positive. Subsequent CT-venography was performed showing an occlusive thrombus in the left transverse and sigmoid sinus compatible with VITT (figure 2B). There were also accompanying signs of

venous hypertension with medullary venous dilatation in the left temporal lobe. Treatment was commenced with 1 g/kg IVIg and an argatroban infusion.

Day 2 post-admission, the patient developed new right-sided weakness necessitating repeat CT-head and CT-venography revealing an enlarging left temporoparietal hemorrhage (figure 2C) and occlusion of the straight sinus (figure 2D).Given the clinical and radiological deterioration, EVT was offered. Craniotomy to evacuate the clot was not undertaken as the patient remained rousable throughout in a monitored intensive care unit bed and due to the eloquence of the hemorrhagic and the peri-hemorrhagic area craniotomy was reserved for any decrease in the patient's conscious level associated with any progression in the extent of midline shift or uncal herniation.

Right CFA and venous access were obtained and a left CCA control catheter was again used. Angiography confirmed a straight sinus occlusion (figure 2E) in addition to left transverse/sigmoid sinus occlusion. Heparin use was avoided but argatroban was given intravenously during the procedure. A Cerebase (Cerenovus) sheath was navigated to the left internal jugular vein. Venography demonstrated a large internal jugular vein thrombus which was aspirated directly though the Cerebase sheath (figure 2F). A Velocity microcatheter, Syncho two microwire and EMBOVAC 071 (Cerenovus) catheter were then advanced to the transverse sinus. Multiple passes were made using an Aperio (Acandis) 6×50 mm stentriever and the EMBOVAC catheter. A large volume clot was removed on each pass and angiography demonstrated gradual improvement. With the Cerebase then sited in the transverse sinus, the EMBOVAC catheter was positioned in the straight sinus and aspiration resulted in recanalization. A new small parenchymal extravasation was seen at the superior aspect of the original venous hemorrhage on completion angiography. This was demonstrated on Dyna CT (figure 2G). The argatroban infusion was stopped and no further hemorrhage was seen on serial Dyna CTs performed over an hour. Final angiography confirmed recanalization of the straight sinus, left transverse sinus, left sigmoid sinus and left internal jugular vein (figure 2H).

Argatroban was restarted after successful recanalization with stable hemorrhagic appearances on interval CT-brain after 12 hours. Day 4 imaging showed no further hemorrhage and continued patency of the sinuses (figure 2I). Apixaban was commenced on day 9 due to clinical stability and improving platelet count. The patient was discharged for rehabilitation on day 18 and follow-up mRS was 2 at 90 days.

Case 3

A woman in her 50s presented following a collapse and multiple generalized seizures. She complained of ongoing headache and exhibited a left-sided hemiparesis. She received her first dose of the ChAdOx1 nCoV-19 vaccination 27 days prior. CT-head revealed a right frontal lobe parenchymal hemorrhage with associated SAH (figure 3A). CT-venography demonstrated extensive thrombosis of the SSS and right internal jugular vein, sigmoid and transverse sinuses. Admission platelet count was 35 $\times 10^9$/L. Anti-PF4 antibodies returned positive and 1 g/kg IVIg was commenced. Status epilepticus following transfer prompted tracheal intubation. Repeat CT-head demonstrated new right frontal intraparenchymal hemorrhage (figure 3B). Given the rapid clinical and radiological deterioration, EVT was offered.

On table CT-venography confirmed extensive venous sinus thrombus (figure 3C). A right CCA control catheter was again used and heparin was not used. A 6F Cerebase sheath was positioned in the right internal jugular vein. Venography demonstrated a large
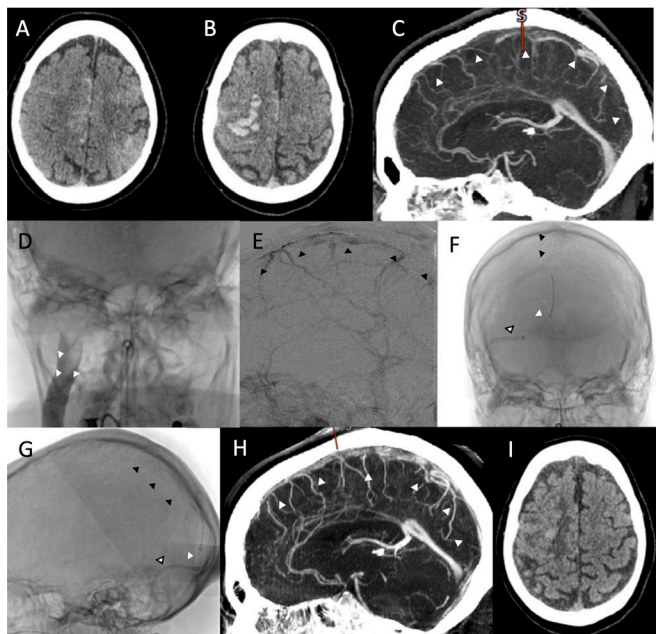
Figure 3 Case 3. Initial non-contrast axial computed tomography of the head (CT-head) demonstrating bilateral frontal lobe edema with subarachnoid hemorrhage over both convexities (A). Axial CT imaging following generalized seizure demonstrating new right frontal parenchymal hemorrhage (B). On table sagittal Dyna CT venogram confirmed superior sagittal sinus (SSS) occlusion prior to endovascular treatment (C, arrowheads). Frontal venographic image following right internal jugular vein (IJV) injection showing large right jugular bulb thrombus projecting into the right IJV (D, arrowheads). Lateral projection venous phase angiography following right internal carotid artery (ICA) injection showing occlusion of the SSS (E, arrowheads). Frontal (F) and lateral (G) fluoroscopic imaging showing positioning of the stent-retriever in the SSS (black arrowheads), to track an aspiration catheter to target (white arrowhead), supported by distal guide-sheath positioning in the transverse sinus (outlined white arrowhead). Completion sagittal Dyna CT venography demonstrating partial SSS recanalization (H, arrowheads). Axial CT imaging on day 9 showed stable, maturing right frontal hemorrhage (I).

volume right internal jugular vein thrombus which was aspirated through the Cerebase sheath. Angiography confirmed extensive venous sinus thrombosis (figure 3E). Using an EMBOVAC 071 catheter with Solitaire X 6x40 mm (Medtronic) and Aperio 6×50 mm stentrievers a combination of stent-retrieval and aspiration were employed to clear the thrombus from the sigmoid sinus and SSS (figure 3F,G). A significant volume of thrombus was removed but it was not possible to fully clear the sinuses. A number of channels through the thrombus were made and the final on table CT-venography showed contrast opacification of the cortical veins draining to the partially recanalized SSS (figure 3), patent transverse and sigmoid sinuses and a partially recanalized right jugular bulb.

Argatroban infusion was then commenced immediately post-procedure and later changed to oral apixaban following a period of sustained clinical improvement. Day 9 imaging demonstrated improving intracranial appearances (figure 3I). Corticosteroids were required to correct persistent thrombocytopenia. After 23 days in hospital the patient was transferred to a local rehabilitation unit before discharge home. Follow-up mRS was 2 at 90 days.

Summary of cases

For the three cases of endovascular treatment in CVST in the context of VITT all were female and the median age was 52 (range 26–53) years. Following a first dose of the ChAdOx1 nCov-19 vaccine, the median time to headache was 8 (range 8–27) days. Focal neurological symptoms developed after a median of 13 (range 12–27) days. Thrombocytopenia, low serum fibrinogen and a high serum D-dimer were present on admission in all cases (platelet mean count: 47.7×10^9/L, range $23–85 \times 10^9$/L; fibrinogen mean: 1.9 g/L, range: 1.1–3.8 g/L; D-dimer mean: 21.51 µg/mL, range: 15.83–30.34 µg/mL). Anti-PF4 antibodies were present in all patients. The location of the CVST was highly variable. Two patients had multifocal dural sinus thromboses (sigmoid, transverse, straight and superior sagittal) as well as internal jugular vein thromboses. Intracerebral hemorrhage occurred in all patients; subarachnoid blood was noted in two of them, and intraparenchymal hemorrhage occurred in all. Outcome data revealed a 90-day mRS score of 2 in all cases. All patients were discharged on apixaban anticoagulation. Additional clinical details are summarised in the online supplemental table 1.

DISCUSSION

VITT typically presents between 5 and 30 days post-ChAdOx1 nCoV-19 vaccination and is characterized by venous or arterial thromboses, thrombocytopenia and positive anti-PF4 antibodies. Despite the severity of VITT CVST, it is important to weigh this against the clear benefits of the vaccination programme, with an estimated 13 000 adult deaths prevented in the UK aged 60 years and younger up to 9 May 2021, and indeed many more worldwide.[18] Moreover, COVID-19 itself can precipitate CVST with a higher frequency of 4.28 per 100 000 population as described in a US preprint retrospective study.[20]

A literature search via MEDLINE and EMBASE identified three publications reporting EVT for VITT-related CVST and identified five patient cases from 1 January 2021 to 20 July 2021, with more publications anticipated.[5 8 21] In four of these cases, sufficient detail was available to identify the timing and circumstances of EVT.[5 21] All were female and exhibited mild-moderate thrombocytopenia, elevated D-dimer, hypofibrinogenemia and positive anti-PF4 antibodies. Medical management varied across the reported cases, and with time. The first patient treated at our center initially received intravenous heparin, which was discontinued within the first 24 hours, and replaced by argatroban in line with emerging guidelines. The other two patients in our center received argatroban in line with established guidelines. The four cases from the literature received heparin-based anticoagulants, reflecting practice prior to the emergence of international guidelines for VITT. Two patients received a platelet transfusion. Four cases received IVIg and two had high-dose corticosteroids. ICP monitoring was measured in two patients,[5] including one from our center, although evidence for this is currently unsubstantiated.

A recent multicenter UK cohort study[17] reported that 3/9 patients who underwent EVT for VITT died and a further 2/9 were dependent. No procedural data were available for cases for direct comparison to this series in which each of the three cases demonstrated good outcomes following EVT. In this series, partial recanalization was achieved in two patients and complete recanalization was attained in one case. In the further four cases identified in the literature, all reported partial, complete or non-specific 'recanalization'. There were no cases of post-procedure hemorrhage. There was a small extravasation bleed adjacent to the existing hematoma in case 2 of this series but no other

periprocedural complications of EVT at our center, nor in three of the four cases described in the literature. In one case from the literature, the patient developed signs of uncal herniation following EVT requiring decompressive hemicraniectomy but the patient died 2 days later.[5] The median 90-day mRS score was 2 (range 0–6). Outcome data from our case series were derived from the overseeing neurology team with experience in mRS evaluations.

It is important to highlight that the decision to escalate to EVT was partly informed by initial experience with three earlier patients who presented with CVST secondary to VITT. These patients rapidly deteriorated with multifocal intracranial hemorrhage and death and, as a result, a more aggressive stance to treatment of this condition in patients who began to clinically deteriorate was established. Furthermore, anticoagulation timing and discontinuation decisions were made at the discretion of the multidisciplinary team (including neurology, neurosurgery, intensive care and interventional neuroradiology) based on past experiences, to judiciously conclude escalation to EVT was most appropriate.

Our case series differs from selection into the TO-ACT trial[22] wherein patients were randomized to EVT plus heparin if suffering intracranial hemorrhage, thrombosis of the deep cerebral venous system, any mental status disorder or coma state (Glasgow Coma Scale score <9). Independence (mRs 0–2) was achieved at 12 months in 85% of patients treated with EVT plus anticoagulation but, similarly, 82% were independent when treated with medical therapy alone. Symptomatic hemorrhage was actually higher in the medical arm (9% vs 3%) suggesting that EVT may be effective in reducing venous hypertension and risk of further bleeding. Further relevant limitations were the exclusion of thrombocytopenic patients and immediate recanalization success was not assessed.

EVT techniques used in this study also differed from that used in the TO-ACT trial. The latter employed chemical thrombolytics and the Angiojet device. Stent-retrievers and aspiration catheters were used in only a small minority. Interestingly, in a systematic review of 185 CVST cases treated with EVT,[9] Angiojet was associated with lower rates of complete recanalization (odds ratio (OR) 0.2, 95% CI 0.09–0.4) and lower chance of good functional outcome (OR 0.5, 95% CI 0.2–1.0) compared with alternative methods (intrasinus thrombolysis, aspiration catheters and thrombectomy devices including stent-retrievers, MERCI retriever and balloon angioplasty) . These authors cited the relative stiffness and bulkiness of the device as a reason for this. In the cases treated in this series, no chemical thrombolytics were used due to uncertainty of hematological interaction and to minimize the risk of further parenchymal hemorrhage. Furthermore, guide and wide-bore aspiration systems in addition to larger stent-retrievers (all more recently developed for use in cerebral arterial thrombectomy) were used. Both Neuron MAX and Cerebase sheaths were navigated over aspiration catheters into the transverse sinus to maintain access (taking advantage of the relative trackability of the distal ends of these devices). Stent-retrievers were used in combination with aspiration catheters (JET7 and EMBOVAC) to facilitate thrombectomy. Subjectively, ability to recanalize the occluded sinuses was improved in patients who were concomitantly anticoagulated; however, a small parenchymal extravasation was encountered during angiography in an anticoagulated patient with critical venous hypertension.

CONCLUSIONS
Our results suggest EVT is feasible and can be safe in cerebral venous sinus thrombosis in the context of vaccine-induced thrombosis and thrombocytopenia. Extensive clot burden, concomitant hemorrhage, rapid clinical progression and persistent rises in intracranial pressure should initiate multidisciplinary team discussion for EVT in appropriate cases. Larger case series are required to demonstrate the appropriate clinical/paraclinical factors and the optimal method, timing and delivery of EVT to influence impactful decision-making for optimal patient outcomes. We suggest EVT procedural outcomes are added to existing registries of VITT.

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