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Technical Note

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Summary: Catheter placement for blood brain–barrier disruption and enhanced chemotherapy delivery can sometimes trigger arterial spasm of moderate-to-severe degree. A slow infusion of a small quantity of intraarterially administered mannitol (10 mL of 25% mannitol) was evaluated as a means to obtain a rapid resolution of catheter placement–induced spasm. We prospectively report 12 consecutive cases of blood brain–barrier disruption among patients who developed catheter placement–induced spasm that was treated by this means without side effects, resulting in rapid resolution of spasm.

Blood brain–barrier disruption has been used at Oregon Health Sciences University since 1981 to treat brain tumors. The blood-brain barrier is usually identified as one of the important obstacles to the delivery of antineoplastic agents (1). Tight junctions (zonula occludens) between endothelial cells in the brain capillaries create this barrier. These junctions restrict diffusion between endothelial cells and prevent most available chemotherapeutic agents from penetrating the normal parenchyma of the CNS. It is with this understanding that osmotic blood brain–barrier disruption was developed (2). Preclinical and clinical studies have clearly established that this approach significantly increases the delivery of antineoplastic agents to the tumor, brain around tumor, and brain distant to tumor (1, 2).

The technique requires placement of a catheter in the proximal internal carotid artery or vertebral artery, which can induce varying degrees of spasm. Such spasm virtually always resolves immediately after mannitol infusion to open the blood-brain barrier (150−300 mL of 25% mannitol over 30 s). Based on this observation, a small bolus of 25% mannitol (10 mL over 30−60 s) was assessed as a new means to reverse catheter-induced spasm rapidly. The same consistent response was identified. We now use intraarterially administered mannitol as our agent of choice to treat iatrogenic spasm caused by catheterization of the large cerebral vessels and achieve consistent and rapid resolution of spasm. We herein report 12 consecutive cases of iatrogenic spasm produced by therapeutic angiography of cerebral vessels treated with intraarterial infusion of 10 mL of 25% mannitol.

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Description of the Technique

The blood brain–barrier disruption technique involves the following steps: 1) selective catheterization via percutaneous transfemoral puncture of the left internal carotid artery, right internal carotid artery, left vertebral artery, or right vertebral artery; 2) determination of rate of infusion of mannitol by injection of iodinated contrast material and fluoroscopy as the lowest infusion rate in which there is retrograde flow from the arterial catheter (volume of mannitol infused is determined in mL/s × 30 s, usually between 4 and 12 mL/s in carotid circulation and between 4 and 10 mL/s in vertebral circulation); 3) osmotic disruption of the blood brain–barrier by infusing 25% mannitol at a defined rate in an artery in which catheterization was previously performed; 4) contrast infusion to confirm catheter position and rule out arterial injury after disruption; 5) intraarterial infusion of antineoplastic agent in the disrupted circulation; and 6) documentation of the degree of disruption by enhanced CT with iodinated contrast agent typically IV administered 5 minutes after the disruption for that purpose.

The spasm was typically identified (Fig 1) when testing to confirm the position of the catheter (step 1) or during infusion of iodinated contrast material to establish the subsequent rate of mannitol administration (step 2). Ten milliliters of 25% mannitol was intraarterially infused over 30 to 60 seconds whenever the presence of a moderate-to-marked spasm was identified and likely to be hemodynamically significant. In this report, general anesthesia had been induced in all patients when mannitol was infused. We have, however, used slow intraarterial infusion of mannitol to relieve spasm in awake patients undergoing intraarterial chemotherapy infusion without blood brain–barrier disruption in at least two patients. No side effects were noted.

Only patients with spasm judged to be hemodynamically significant were considered for this report. Spasm degree and residual spasm were calculated by using the equation, $100 - M_s/P_n$, where M_s is the maximal spastic segment and P_n is the closest proximal normal segment of the same vessel (Table).

The study was prospective and encompassed a period of 6 months. During that interval, 38 patients underwent 186 catheter-placement procedures for intraarterial chemotherapy or osmotic blood brain–barrier disruption for enhanced chemotherapy delivery. In the study group, 12 consecutive patients developed moderate-to-severe spasm. The radiologic characteristics of the spasm for this group of patients are summarized in the Table.

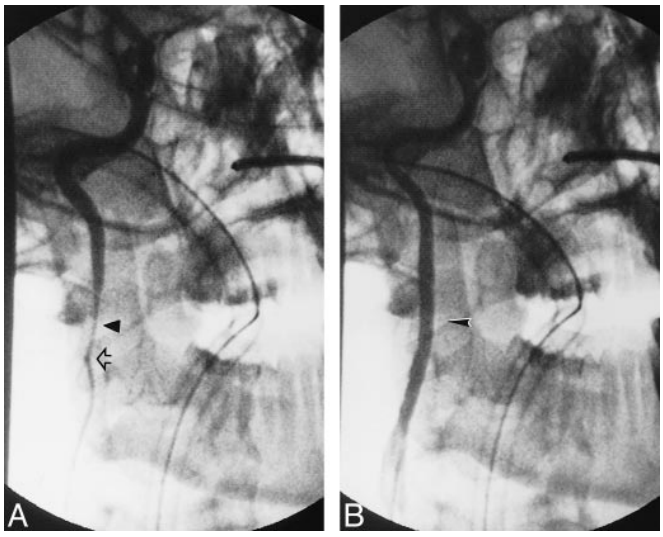

FIG 1. Spasm was typically identified when testing to confirm catheter position.

A, Arterial spasm in the right internal carotid artery identified at the time of catheter placement before mannitol infusion in patient 11. *Open arrow* depicts the tip of the catheter in the right internal carotid artery, with 80% concentric spasm extending up for 1.5 cm (*arrowhead*) after infusion of a nonionic iodinated contrast agent.

B, Complete resolution of spasm (*arrowhead*) after slow intraarterial infusion of 10 mL of mannitol in the right internal carotid artery.

Spasm characteristics

Patient (No.)	Artery	Level of Spasm	Degree	Vertical Extent	Morphologic Characteristics	Time to Assessment	Degree of Residual Spasm
#1	LICA*	C2	60–75%	1.0 cm	Eccentric multisegmental	5 min	0–10%; 1 segment 2 mm 40%
#2	RICA†	C1–C2	50%	1.2 cm	Concentric with smooth borders	2.5 min	10%
#3	RICA	C1–C2	70–90%	1.5 cm	Concentric multisegmental	2.5 min	10%; 1 segment 2 mm 50%
#4	LICA	C2	60%	1.0 cm	Concentric one segment	3 min; 11 min	50%; 0%
#5	LICA	C2	60%	0.4 cm	Concentric one segment	3.5 min	0%
#6	LICA	C1–C2	70–90%	1.5 cm	Concentric multisegmental	2 min	0%; 1 segment 2 mm 80%
						3 min	0%; 1 segment 2 mm 60%
#7	RICA	C1	50%	0.5 cm	Concentric	4 min; 12 min	20%; 0%
#8	RICA	C2–C3	50%	0.5 cm	Concentric	7 min	10%
#9	RICA	C1–C2	40–60%	1.0 cm	Concentric multisegmental	6 min	10%
#10	RICA	C1–C3	80–90%	1.0 cm	Concentric multisegmental	4 min	0%
#11	RICA	C1–C2	80%	1.5 cm	Concentric with smooth borders	2 min	0%
#12	RICA	C2–C3	50%	0.5 cm	Concentric one segment	3 min	20%

* LICA: left internal carotid artery.

† RICA: right internal carotid artery.

In the current series, when the spasm was identified, the catheter was left in place at the same level and the mannitol (10 mL) was infused via the catheter. After a short interval of 2 to 5 minutes, a control study was obtained to document and quantify the decrease in arterial spasm.

The results are also summarized in the Table. Time between the identification of the spasm and assessment of the residual spasm varied from 2.5 to 11 minutes (average, 4.7 min). Technical reasons explain this discrepancy in the delay of evaluation. The level of spasm is fairly constant, occurring at C1−C3, and is simply a reflection of the actual position of the tip of the catheter. In the majority of patients included in this series, spasms were concentric, segmental, or multisegmental. After an average assessment interval of 4.7 minutes, the spasm radiologically resolved to a residual stenotic segment of 20% or less in nine patients, whereas three patients presented a marked decrease in spasm but maintained a stenotic segment for a longer interval.

After mannitol infusion, the spasm rapidly resolved in a consistent manner in all the patients. This resolution was a function of time, with the majority of the spasm being significantly reduced within 3 minutes and all except two being significantly reduced within 5 minutes. This interval of resolution is significantly shorter than what we experienced for spontaneous spasm resolution. No significant spasm arose in the vertebral artery during the data-gathering period for this study. This is probably a reflection of the more proximal position of the tip of catheter in the vertebra (C6) that was usually used. No adverse effects were noted with the use of mannitol.

Discussion

Typically, when spasm occurs during catheter placement for diagnostic or therapeutic manipulation of extracranial cerebral vessels, the catheter is withdrawn proximally to the spastic segment. The spasm is usually self-limited and typically resolves spontaneously within a matter of several minutes to an hour or so. Therefore, in such a circumstance, one can simply wait for the spasm to resolve spontaneously. In cases of long-lasting spasm, the procedure can be aborted or postponed.

For active treatment of the spasm, intraarterial infusion of papaverine is commonly used (3–5). This can be specifically indicated in cases of severe or long-lasting spasm or when the catheter placement serves a therapeutic purpose. Other agents have also been suggested to treat arterial spasm (6, 7). To our knowledge, this is the first report of the

use of a small quantity of intraarterially administered mannitol to relieve iatrogenic arterial spasm. Initially, it was used only in patients in whom general anesthesia was induced, but it has since been used with awake patients without adverse consequences, suggesting that this spasm-relieving technique could be used in all patients undergoing cerebral catheterization provided that the mannitol is slowly infused (over 1 minute or so).

One can only speculate about the mechanism through which mannitol exerts its effect. Mannitol is a stereoisomeric mixture of osmolytes. It is typically used as an IV administered osmotic diuretic in conditions as diverse as cardiovascular surgery, severe traumatic injury, and management of hemolytic transfusion (8, 9). In a neurosurgical context, it is frequently IV used to decrease intracranial pressure in cases of closed head injuries and tumor surgery.

Intraarterially administered mannitol is also used as a permeabilizer to open the blood-brain barrier to increase the delivery of various molecules to the brain parenchyma and pathologically abnormal tissue contained within the brain (2). The mechanism through which mannitol increases the blood brain–barrier permeability is thought to be by shrinkage of the endothelial cells, thereby opening the tight junctions of the blood-brain barrier. The 30-second continuous intraarterial infusion of mannitol in a particular circulation at a rate sufficient to fill the whole vascular tree of that circulation produces an osmotic gradient that probably draws free water from endothelial cells and osmotically shrinks the cells. This mechanism, however, cannot be accounted for to explain the spasm-relieving effect of slow intraarterial infusion of mannitol.

A small dose (10 mL of 25% mannitol, 2.5 g of mannitol) is unlikely to produce a significant volume expansion, resulting in increased cardiac output and increased blood pressure that could have a mechanical effect on the spasm (8). The mannitol must therefore have a direct effect on the endothelial cells or on the smooth-muscle cells of the vascular wall (10). In a study conducted to assess the effect of mannitol on cultured endothelial cells, Machi et al (11) found that the increase in vasopermeability with mannitol was not associated with cell shrinkage, as opposed to the increase in permeability provided by urea. It was concluded that mannitol may exert its effect through a different mechanism than hyperosmolality and cell shrinkage (11).

Mannitol has been shown to inhibit the adenosine 5′-triphosphate-dependent Ca^{2+} transport in vesicles derived from basolateral membranes from kidney proximal tubules (12). It might exert the same effect on Ca^{2+} transport in the vascular smooth muscle cells and therefore relieve spasm by decreasing calcium uptake and thus contractility. Mannitol was also found to inhibit the Na,K-ATPase in cultured bovine corneal endothelial cells (13). This inhibition could ultimately lead to temporary disruption in the contractile function of the cell because of alteration in the concentration of the different electrolytes, including Ca^{2+}.

Independent of the mechanism of action, a slow intraarterial infusion of 10 mL of mannitol is a reliable means to decrease the interval of recovery of catheter-induced arterial spasm, permitting the resumption of an ongoing procedure and occasionally preventing premature abortion of the procedure.

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