

## TREATMENT OF CEREBRAL VASOSPASM WITH BIOCOMPATIBLE CONTROLLED-RELEASE SYSTEMS FOR INTRACRANIAL DRUG DELIVERY

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**OBJECTIVE:** The pharmacological treatment of cerebral vasospasm (CVS) now includes the experimental use of controlled-release biocompatible compounds that deliver a desired drug locally into the subarachnoid space. A controlled-release system consists of an active material that is incorporated into a carrier, usually in the form of a pellet or a gel. With such systems, the desired agent is delivered slowly and continuously, for long periods of time, directly to the desired site. This technology makes it possible to achieve high local concentrations of therapeutic agents while minimizing systemic toxicity and circumventing the need to cross the blood-brain barrier. This review describes controlled-release systems developed to date for local drug delivery in the treatment of CVS in both animal models and humans.

**METHODS:** A MEDLINE PubMed database search was performed for articles published from 1975 to 2007 with the following search topics: "controlled-release system/polymer," "controlled-release implants," "cerebral vasospasm," "subarachnoid hemorrhage," "subarachnoid space," and "intracranial drug delivery."

**RESULTS:** Over the past several decades, several controlled-release systems (lactic/glycolic acid pellets, ethylene vinyl acetate copolymer, liposomes, silicone elastomers) have been developed to deliver various pharmacological agents (papaverine, nicardipine, ibuprofen, nitric oxide donor, calcitonin gene-related peptide, fasudil, recombinant tissue plasminogen activator) intracranially to treat subarachnoid hemorrhage in animal models (rats, rabbits, dogs, and primates). Animal studies have shown promising results, and the few human studies that have been published using controlled-release systems with papaverine or nicardipine report similarly encouraging outcomes.

**CONCLUSION:** Controlled-release systems have evolved over the past few years and have been shown experimentally to be an effective strategy for the local delivery of drugs to treat CVS.

**KEY WORDS:** Cerebral vasospasm, Controlled release, Intracranial drug delivery, Subarachnoid hemorrhage

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**A**neurysmal subarachnoid hemorrhage (SAH) is a devastating manifestation of cerebrovascular disease that results in the deaths of approximately 30 to 50% of affected patients (55, 60–62). Patients who survive the initial insult may be clinically stable in the first few days, yet they may succumb to cerebral vasospasm (CVS) thereafter. CVS may present as early as posthemorrhage Days 3 to 4, but it exerts its

**ABBREVIATIONS:** **CGRP**, calcitonin gene-related peptide; **CVS**, cerebral vasospasm; **DETA**, diethylenetriamine; **EVAC**, ethylene vinyl acetate copolymer; **NO**, nitric oxide; **NPRI**, nicardipine-based, prolonged-release implant; **rt-PA**, recombinant tissue plasminogen activator; **SAH**, subarachnoid hemorrhage

maximal effects on posthemorrhage Days 7 to 10. In general, 70% of patients with SAH develop radiographic evidence of vasospasm, and 30% develop clinically relevant CVS and delayed ischemic neurological deficits (17, 22, 44, 45, 62).

The current goal of the treatment of vasospasm is to counteract its detrimental effects, that is, minimization of stroke occurrence by inducing hypertension and hemodilution to improve cerebral blood flow and by inducing hypervolemia to improve high circulating blood volume; this strategy is also known as triple-H therapy (26). Although the pathogenesis of CVS remains poorly understood, it is likely that changes in cerebrovascular reactivity after aneurysmal SAH may cause abnormalities in the pathways that maintain equilibrium between

dilator and constrictor mechanisms in the cerebral arteries (9, 10). Significant advances in the treatment of SAH and CVS have occurred over the past several decades, but outcomes remain poor for those with severe CVS. There is still no satisfactory pharmacological treatment to abort CVS or to treat established cerebrovascular dysfunction. The administration of nimodipine, a calcium channel blocker that is relatively selective for cerebral arteries (30), has proven to be somewhat beneficial after SAH in reducing the severity of delayed ischemic neurological deficit despite evidence that this agent has only a small effect on the incidence or severity of angiographic vasospasm (43, 45). Improved understanding of the pathophysiology of CVS and the discovery of new pharmacological treatments as well as refinement of some existing treatments for CVS will help to reduce the impact of this devastating complication of aneurysmal SAH.

One of the recent advances in treating CVS pharmacologically is the introduction of controlled-release systems to deliver a desired drug to a specific site, e.g., the subarachnoid space. A controlled-release system consists of an active material that is incorporated into a biocompatible carrier, usually polymeric, made in the form of a pellet or gel (4, 5, 11, 32, 36). In such systems, the drug is released by one of several different mechanisms such as diffusion, chemical reaction by either polymer degradation or cleavage of the drug from the polymer, and solvent activation by way of polymer swelling and porous openings that permit release of the drug (32–35). The released agent is delivered slowly and continuously for varying periods of time at predetermined rates (4, 32, 35). This technology makes it possible to administer newer and complex therapies such as proteins and larger molecules and to achieve predictable high local concentrations of therapeutic agents while minimizing systemic toxicity and circumventing the need to cross the blood-brain barrier (8, 20, 32). Other potential advantages of controlled-release systems include preservation of the drug and prevention of its modification by the body before it reaches its target, reduced need for follow-up care, increased comfort, and increased compliance. Implantable controlled-release systems have been used safely and effectively in the treatment of brain tumors, seizures, CVS, and brain abscesses (4, 11, 18, 20, 27, 29, 48). Various agents have been evaluated specifically for CVS as part of extravascular controlled-release systems. All of these agents have been shown previously to act on particular targets in the vasospasm cascade. In this review, we focus on the development of the various extravascular methods that have been studied using controlled-release implants to deliver drug intracranially in an effort to treat CVS.

## MATERIALS AND METHODS

A search of the PubMed database was conducted on articles published from 1975 to 2007. Search terms initially included “subarachnoid hemorrhage” (12 161 items retrieved) and “cerebral vasospasm” (2587 items retrieved). Further searching was performed with the addition of the terms “controlled-release system,” “implant,” “polymer,” “gel,” and “intracranial drug delivery.” From the results

obtained with these secondary key words, articles relating to controlled-release systems for the treatment of CVS in both animals and humans were chosen for inclusion.

## RESULTS

Several different types of controlled-release systems for the treatment of CVS have been studied.

### Nicardipine Controlled-release System

It is postulated that hemoglobin, contained in the erythrocytes exposed to the adventitial side of cerebral arteries after SAH, may be the main mediator causing vasospasm (9, 38, 46, 59, 61). One possible effect that hemoglobin has on the vasospasm cascade is the disturbance of intracellular calcium equilibrium (6, 38, 46), resulting in smooth muscle contraction (6). Likewise, it has been shown that the vasodilatory effect of calcium channel antagonists is reduced in the presence of hemoglobin in the extravascular space (59). Nicardipine is a well-known calcium channel blocker (Table 1). When given intravascularly, nicardipine leads to relaxation of smooth muscle in blood vessels, resulting in vasodilation.

A nicardipine-based, prolonged-release implant (NPRI) was developed that provides a reliable method of delivering nicardipine extravascularly (28, 29, 31, 50). Implants were made of rod-shaped pellets consisting of lactic/glycolic acid copolymer, measuring 2 mm in diameter and 10 mm in length, and containing 4 mg nicardipine.

A safety and efficacy study by Sasahara et al. (50) using 10 dogs in a double hemorrhage model demonstrated severe vasospasm in all 5 animals in the control group, whereas in the nicardipine treatment group, only 2 animals had very mild vasospasm and 3 had none. No specific histological changes or clinical symptoms related to the implants were observed.

In a study by Kawashima et al. (30), SAH was induced in 18 dogs that were randomly assigned to 3 treatment groups: placebo, low-dose nicardipine (0.8 mg), and high-dose nicardipine (8 mg). The pellets were placed in the sylvian fissure, and angiography was repeated on Days 7 and 14 after treatment. The average percentages of reduction in the diameter of the middle cerebral artery on Day 7 were 43% for the placebo group, 14% for the low-dose group, and 7% for the high-dose group ( $P = 0.0319$ ).

After a safety and efficacy study in humans that indicated no complications was performed (27), Kasuya et al. (28) used this delivery system in 97 patients undergoing surgical clipping for ruptured aneurysms and demonstrated potential efficacy to set the stage for future randomized investigation. Patients in whom pellets were placed intraoperatively were compared with a cohort of 28 patients who did not have pellets placed during surgery. Although their results were not statistically significant, they suggest a decrease in the development of delayed ischemic neurological deficits in the treatment group (6% NPRI versus 11% control) (28).

In an extension of this work, Barth et al. (2) recently reported the results of a prospective, randomized, double-blind Phase

**TABLE 1. Nicardipine controlled-release system (lactic/glycolic acid copolymer)<sup>a</sup>**

Series (ref. no.)	Model (no.)	Outcome measures	Results
Kasuya et al., 2005 (28)	Humans (69) Humans (20)	DINDs present	6% T versus 11% C
		DINDs present	T (1 patient)
		Angiographic vasospasm	T (0 patients)
Kawashima et al., 2000 (30)	Dogs (18)	Mean reduction in middle cerebral artery diameter	
		<i>High dose</i>	7% T
		<i>Low dose</i>	14% T
		<i>Placebo</i>	43% C
Kawashima et al., 1998 (31)	Dogs (12)	Mean reduction in vessel diameter	
		<i>Internal carotid</i>	10% T versus 37% C
		<i>Middle cerebral</i>	3% T versus 48% C
		<i>Anterior cerebral</i>	1% T versus 28% C
Sasahara et al., 2000 (50)	Dogs (10)	Vasospasm	
		<i>Severe</i>	0 T versus 5 C
		<i>Mild</i>	2 T versus 0 C
		<i>None</i>	3 T versus 0 C
		Vessel diameter	0.5 mm T versus 1.1 mm C
		Histological changes related to implants	None
Barth et al., 2007 (2)	Humans (32)	Angiographic vasospasm	7% T versus 73% C
		Delayed ischemic lesions	14% T versus 47% C
		Mortality	6% T versus 38% C

<sup>a</sup> DINDs, delayed ischemic neurological deficits; T, treatment group; C, control group.

Ila study of nicardipine implants in 32 patients with severe SAH. They found significant reductions in angiographic vasospasm (in proximal vessels, 7% NPRI versus 73% control), delayed ischemic lesions (14% NPRI versus 47% control), and mortality (6% NPRI versus 38% control), as well as an increase in positive outcomes as defined by the modified Rankin Scale and the National Institutes of Health Stroke Scale. These studies demonstrated that nicardipine has great potential for use as an extravascular pharmacological treatment in CVS.

**Ibuprofen Controlled-release System**

Efforts to target a different part of the vasospasm cascade are based on research showing that leukocyte-endothelial cell interactions are implicated in the origin of CVS after SAH (47).

A controlled-release polymer, ethylene vinyl acetate copolymer (EVAC), coupled with ibuprofen, was constructed by Thai et al. (56) for periadventitial delivery in a rat femoral artery model. The 3-part study involved 133 rats. The in vitro pharmacokinetics study showed that the 50% loaded-ibuprofen polymer released its total drug load over a 12-day period. The toxicity study (n = 15) showed a nonsignificant arterial vasodilation at higher doses, and no deleterious effects were observed on the vessel wall histology. The efficacy study demonstrated significant vasospasm inhibition when treatment was initiated at 0 and 6 hours, but not at 12, 24, or 48 hours.

Frazier et al. (18) and Pradilla et al. (48) later tested the ibuprofen-loaded polymer in rabbit and monkey SAH models, respectively, with the theory that an anti-inflammatory agent

such as ibuprofen can potentially disrupt leukocyte-endothelial cell interactions through the inhibition of cell adhesion molecule expression, thus reducing the occurrence of CVS (Table 2) (21, 25, 40).

The results of these studies showed that ibuprofen is tolerated at high doses (6 mg/kg). When treatment was initiated early, EVAC-ibuprofen significantly inhibited vasospasm in rabbits, as demonstrated by arterial lumen patency (18).

**TABLE 2. Ibuprofen controlled-release system (ethylene vinyl acetate copolymer)<sup>a</sup>**

Series (ref. no.)	Model (no.)	Outcome measures	Results
Frazier et al., 2004 (18)	Rabbits (54)	Vasospasm (patency): administration post-event	
		<i>30 min</i>	92% T versus 52% C
		<i>6 h</i>	70% T versus 47% C
		<i>12 h</i>	No effect
		<i>24 h</i>	No effect
Pradilla et al., 2005 (48)	Monkeys (14)	Vasospasm (patency)	91% T versus 53% C

<sup>a</sup> T, treatment group; C, control group.

However, when this therapy was initiated late (12 and 24 hours), no difference was observed between the treatment and control groups. Similar efficacy of early initiation was found in a follow-up study in monkeys, also demonstrated by arterial patency (48). These studies indicate that ibuprofen may reduce CVS when initiated early after SAH.

### Nitric Oxide Donor Controlled-release System

Nitric oxide (NO), a potent vasodilator, is another agent being studied in the treatment of CVS based on interactions of NO concentration and free hemoglobin (Table 3). On one front, hemoglobin avidly binds to NO, thereby reducing the concentration of basal NO as well as its second messenger, cyclic guanosine monophosphate, in vascular smooth muscle cells and leading to vasospasm (14). Furthermore, hemoglobin is capable of generating reactive oxygen species such as superoxide anion, hydrogen peroxide, and hydroxyl radicals that may also destroy NO (10, 36). It has also been proposed that endothelial damage results in the decreased production of

endothelium-derived relaxing factors, e.g., NO and prostacyclin (prostaglandin I<sub>2</sub>) and increased production of endothelium-derived constricting factors, e.g., endothelin (19, 55).

Based on these properties, Gabikian et al. (20), Pradilla et al. (49), Tierney et al. (57, 58), and Clatterbuck et al. (7) constructed the controlled-release polymer EVAC coupled with an NO donor, diethylenetriamine (DETA)-NO, and performed toxicity and efficacy studies in rabbits (20), rats (20, 57), and cynomolgus monkeys (7, 58). Gabikian et al. (20) demonstrated the safety and efficacy of this system for the prevention of CVS in the rabbit basilar artery model. Initial studies on rats showed that doses as high as 3.4 mg/kg were tolerated, suggesting the safety of this mixture for local delivery to the central nervous system (20).

After these findings, Pradilla et al. (49) introduced their DETA-NO/EVAC system into the rabbits' cisterna magna at 24 and 48 hours after hemorrhage. They demonstrated that CVS can be prevented in the rabbit basilar artery model even after delayed administration of local antivasospasm drugs. The effi-

**TABLE 3. Nitric oxide donor controlled-release system (ethylene vinyl acetate copolymer)<sup>a</sup>**

Series (ref. no.)	Model (no.)	Outcome measures	Results
Gabikian et al., 2002 (20)	Rats (28) Rabbits (20)	LD <sub>20</sub> Vasospasm (patency)	3.4 mg/kg 93% 0.48 mg/kg T versus 73% empty/EVAC versus 71% no treatment
Pradilla et al., 2004 (49)	Rabbits (52)	Vasospasm (patency) Administration post-event <i>1.3 mg/kg at 24 h</i> <i>1.3 mg/kg at 48 h</i> <i>0.5 mg/kg at 24 h</i> <i>0.5 mg/kg at 48 h</i>	97% T versus 73% C 94% T versus 71% C 74% T versus 65% C 82% T versus 68% C
Clatterbuck et al., 2005 (7)	Monkeys (10)	Vasospasm (patency) Angiographic Histological <i>Internal carotid artery</i> <i>Middle cerebral artery</i> <i>Anterior cerebral artery</i>	85% T versus 57% C 99% T versus 60% C 98% T versus 56% C 89% T versus 56% C
Tierney et al., 2001 (57)	Rats (35)	Vasospasm (patency) Administration post-event <i>1 d</i> <i>3 d</i> <i>7 d</i>	95% T versus 68% C 105% T versus 65% C 102% T versus 74% C
Tierney et al., 2006 (58)	Monkeys (13)	Complications at dose <i>0.0 mg/kg (n = 3)</i> <i>0.5 mg/kg (n = 3)</i> <i>0.9 mg/kg (n = 3)</i> <i>1.9 mg/kg (n = 3)</i> <i>3.2 mg/kg (n = 1)</i>	None None None 1 seizure 1 death
	Histopathological changes	Hemorrhagic and ischemic changes at 0.9 mg/kg	

<sup>a</sup> LD<sub>20</sub>, dose lethal to 20% of subjects; T, treatment group; EVAC, ethylene vinyl acetate copolymer; C, control group.

cacy was evaluated by the increase in basilar artery lumen patency at 24 and 48 hours post-SAH (49). Smaller doses were not statistically significant at 24 hours post-SAH ( $74 \pm 7\%$  0.5 mg/kg DETA-NO/EVAC versus  $65 \pm 9\%$  empty/EVAC;  $P = 0.16$ ) but were significant at 48 hours post-SAH ( $82 \pm 8\%$  DETA-NO/EVAC versus  $68 \pm 12\%$  empty/EVAC,  $P = 0.03$ ) (49).

In their most recent studies, Tierney et al. (58) and Clatterbuck et al. (7) demonstrated both the safety and efficacy of their DETA-NO/EVAC system in nonhuman primates (e.g., cynomolgus monkeys). These studies estimate that the maximum safe dose of DETA-NO/EVAC for these primates is approximately 1.0 mg/kg, as determined by survival and histopathological studies. Animals receiving doses in excess of 0.9 mg/kg experienced hemorrhagic and ischemic changes in brain tissue (58). Efficacy studies showed a significant decrease in vasospasm with 4.3 mg/kg (20% wt/wt) DETA-NO/EVAC compared with controls using both angiographic and histological studies of the internal carotid artery, middle cerebral artery, and anterior cerebral artery (7). These studies demonstrated that the DETA-NO/EVAC system consistently reduces vasospasm after SAH.

**Papaverine Controlled-release System**

Papaverine is an opiate alkaloid that functions as a direct-acting smooth muscle relaxant, possibly through direct inhibition of calcium channels and nonselective inhibition of phosphodiesterases (23, 37). Papaverine in a controlled-release format has been studied in humans and animals by several groups (Table 4). Oda et al. (41, 42) mixed papaverine with silicone elastomers and polymerized the mixture for a steady-state release rate lasting 5 weeks. This system was then used in 30 patients with SAH with the pellet implanted at the time of surgery. Results showed that papaverine was present in the cerebrospinal fluid 2 to 3 days after pellet implantation and that the delivery system was able to act as a vasodilator (41).

Shiokawa et al. (52) developed a papaverine prolonged-release pellet with lactic acid/glycolic acid copolymer impregnated with papaverine (25 mg) and tested it in the SAH dog model. Sixteen dogs were assigned randomly to either the papaverine or placebo group, and pellets were placed in the cisterns surrounding the arteries that were vulnerable to vasospasm. Cerebral angiography was performed initially and repeated on Day 7. Results showed a significant reduction in vessel vasospasm in the papaverine group compared with the placebo group ( $P < 0.001$ ). However, when papaverine was used at a low dose (5 mg) in a similar experiment using an additional 16 dogs, no statistically significant difference was found in vessel diameter between the treated and control groups (52).

Dalbasti et al. (10) made pellets from lactic acid/glycolic acid copolymer and impregnated them with approximately 7.2 mg of papaverine. In their study, 44 patients with aneurysmal SAH were assigned to the papaverine controlled-release pellet group; the pellet was placed near arteries in close association with the hemorrhage at the time of surgery. The control group consisted of data collected from the charts of 73 patients with aneurysmal SAH who were previously treated with open surgery. Results showed some difference, although not a statistically significant one, in vasospasm reduction between the treatment group and the retrospective cohort (10).

Although papaverine showed promise in multiple systems as a treatment of CVS, not all studies have shown statistically significant benefits in humans. This limitation is likely related to the study designs. Prospective, randomized, blinded studies are needed to clarify the dosing required to effect reduction in CVS.

**Calcitonin Gene-related Peptide Controlled-release System**

Calcitonin gene-related peptide (CGRP) is a potent endogenous vasodilator (Table 5) (3). Because vasoactive neuropep-

TABLE 4. Papaverine controlled-release systems <sup>a</sup>			
Series (ref. no.)	Model (no.)	Outcome measures	Results
<b>Carrier: silicone elastomers</b>			
Oda et al., 1983 (42)	Dogs (1)	Complications	None
<b>Carrier: lactic/glycolic acid copolymer pellet</b>			
Shiokawa et al., 1998 (52)	Dogs (16)	Vasospasm	ICA, MCA, ACA
		Placebo (8)	53%, 40%, 44%
		Papaverine, 25 mg (8)	76%, 80%, 66%
Dogs (16)	Vasospasm	ICA, MCA, ACA	
	Placebo (8)	58%, 55%, 71%	
	Papaverine, 5 mg	66%, 50%, 62%	
Dalbasti et al., 2001 (10)	Humans (117)	Clinical vasospasm	
		Papaverine (n = 44)	1 patient
		Control (n = 73)	34 patients

<sup>a</sup> ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery.

**TABLE 5. Calcitonin gene-related peptide controlled-release system (lactic/glycolic acid copolymer)<sup>a</sup>**

Series (ref. no.)	Model (no.)	Outcome measures	Results
Inoue et al., 1996 (24)	Monkeys (10)	Vasospasm (patency) CGRP Non-CGRP	ICA, MCA, ACA 82%, 81%, 75% 55%, 62%, 51%

<sup>a</sup>ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; CGRP, calcitonin gene-related peptide.

tides are depleted after SAH (3, 12, 13), Ahmad et al. (1) and Inoue et al. (24) tested the effect of lactic/glycolic acid copolymer impregnated with CGRP in the treatment of CVS in an SAH monkey model. Inoue et al. placed 3 tablets (400 µg each) in the vascular territory of SAH in 5 monkeys. For the 5 monkeys used as the controls, CGRP-free tablets were placed in 2 monkeys (placebo group) and no tablets in 3 monkeys (SAH group). Serial cerebral angiography performed at the time of SAH induction and on Days 7 and 14 demonstrated a reduction of vasospasm in the treated group versus both control groups. No difference in vasospasm was detected in the CGRP-free tablet group versus the untreated SAH group. The cerebrospinal fluid concentration of CGRP was approximately 6.5 nmol/L in the CGRP group and 0 in the non-CGRP group (24). Studies with CGRP controlled-release systems have not been reported in humans.

**Liposome-entrapped Fasudil Controlled-release System**

Fasudil acts as a potent vasodilator through multiple mechanisms, including inhibition of myosin light-chain kinase, protein kinase C, and Rho kinase (implicated specifically in CVS) (Table 6) (39, 51, 63). Takanashi et al. (53, 54) developed sustained-release liposome-entrapped fasudil and injected it into the cisterna magna of 12 rats and 6 dogs, with both groups balanced against controls in their respective species. They observed no significant mean arterial blood pressure changes and no seizures. In addition, their study demonstrated a signif-

icant reduction in basilar artery vasospasm in the treatment groups compared with controls (54).

In a follow-up experiment, Takanashi et al. (53) demonstrated that rats receiving 0.417 mg of liposome-entrapped fasudil via the cisterna magna had significantly reduced vasospasm compared with animals that received liposomes alone, as demonstrated by the percentage of pre-event arterial diameter (88 ± 6% liposome-entrapped fasudil versus 66 ± 1% empty liposome). Further evaluation of fasudil as an extravascular means of treating CVS is warranted.

**Recombinant Tissue Plasminogen Activator Slow-release System**

Recombinant tissue plasminogen activator (rt-PA) is a serine protease that converts the proenzyme plasminogen to plasmin, a fibrinolytic enzyme that promotes thrombolysis. In a randomized, placebo-controlled trial, Findlay et al. (15) (Table 7) injected a slow-release gel consisting of a hyaluronidase preparation combined with rt-PA into the subarachnoid space in the vicinity of the sylvian fissure of 8 cynomolgus monkeys. They found no significant differences between the placebo and treated groups in mean arterial blood pressure, heart rate, or arterial carbon dioxide pressure, and there were no instances of incisional bleeding. Although the placebo group showed significant vasospasm in all major right- and left-sided anterior cerebral vessels, no vasospasm occurred in the rt-PA-treated animals.

In another study, Findlay et al. (16) specifically addressed dosing of sustained-release hyaluronidase gel rt-PA to prevent vasospasm in a primate SAH model. Sixteen monkeys were divided into 4 groups that received different doses of the rt-PA preparation. No vasospasm (defined as <10% decrease in vessel diameter) was found at 7 days in the groups receiving 0.5- and 0.75-mg doses. Mild to moderate vasospasm (between 10 and 50% reduction in vessel diameter) was present in the groups receiving 0.125- and 0.25-mg doses. Furthermore, gross clot remained in the subarachnoid space of all 8 animals in the 0.125- and 0.25-mg dose groups and in only half of the animals in the 0.5-mg dose group and was absent in all animals in the 0.75-mg dose group. Although further studies are needed, these studies demonstrate the safety and efficacy of sustained-release

**TABLE 6. Fasudil controlled-release system (liposome)**

Series (ref. no.)	Model (no.)	Outcome measures	Results
Takanashi et al., 2001 (54)	Rats (18)	Adverse effects in treatment group (n = 12) (lumen patency compared with sham)	None
	Dogs (15)	Vasospasm	% of pre-event diameter
		0.94 mg/kg fasudil liposome Empty liposome Placebo	86% 53% 56%
Takanashi et al., 2001 (53)	Rats (18)	Vasospasm 0.417 mg/kg fasudil liposome Empty liposome	% of pre-event diameter 88% 66%

**TABLE 7. Recombinant tissue plasminogen activator controlled-release system (hyaluronidase)<sup>a</sup>**

Series (ref. no.)	Model (no.)	Outcome measures	Results
Findlay et al., 1989 (15)	Monkeys (16)	Adverse effects in treatment group (n = 8) Vasospasm (>10% of pre-event diameter)	None 0 T versus 8 C
Findlay et al., 1989 (16)	Monkeys (16)	Vasospasm (>10% of pre-event diameter) Combined 0.125- and 0.25-mg dose groups <i>0.5-mg dose group</i> <i>0.75-mg dose group</i> Gross subarachnoid clot remaining <i>0.125-mg dose group</i> <i>0.25-mg dose group</i> <i>0.5-mg dose group</i> <i>0.75-mg dose group</i>	Present Absent Absent 4 animals 4 animals 2 animals 0 animals

<sup>a</sup> T, treatment group; C, control group.

**TABLE 8. Polymer types and characteristics**

Polymer type	Properties	Release duration <sup>a</sup>	Drug delivered	Refs.
Lactic/glycolic acid	2 × 10-mm pellets	9 d	Nicardipine	2, 28, 30, 31, 50
	Copolymer (1- or 3 × 10-mm pellets)	15 d	Papaverine	10, 52
	2 × 6-mm tablets	12 d	Calcitonin gene-related peptide	24
Ethylene vinyl acetate copolymer	1 × 6-mm cylinders	12 d	Ibuprofen	18, 48
	1 × 6-mm cylinders	9 d	Nitric oxide donor	7, 20, 49, 57, 58
Silicone elastomers	4 × 45-mm pellets	5 wk	Papaverine	42
Liposomes	110 ± 10-nm vesicles	10 d	Fasudil	53, 54
Hyaluronidase	1.75 mL of gel	7 d	Recombinant tissue plasminogen activator	15, 16

<sup>a</sup> Release durations are based on the length of the study as documented in references.

hyaluronidase gel rt-PA in the thrombolysis of subarachnoid clots and the prevention of vasospasm in a primate model.

## DISCUSSION

The occurrence of CVS after SAH carries with it high rates of mortality and morbidity. Prophylactic treatment of CVS is desired before ischemic changes occur. Although it is not clear which patients with aneurysmal SAH will develop CVS, it would be advantageous to readily administer prophylactic pharmacological therapy at the time that the aneurysm is treated rather than have to reverse existing CVS.

The introduction of drugs intracranially and extravascularly through a controlled-release system (Table 8) to minimize or eliminate CVS has been shown to be effective in research studies. This therapeutic strategy, by definition, requires surgically entering the cranial cavity. With the increasing number of aneurysms being treated with endovascular coiling rather than

surgical clipping, the controlled-release systems could potentially be employed by means of a ventricular catheter or lumbar puncture in cases in which aneurysmal treatment is carried out endovascularly. However, the fact that most of the controlled-release systems reported in the literature are solid, except for liposomes, would limit the use of narrow catheters as a means of delivery to the ventricular system.

To compensate for the different treatments, a controlled-release system may need to be converted from a pellet or solid substance to a flowing, low-viscosity implant. Also, a flowing polymer or hydrogel would favor treatment of vasospasm on the contralateral side of a craniotomy in terms of placement. For instance, if a patient were to have a craniotomy for a right posterior communicating artery aneurysm but developed vasospasm in the left middle cerebral artery, a flowing implant might be beneficial compared with a solid controlled-release system such as a pellet. However, it remains a hypothesis that a low-viscosity hydrogel or liposome may have a more signif-

icant effect in treating diffuse SAH-induced vasospasm than a pellet strategy. It is difficult to speculate that a specific controlled system, e.g., a hydrogel or liposome, will affect all vessels equally without appropriate animal data. Although the hydrogel or liposome system may allow injection through a ventricular catheter, the cerebrospinal fluid flow patterns would need to be studied to determine whether the large cerebral vessels are in contact with the drug released from the delivery system. In addition, a number of pharmacological agents have been assessed, but there needs to be some sort of agreement on the most optimal drug. The optimal drug is a more difficult problem than the mechanism of delivery—pellet versus gel. However, continued animal studies propel the research into new frontiers, perhaps leading to a successful pharmacological agent and delivery system.

## CONCLUSIONS

Although each of the controlled-released systems described has shown some positive results in minimizing CVS angiographically, an ideal drug or combination of drugs that would treat CVS is still pending. Several pharmacological compounds have shown promising antivasospasm effects when administered systemically but have not been tested intracranially. These drugs merit investigation to see their effects when administered locally via controlled-release carriers.

## Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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## COMMENTS

This is a review of agents that have been used intrathecally to prevent or reverse cerebral vasospasm after subarachnoid hemorrhage (SAH). The review may not be entirely inclusive because, in the authors' search of the PubMed database, they may not have used as key words the terms chosen for the secondary search, but this review nevertheless appears comprehensive. The variety of agents examined in the past several decades reflects the many different pathogenetic theories of vasospasm. All seem to have worked to some degree in animal models, although those studies have not proven terribly useful in understanding the condition of vasospasm and narrowing down its actual pathogenesis and the best means of prevention.

The true litmus test of an agent is testing in patients with ruptured aneurysms. Nicardipine, a calcium channel antagonist and vasodilator, has graduated to this stage and has shown promise in small trials in Japan and Germany (1, 3–5). Clot lysis using recombinant tissue plasminogen activator was also trialed in humans a number of years ago, although not in a slow or controlled-release system (2). Although nicardipine reduced severe vasospasm, the small, randomized, controlled trial was not powered to demonstrate any improvement in clinical outcome.

As attractive as the concept might be, the future of intracisternal treatment of vasospasm has been dictated by the advancement of endovascular obliteration of ruptured aneurysms. It is simply not clear that intraventricular or intraspinal administration of an agent into the cerebrospinal fluid is able to effectively target vessels buried by clot in the basal subarachnoid cisterns. Systemic treatment seems far more practical.

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Cerebral vasospasm is ideally suited to a treatment with drug delivered with biocompatible controlled-release systems. Microsurgical dissection of the subarachnoid spaces enables easy implantation of pellets or gels during surgery. Vasospasm is brief and follows immediately after implantation to match the time course of drug delivery. This article summarizes attempts to treat cerebral vasospasm using controlled-release systems and makes it clear that controlled-release systems hold great promise.

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Experimental data suggest that vasospasm is largely a problem of smooth muscle contraction. Secondary structural changes occur, and it is a reasonable hypothesis that they are secondary remodeling events that are caused by the initial prolonged, abnormal contraction (1, 2, 4). This would suggest that preventing or decreasing the primary contractile process would be effective, first, at preventing vasospasm and, second, at preventing this remodeling. Furthermore, there is some evidence that the stimuli for the contraction are at least partly the same as those for the remodeling (1, 5). Therefore, drugs to prevent the contraction also could prevent remodeling, even if it were primarily attributable to SAH. Key mediators of contraction are voltage-gated calcium channels and receptor-mediated mechanisms (7). Drugs to block the former effectively are dihydropyridines, such as nicardipine. An important receptor-mediated contraction seems to occur in vasospasm owing to activation of endothelin receptors by endothelin (6). Problems with systemic administration of nicardipine or endothelin receptor antagonists include systemic hypotension and pulmonary complications (3).

Omeis et al. present a well-written, succinct summary of attempts to overcome the problems of systemic delivery by local subarachnoid implantation. As stated by the authors, more preclinical data are needed for most of these drugs, but they hold promise for treatment of vasospasm. The added problem is how to deliver them to patients undergoing endovascular treatment.

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Omeis et al. have reviewed the treatment of cerebral vasospasm using biocompatible controlled-release systems. The concept and follow-up question are straightforward: vasospasm after SAH lasts for approximately 2 weeks after the initial hemorrhage; therefore, can a vasodilatory drug be delivered in a continuous high-dose fashion during that interval using a local slow-release polymer?

The authors review some of the foundational evidence that slow release via polymer can be done and that it can be beneficial on local vessel diameter in vasospasm preclinical models. However, the real world situation of diffuse vasospasm, which now occurs more frequently in the setting of an endovascular coiling procedure, remains a challenge in terms of polymer drug delivery. The local implantation of a slow-release pellet is perhaps most useful for a small focal hemorrhage around a clipped (e.g., middle cerebral artery) aneurysm. Further preclinical work needs to be performed to assess whether a minimally invasive delivery of either a liquid polymer or liposomes could achieve bilateral contact (and vasodilation) of large intracranial vessels at risk for vasospasm in SAH models.

**Bob S. Carter**  
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Omeis et al. have written a thorough and timely review of controlled-release systems in vasospasm after SAH. Implantable controlled-release polymers are ideally suited to deliver drugs in the central nervous system. When a polymer is implanted in either the brain or the subarachnoid space, it bypasses the blood-brain barrier and typically yields high drug concentrations in this compartment, although with only limited systemic drug exposure or toxicity.

Treatment of vasospasm after SAH with implantable controlled-release polymers has several appealing features. Two of the concerns usually raised about using controlled-release polymers in the brain are how to get the polymers into the central nervous system, and what to do when the drug supply in the polymer is depleted. From both of these perspectives, vasospasm after SAH is an ideal target for controlled-release drug delivery. In patients with an aneurysmal SAH who undergo a craniotomy for aneurysm clipping, controlled-release polymers can be left in the subarachnoid space at the time of surgery. Controlled-release materials such as ethylene vinyl acetate are biocompatible and would be no more deleterious to the brain than shunt catheters. We have shown that a controlled-release drug in the subarachnoid space would effectively travel a distance of at least 40 cm, which is greater than the longest dimension of the hemicircumference of the subarachnoid space around the human brain (6). In patients who undergo endovascular coiling, other insertion modalities would be necessary. These could include injecting “string polymers” or microspheres into the lumbar thecal sac through a 14-gauge spinal needle or, alternatively, inserting a temporary, indwelling spinal or intraventricular catheter (in patients with symptomatic hydrocephalus) with a tip

made of a controlled-release material containing an antivasospasm agent, such as diethylenetriamine-nitric oxide. The fact that the drug in the polymer would be depleted after a few days or weeks would not be an issue, since vasospasm after SAH is transient and typically needs to be treated for only 14 days after the hemorrhage. Indeed, depletion of the controlled-release drug supply within 2 weeks would be advantageous in this scenario.

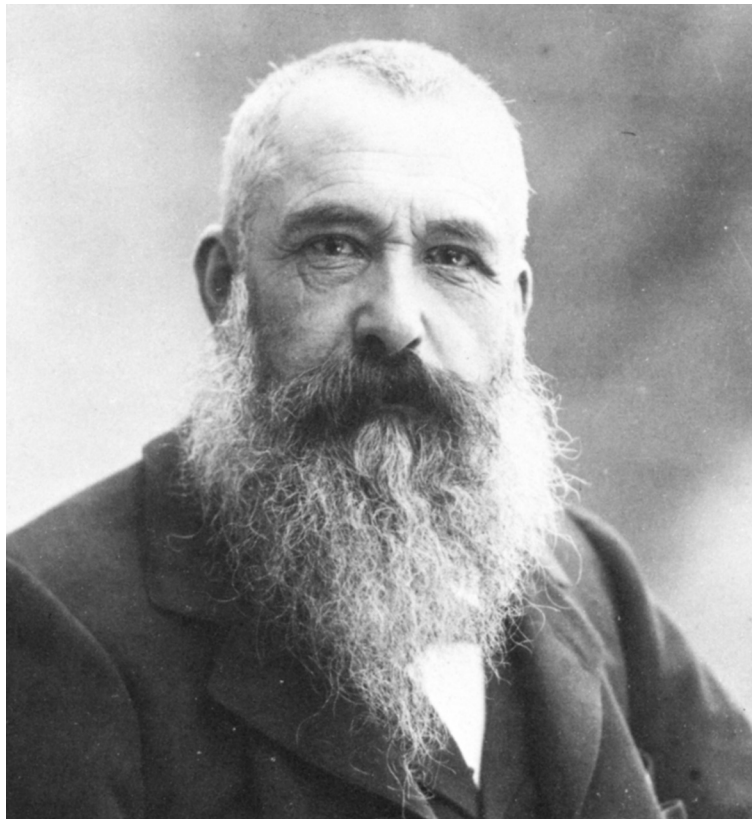
Therapy for vasospasm after SAH is at a crossroads, which requires that we change the way that we think about this problem and expand the range of drugs that we may use to treat this condition. Other than hypertensive-hypervolemic-hemodilutional ("triple H") therapy and angioplasty, we have no effective therapies against this condition. Nimodipine improves clinical outcomes slightly but does not prevent vasospasm (1). The disappointing results of the clazosentan (4) and nicardipine (3) trials, which prevented angiographic arterial narrowing but did not improve clinical outcomes, suggest that our understanding of the pathophysiology of vasospasm after SAH is incomplete.

Interestingly, inflammation is emerging as a major potential source of injury in SAH (2). Other mechanisms such as microcirculatory dysfunction and cortical spreading depression are also being considered (5). It is likely that an effective therapeutic strategy against vasospasm will require a combination of vasodilatory and anti-inflammatory drugs. Implantable controlled-release polymers will allow us to test and potentially use a wide variety of drugs, not just those that cross the blood-brain barrier and have low systemic side effects. This strategy is proving effective in the treatment of malignant gliomas using implantable controlled-release polymers and multiple drug combina-

tions (7), and it should be applicable to a wide range of conditions in neurosurgery, including vasospasm after SAH.

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Claude Monet, (1840–1926), Modernist Painter and father of Impressionism. See Apuzzo et al., pp 1035–1044.