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Endovascular Treatment of Cerebral Vasospasm: Transluminal Balloon Angioplasty, Intra-Arterial Papaverine, and Intra-Arterial Nicardipine

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Cerebral vasospasm remains one of the leading causes of morbidity and mortality with subarachnoid hemorrhage [1], and it is seen angiographically in 70% and clinically in 20% to 30% of patients with aneurysmal subarachnoid hemorrhage [2,3]. In a study of serial CT scans in 619 consecutive patients with subarachnoid hemorrhage treated at the Massachusetts General Hospital, vasospasm was the leading cause for new infarcts in patients treated with surgical clipping or endovascular coiling [4].

A number of reports contend that there is lower incidence of cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage treated with endovascular coiling compared with surgical clipping [5–8]. We studied 515 consecutive patients with subarachnoid hemorrhage treated at the Massachusetts General Hospital using multivariate statistical methods controlling for clinical and radiologic factors, such as patient age, neurologic condition (Hunt and Hess grade), amount of hemorrhage on the CT scan (Fisher score), and aneurysm location, and found no difference in the incidence of vasospasm between endovascular coiling and surgical clipping [9]. In the patients treated with surgical clipping, there was 63% vasospasm, of which 28% was symptomatic. In the patients treated with endovascular coiling, there was 54% vasospasm, of which 33% was symptomatic (no statistical difference) [9]. Significant hemorrhage on the CT scan (Fisher score of 3 or 4) and poor neurologic condition (Hunt and Hess grade of 4 or 5) significantly predicted symptomatic vasospasm, and symptomatic vasospasm was a strong predictor of poor clinical outcome and in-hospital mortality [9].

Transluminal balloon angioplasty

Although medical management of cerebral vasospasm consists largely of nimodipine and hypertensive hyperdynamic therapy [10], there are patients who experience vasospasm refractory to these therapies. Endovascular treatment can be effective in these patients with medically refractory vasospasm.

In 1984, Zubkov and colleagues [11] were the first to report using a balloon catheter for angioplasty of cerebral vessels in vasospasm. Since then, there have been a number of clinical studies reporting series of patients with cerebral vasospasm treated with transluminal balloon angioplasty [12–29] (Table 1; Fig. 1). The efficacy of transluminal balloon angioplasty to reverse neurologic deficits related to cerebral vasospasm is variably reported in the literature as ranging from 11% to 93%. We reviewed the literature to date in the English language for reports of clinical series of endovascular therapy for cerebral vasospasm, and from selected reports, there were 530 patients treated with transluminal balloon angioplasty for cerebral vasospasm, of whom 328 (62%) improved clinically (see Table 1).

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Table 1
Selected series of transluminal balloon angioplasty for cerebral vasospasm in the literature

Authors	Number of patients	Clinical improvement	Transcranial doppler	Cerebral blood flow	Major complications	Vessel rupture
Newell et al [12]	10	8/10 patients (80%) improved	2/2 patients (100%) improved		3/10 patients (30%)	0/10 patients (0%)
Higashida et al [13]	13	10/13 patients (77%) improved or remained in excellent condition			1/13 patients (7.7%)	0/13 patients (0%)
Newell et al [14]	41	28/39 patients (72%) improved, 2 performed prophylactically	27/29 patients (93%) improved	SPECT: 8/10 patients (80%) improved	4/41 patients (9.8%)	1/41 patients (2.4%)
Zubkov et al [15]	95	82/95 patients (87%) improved		^{133}Xe-clearance: 62/69 patients (90%) improved [16]	4/95 patients (4.5%)	1/95 patients (1%)
Mayberg et al [17]; Eskridge et al [18]	50	32/50 patients (64%) improved	"In patients demonstrating clinical improvement, TCD blood flow velocities decreased and remained below pre-angioplasty levels." [17]	"Improvement in cerebral perfusion was demonstrated by resolution of perfusion defects on SPECT scans in the majority of patients." [17]	5/50 patients (10%)	1/50 patients (2%)
Coyne et al [19]	13	4/13 patients (31%) improved			1/13 patients (8%)	0/13 patients (0%)
Fujii et al [20]	19	12/19 patients (63%) improved		SPECT: 3/5 patients (60%) improved		
Takis et al [21]	8	5/8 patients (63%) good outcome			1/8 patients (12.5%)	0/8 patients (0%)
Terada et al [22]	7	5/7 patients (71%) GOS 1-2 outcomes			0/7 patients (0%)	0/7 patients (0%)
Firlik et al [23]	13	12/13 patients (93%) improved		^{133}Xe-CT: 12/12 patients (100%) improved mean CBF in at-risk regions of interest. Pre-TBA to post-TBA mean CBF: 13 ± 2.1 to 44 ± 13.1 ml/100g/min ($P < 0.00005$)	1/13 patients (7.7%)	0/13 patients (0%)

Elliot et al [24]	39	30/39 patients (77%) improved	Pre-TBA to post-TBA mean velocity: 166 ± 9 to 92 ± 4 cm/sec ($P < 0.001$)	SPECT: 30/42 territories (71%) improved	1/39 patients (2.5%)	0/39 patients (0%)
Bejjani et al [25]	31	22/31 patients (72%) improved			3/31 patients (9.7%)	0/31 patients (0%)
Rosenwasser et al [32]	93	36/93 patients (39%) good outcomes at >6 months			0/93 patients (0%)	0/93 patients (0%)
Muizelaar et al [26]	13 prophyl actic	no patient developed DIND, 10/13 patients (77%) favorable outcome	no velocities >200 cm/sec		1/13 patients (7.7%)	1/13 patients (7.7%)
Polin et al [27]	38	4/38 patients (11%) immediate improvement; 11/38 patients (29%) improvement at 4 day follow-up	15/38 patients (39%) patients improved		"In our series, it was impossible to determine if any of the unfavorable outcomes were caused by complications of vasospasm."	
Oskouian et al [28]	12	6/12 patients (50%) improved	Decreased mean velocities post-TBA: MCA 12/12 patients (100%) EC-ICA 10/12 patients (84%) hemispheric ratio 10/12 patients (84%) MCA spasm index 12/12 patients (100%) Pre-TBA to post-TBA mean velocities: MCA 157.6 ± 9.4 to 76.3 ± 9.3 cm/sec ($P < 0.05$) EC-ICA 31.0±3.7 to 39.9±3.8 cm/sec (P = NS) hemispheric ratio 4.1 ± 2.9 to 2.5 ± 3.0 cm/sec (P = NS) MCA spasm index 6.1 ± 0.4 to 2.8 ± 0.5 cm/sec ($P < 0.05$)	^{133}Xe-clearance: 7/12 patients (58%) improved. Pre-TBA to post-TBA mean CBF: 27.8±2.8 to 28.4 ± 3.0 ml/100g/min (P = NS)	0/12 patients (0%)	0/12 patients (0%)

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Table 1 (*continued*)

Authors	Number of patients	Clinical improvement	Transcranial doppler	Cerebral blood flow	Major complications	Vessel rupture
Rabinstein et al [29]	35	15/35 patients (43%) good outcomes			2/105 procedures (TBA and/or IAP) (1.9%)	1/35 patients (2.9%)
Total	530	328/530 patients (62%) with improvement or good outcome	56/81 patients (69%) improved	92/108 patients (85%) improved; 30/42 territories (71%) improved	27/543 patients or procedures (5.0%)	5/473 patients (1.1%)

Abberivations: CBF, cerebral blood flow; DIND, delayed ischemic neurologic deficit; EC-ICA, exracranial-internal carotid artery; MCA, middle cerebral artery; NS, not significant; SPECT, serial single photon emission computerized tomography; TBA, transluminal balloon angioplasty; TCD, transcranial doppler ultrasonography; Xe, xenon.

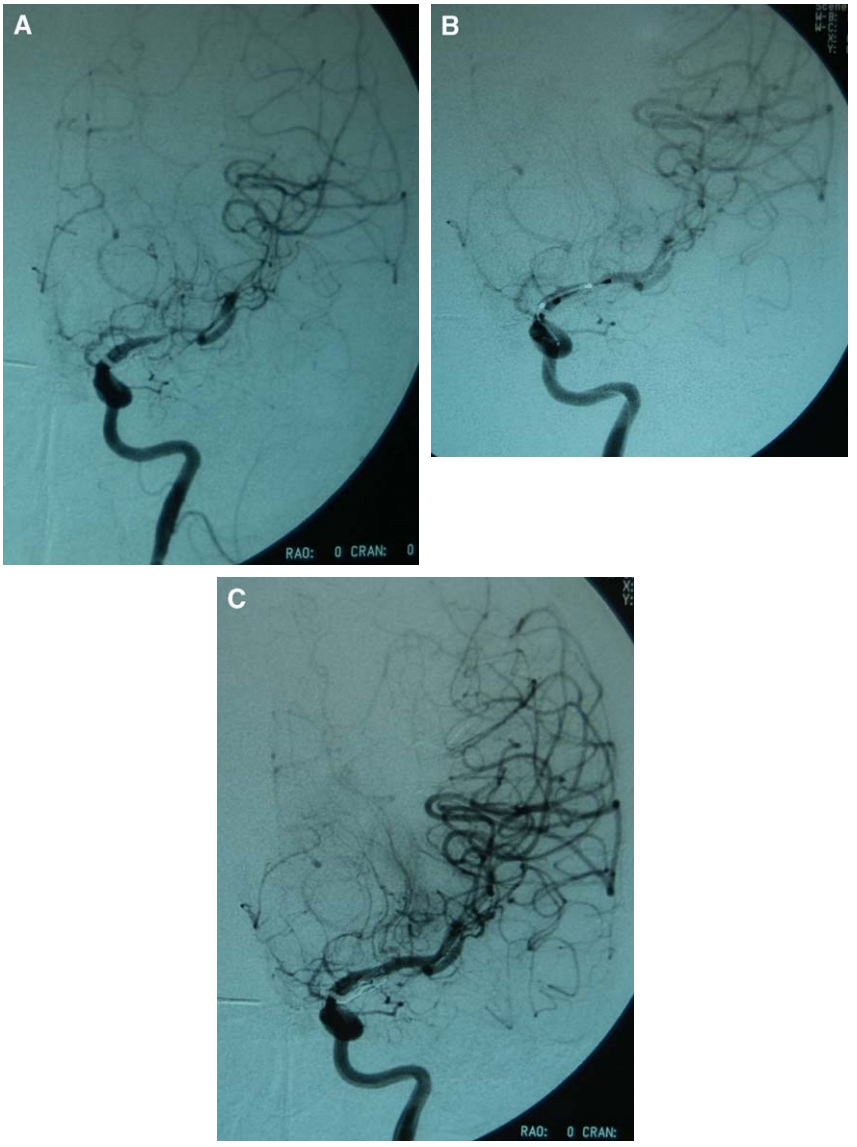

Fig. 1. Transluminal balloon angioplasty for cerebral vasospasm. (*A*) AP left internal carotid artery (ICA) injection digital subtraction angiography (DSA) demonstrating severe vasospasm of the left middle cerebral artery (MCA). (*B*) Transluminal balloon angioplasty of the left MCA. (*C*) Post-angioplasty AP left ICA injection DSA demonstrating angiographic reversal of vasospasm in the left MCA.

Transluminal balloon angioplasty is not without its complications, however. Complications can include arterial dissection, thromboembolism, branch occlusion [14,27], reperfusion hemorrhage into infarcted territories [13], bleeding from unsecured aneurysms [14,27], and vessel rupture [14,15,17,18,26,29–31]. In our review of selected reports in the English language literature in which complications were reported of transluminal balloon angioplasty, there were major complications in 5.0% and vessel rupture occurred in 1.1% (see Table 1).

Several reports have demonstrated improvement in transcranial Doppler (TCD) ultrasonography flow velocities after compared with before transluminal balloon angioplasty. There are two methods in which this has been reported: to report the number of patients in whom TCD velocities

improved or to report the mean TCD velocities for the cohort of patients after compared with before transluminal balloon angioplasty. Using the former method, several studies have demonstrated that TCD velocities were improved after compared with before transluminal balloon angioplasty in 39% to 100% of patients [12,14,27,28]. In our review of selected reports in the English language literature, of 81 patients in whom before and after transluminal balloon angioplasty TCD velocities were reported, there were 56 (69%) in whom TCD velocities improved (see Table 1). The latter method of reporting TCD velocities has been reported in several studies as well. Elliott and coworkers [24] demonstrated improvement in mean TCD velocities from 166 $\pm$ 9 cm/s before transluminal balloon angioplasty to 92 $\pm$ 4 cm/s after transluminal balloon angioplasty ($P <$ 0.001). Oskouian and colleagues [28] reported improvement in mean TCD velocities before and after transluminal balloon angioplasty of the middle cerebral artery (MCA) and external carotid artery (ECA)–internal carotid artery (ICA) as well as in hemispheric ratios and the MCA spasm index: 157.6 $\pm$ 9.4 to 76.3 $\pm$ 9.3 cm/s ($P <$ .05), 31.0 $\pm$ 3.7 to 39.9 $\pm$ 3.8 cm/s ($P =$ not significant), 4.1 $\pm$ 2.9 to 2.5 $\pm$ 3.0 cm/s ($P =$ not significant), and 6.1 $\pm$ 0.4 to 2.8 $\pm$ 0.5 cm/s ($P <$ .05), respectively.

The effect of transluminal balloon angioplasty on cerebral blood flow (CBF) has been demonstrated with perfusion techniques: ^{133}Xenon clearance, ^{133}Xenon CT, or serial single photon emission computerized tomography (SPECT). Using ^{133}Xenon clearance techniques, a few reports have demonstrated improvement in CBF in 58% to 90% of patients treated with transluminal balloon angioplasty [16,28]. When the mean CBF for the cohort in one study was compared before and after transluminal balloon angioplasty, however, there was not a statistical difference before (27.8 $\pm$ 2.8 mL/100 g/min) compared with after (28.4 $\pm$ 3.0 mL/100 g/min) ($P =$ not significant) [28]. Firlik and coworkers [23] used ^{133}Xenon CT and demonstrated that all 12 patients (100%) they studied had an improved mean CBF in at-risk regions of interest (ROIs). They also reported a significant improvement in before to after transluminal balloon angioplasty mean CBF: 13 $\pm$ 2.1 mL/100 g/min to 44 $\pm$ 13.1 mL/100 g/min ($P <$ .00005) [23]. Other studies used SPECT to demonstrate improvement in CBF in 60% to 80% of patients [14,20] or an improvement in CBF to 71% of territories treated [24]. In our review of selected reports in the English language literature, of 108 patients in whom before and after transluminal balloon angioplasty CBF was studied by perfusion techniques, there were 92 patients (85%) in whom CBF improved (see Table 1).

The optimal timing of transluminal balloon angioplasty in relation to the onset of cerebral vasospasm or signs and symptoms is not well defined. Rosenwasser and colleagues [32] reported significantly better and sustained clinical outcomes in patients they had treated with transluminal balloon angioplasty within 2 hours of symptom onset (70% improvement) compared with patients they had treated at more than 2 hours after symptom onset (40% improvement) in a retrospective non–case-controlled review of the patients' outcomes. Muizelaar and coworkers [26] performed a pilot study of prophylactic transluminal balloon angioplasty for patients with Fisher grade 3 subarachnoid hemorrhage. Of the 13 patients reported in the pilot study, no patient developed delayed ischemic neurologic deficit and 10 (77%) of the 13 patients had favorable outcomes. TCD ultrasonography was performed, and none of the 13 patients had postangioplasty TCD velocities greater than 200 cm/s. There was, however, 1 patient who died after vessel rupture during transluminal balloon angioplasty, resulting in a complication rate of 7.7%.

Although the exact mechanisms for the effects of transluminal balloon angioplasty are not entirely elucidated, there have been several animal and human autopsy studies to examine this question. In a study of nonhuman primates (*Macaca fuscata* monkeys), scanning electron microscopy and transmission electron microscopy demonstrated that untreated vessels in vasospasm were characterized by endothelial convolutions and marked corrugations of the internal elastic lamina, whereas vessels treated with angioplasty were characterized by flatter convolutions, the corrugated internal elastic lamina was extended, and there was only slight endothelial cell damage [33]. In a study in which scanning electron microscopy was performed in three patients at autopsy of vessels with vasospasm that were treated with angioplasty compared with vessels with vasospasm that were untreated, the untreated vessels in vasospasm demonstrated proliferation of connective tissue in the media and intima, whereas vessels treated with angioplasty demonstrated thinning of the arterial wall by compression and stretching, without disruption of cellular and connective tissue elements

and without damage to the endothelium [34]. Several other human autopsy and animal studies have demonstrated the same mechanism for the effects of transluminal balloon angioplasty, that is, compression of the connective tissue which proliferates in the setting of cerebral vasospasm, stretching of the internal elastic lamina, and a combination of compression and stretching of the smooth muscle [35–37].

Intra-arterial papaverine

With the early successful results reported with transluminal balloon angioplasty, there was enthusiasm for developing vasodilating agents that could be delivered intra-arterially as an endovascular therapy for medically refractory vasospasm. Not only were there associated risks of complications with transluminal balloon angioplasty, but navigation of balloon catheters has been limited primarily to the proximal cerebral vessels. Thus, there was hope that intra-arterial injection of vasodilating agents could theoretically treat vasospasm of distal cerebral vessels [38]. Papaverine hydrochloride is a benzylisoquinoline alkaloid derivative of opium known to cause arterial dilatation, probably from inhibition of arterial smooth muscle contraction by phosphodiesterase inhibition. In 1992, Kaku and colleagues [39] were the first to report the intra-arterial injection of papaverine to treat cerebral vasospasm. Since then, there have been a number of clinical series reporting variable results and associated complications with intra-arterial papaverine therapy [24,28,29,39–53] (Table 2). The efficacy of intra-arterial papaverine to improve clinical outcomes in patients with cerebral vasospasm is variably reported in the literature, ranging from 0% to 100%. We reviewed the literature to date in the English language for clinical series of intra-arterial papaverine therapy for cerebral vasospasm, and from selected reports, there were 346 patients treated with intra-arterial papaverine therapy for cerebral vasospasm, of whom 148 (43%) improved clinically (see Table 2).

A significant criticism of intra-arterial papaverine therapy is the relatively short duration of its beneficial effects and the recurrence of vasospasm after treatment. Patients with severe cerebral vasospasm often require more than one session of intra-arterial papaverine treatment. In 2004, Liu and coworkers [53] reported on 17 patients who underwent 91 total sessions of multiple intra-arterial papaverine treatment (5.4 sessions per patient). In our review of selected reports from the English language literature, there were 401 patients who underwent 663 treatment sessions of intra-arterial papaverine, for a mean of 1.7 treatment sessions per patient (see Table 2). Papaverine's effect on vessels has a relatively short half-life. Milburn and colleagues [38] reported excellent angiographic results in patients treated with intra-arterial papaverine therapy, as demonstrated by their measurement of vessel diameters in proximal and distal vessels; however, 9 of the patients underwent repeat angiography the next day, and all had recurrent arterial narrowing. Elliott and colleagues [24] reported that the beneficial effect of intra-arterial papaverine on TCD velocities did not last up to 48 hours. Vajkoczy and colleagues [51] reported that improvement of CBF after intra-arterial papaverine treatment did not continue for up to 12 hours after treatment. Another explanation may be the concept that vessels in vasospasm may be initially responsive to papaverine within a certain time window after subarachnoid hemorrhage but that after an interval of time, they become resistant to papaverine because of histologic changes that have occurred in the vessels or because of a cascade of pathophysiologic events that have taken place. This vessel-responsive phase theory of papaverine's effects in cerebral vasospasm has been demonstrated in a number of animal studies [54–57].

The effect of intra-arterial papaverine on TCD velocities has been reported. Variable results have been reported, ranging from 39% to 85% of patients treated with intra-arterial papaverine therapy reported as having had improvement in their TCD velocities after treatment [28,47]. Other reports have demonstrated significant improvement in mean TCD velocities comparing before and after treatment for cohorts of patients who underwent intra-arterial papaverine therapy. In our review of selected reports in the English language literature, of 51 patients in whom before and after intra-arterial papaverine TCD velocities were reported, there were 29 patients (57%) in whom TCD velocities improved (see Table 2). Yoshimura and colleagues [44] reported improvement in before to after intra-arterial papaverine treatment mean TCD velocities from 100.9 ± 18.6 cm/s to 59.0 ± 18 cm/s ($P < .01$). Likewise, Vajkoczy and coworkers [51] reported improvement in mean TCD velocities in the MCA from 207.3 ± 22.0 cm/s to 152.2 ± 25.3 cm/s ($P < .05$). Oskouian and colleagues [28] reported significant improvements in mean TCD velocities for

Table 2
Selected series of Intra-arterial Papaverine (IAP) therapy for cerebral vasospasm in the literature

Authors	Number of patients	Number of territories	Number of treatments	Clinical improvement	Transcranial doppler	Cerebral blood flow	Complications	Total complications
Kaku et al [39]	10	37	10 (1.0/pt)	8/10 patients (80%) improved			0/10 patients (0%)	0/10 patients (0%)
Kassell et al [40]	12	16	14 (1.2/pt)	4/12 patients (33%) improved			1/12 transient hemiparesis and mental status change (8.3%) 1/12 pupillary dilation (8.3%)	2/12 patients (17%)
Marks et al [41]	2	4	4 (2.0/pt)	1/2 patients (50%) improved			1/2 seizures (50%)	1/2 seizures (50%)
Clouston et al [42]	14	60	19 (1.4/pt)	7/14 patients (50%) improved			1/14 monocular blindness (7.1%) 1/14 arterial dissection (7.1%) 1/14 seizure (7.1%)	3/14 patients (21%)
McAuliffe et al [43]	21	42	27 (1.3/pt)	11/21 patients (52%) improved			1/21 fatal vessel rupture (4.8%) 1/21 large infarct, epidural hematoma (4.8%) 1/21 fatal basal ganglia hemorrhage (4.8%)	3/21 patients (14%)
Yoshimura et al [44]	19	19	19 (1.0/pt)	15/19 patients (79%) improved	Pre-IAP to Post-IAP mean velocity: 100.9 ± 18.6 to 59.0 ± 18 cm/sec ($P < 0.01$)		0/19 patients (0%)	0/19 patients (0%)
Sawada et al [45]	46	90	46 (1.0/pt)	11/46 patients (24%) improved			4/46 transient plegia/paresis (8.7%) 4/46 pupillary dilation (8.7%) 1/46 transient mental status changes (2.2%)	9/46 patients (20%)
Cross et al [46]	28	78	51 (1.8/pt)	not reported			1/28 arrest (3.6%) 1/28 seizure (3.6%) 2/28 transient aphasia (7.1%) 3/28 mental status changes (11%)	7/28 patients (25%)

Polin et al [47]	31	not reported	46 (1.5/pt)	4/31 patients (13%) immediate improvement; 12/31 patients (39%) improvement at 4 day F/U	12/31 patients (39%) improved		not reported	not reported
Fandino et al [48]	10	23	10 (1.0/pt)	10/10 patients (100%) improved		SVJO2: 9/10 patients (90%) improved; Pre-IAP to post-IAP means SVJO2 improved ($P < 0.01$)	0/10 patients (0%)	0/10 patients (0%)
Elliott et al [24]	13	24	21 (1.6/pt)	9/13 patients (69%) improved with initial treatment	Pre-IAP to post-IAP mean velocity: 158 ± 8 to 127 ± 13 cm/sec ($P < 0.01$) mean MCA velocity: 166 ± 10 to 135 ± 15 cm/sec ($P < 0.05$) IC/EC ratio: 4.1 ± 0.4 to 3.7 ± 0.5 (P = NS) *all changes were only transient and did not maintain to post-treatment day 2	SPECT: 5/16 territories (31%) improved	0/13 patients (0%)	0/13 patients (0%)
Firlik et al [49]	15	32	23 (1.5/pt)	6/23 treatments (26%)		^{133}Xe-CT: 6/13 patients (46%) had reduction in number of at-risk regions of interest	1/23 worsened vasospasm, hemispheric infarction (4.3%) 1/23 transient brainstem depression (4.3%) 1/23 seizure (4.3%) 1/23 profound hypotension (4.3%)	4/23 treatments (17%) [3/15 patients (20%)]
Zervas and Ogilvy [50]	39	142	91 (2.3/pt)	not reported			6/39 arterial dissections (15%) 13/39 embolic infarcts (33%)	19/39 patients (49%)

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Table 2 (*continued*)

Authors	Number of patients	Number of territories	Number of treatments	Clinical improvement	Transcranial doppler	Cerebral blood flow	Complications	Total complications
Vajkoczy et al [51]	8	10	8 (1.0/pt)	0/12 patients (0%) good outcomes	Pre-IAP to post-IAP mean MCA velocity: 207.3 ± 22.0 to 152.2 ± 25.3 cm/sec ($P < 0.05$)	Thermal dilution: Pre-IAP to post IAP: 7.3 ± 1.6 to 37.9 ± 6.6 ml/100 gm/min ($P < 0.05$) only transient, did not maintain for long-term (up to 12 hours)	not reported	not reported
Andaluz et al [52]	50	166	94 (1.88/pt)	13/50 patients (26%)			5/50 fatal sustained increased ICP (10%) 1/50 transient aphasia and hemiplegia (2.0%) 1/50 pupillary dilation (2.0%) 1/50 brainstem depression (2.0%) 1/50 aneurysm perforation (2.0%)	9/50 patients (18%)
Oskouian et al [28]	20	not reported	24 (1.2/pt)	9/20 patients (45%) improved	Decreased mean velocities post-IAP: MCA 17/20 patients (85%) EC-ICA 7/20 patients (35%) hemispheric ratio 8/20 patients (40%) MCA spasm index 14/20 patients (70%) Pre-IAP to post-IAP mean velocities: MCA 109.9 ± 9.1 to 82.8 ± 8.6 cm/sec ($P < 0.05$) EC-ICA 33.1 ± 3.6 to 35.2 ± 3.4 cm/sec (P = NS) hemispheric ratio 3.3 ± 2.9 to 2.8 ± 0.3 cm/sec (P = NS) MCA spasm index 4.4 ± 0.3 to 2.5 ± 0.3 cm/sec ($P < 0.05$)	^{133}133Xe-clearance: 11/20 patients (55%) improved Pre-IAP to post-IAP mean CBF: 27.5 ± 2.1 to 38.7 ± 2.8 ml/100 g/min ($P < 0.05$)	0/20 patients (0%)	0/20 patients (0%)

Liu et al [53]	17	33	91 (5.4/pt)	12/17 patients (71%) improved			1/17 transient aphasia (5.9%)	1/17 patients (5.9%)
Rabinstein et al [29]	46	not reported	65 (1.4/pt)	20/46 patients (43%) good outcomes			2/105 treatments (TBA and/or IAP) (1.9%)	2/105 treatments (TBA and/or IAP) (1.9%)
Total	401	>873*	663 (1.7/pt)	148/346 patients (43%) with improvement or good outcome	29/51 patients (57%) improved	26/43 patients (60%) improved; 5/16 territories (31%) improved		60/609 treatments (9.9%)

Abbreviations: CBF, cerebral blood flow; IAP, intra-arterial papaverine; IC/EC, intracranial to extracranial; ICP, intracranial pressure; MCA, middle cerebral artery; NS, not significant; SPECT, serial single photon emission computerized tomography; SVJO2, jugular venous bulb oxygen saturation; TCD, transcranial doppler ultrasonography; Xe, xenon.

* Some series did not report the number of vascular territories treated. In those instances, it was assumed that at least one territory was treated for each patient. Therefore, there was at least 873 territories altogether.

the MCA (109.9 ± 9.1 cm/s to 82.8 ± 8.6 cm/s; $P < .05$) and in the MCA spasm index (4.4 ± 0.3 cm/s to 2.5 ± 0.3 cm/s; $P < .05$), but nonsignificant differences for the ECA-ICA ratios and hemispheric ratios. Finally, Elliott and coworkers [24] reported significant improvements in overall mean TCD velocities (158 ± 8 cm/s to 127 ± 13 cm/s; $P < .01$) and mean TCD MCA velocities (166 ± 10 cm/s to 135 ± 15 cm/s; $P < .05$); however, these improvements were only transient and did not continue to 2 days after intra-arterial papaverine treatment.

Intra-arterial papaverine's effect on CBF has been studied with thermal dilution techniques, jugular venous bulb oxygen saturation, ^{133}Xenon clearance, ^{133}Xenon CT, and serial SPECT. Fandino and colleagues [48] studied jugular venous bulb oxygen saturation to demonstrate significant improvement in CBF in 9 of 10 patients with cerebral vasospasm after intra-arterial papaverine treatment and reported a significant improvement in the overall mean jugular venous bulb oxygen saturation ($P < .01$). Elliott and coworkers [24] used SPECT techniques to demonstrate improvement in CBF in 5 (31%) of 16 vascular territories studied. Vajkoczy and colleagues [51] used thermal dilution techniques to demonstrate improvement from before to after intra-arterial papaverine treatment CBF of 7.3 ± 1.6 mL/100 g/min to 37.9 ± 6.6 mL/100 gm/min ($P < .05$); however, this improvement was only transient and did not continue for up to 12 hours after treatment. Firlik and coworkers [49] studied ^{133}Xenon CT and reported that 6 (46%) of 13 patients had a reduction in the number of at-risk ROIs in CBF. Oskouian and colleagues [28] used ^{133}Xenon clearance to demonstrate significant improvement in CBF after intra-arterial papaverine treatment in 11 (55%) of 20 patients and improvement in mean CBF from before to after intra-arterial papaverine treatment of 27.5 ± 2.1 mL/100 g/min to 38.7 ± 2.8 mL/100 g/min ($P < .05$). In our review of selected reports in the English language literature, of 43 patients in whom before and after intra-arterial papaverine CBF was studied by perfusion techniques, there were 26 patients (60%) in whom CBF improved and 5 (31%) of 16 vascular territories that improved (see Table 2).

One of the most important limitations of intra-arterial papaverine therapy is its effect of increasing intracranial pressure (ICP) [43,46,52]. Cross and colleagues [46] demonstrated that ICP increases with intra-arterial papaverine therapy were significantly associated with adverse outcomes, and Andaluz and colleagues [52] reported a 10% mortality rate from papaverine-induced ICP. The ICP elevations seem to be related to the rate of papaverine administration [46]. The mechanism of increased ICP associated with intra-arterial papaverine is not known; however, it has been speculated that it may have to do with the nonselective dilatation effects of papaverine, resulting in vasodilation and increased capacitance in the venous bed [46,52]. It is strongly cautioned that any intra-arterial papaverine therapy be performed with continuous ICP monitoring [43,46,52].

In the 1990s at the Massachusetts General Hospital, intra-arterial papaverine therapy was used to treat medical refractory vasospasm. We encountered a significant number of complications, however, as we reported previously [50]. In 39 patients in whom 142 vessels were treated with 91 treatment sessions of intra-arterial papaverine, there were 6 arterial dissections (15%) and 13 embolic infarcts (33%) [50]. Papaverine treatment for cerebral vasospasm has also been associated with seizures, the mechanism of which is unknown [22,41,42,46,49,58–60], monocular blindness [42], brain stem dysfunction [49,52,61,62], neurologic deficits that resolve after stopping papaverine infusion [39,40,45,46,52,53], hemorrhage [43], pupillary dilation [40,45,52], respiratory arrest [46], profound hypotension [49], aneurysm perforation [52], formation of crystal precipitate emboli [63], and even paradoxic worsening of vasospasm [49,64]. In our review of selected reports in the English language literature, of 609 treatment sessions with intra-arterial papaverine therapy, there were 60 complications (9.9%) (see Table 2).

Smith and colleagues [65] reported neurotoxic effects of intra-arterial papaverine. In five patients who exhibited neurologic deterioration with papaverine treatment, they demonstrated selective gray matter only signal changes within the territories infused with papaverine on MRI. Histologic analysis performed on autopsy of one of the patients demonstrated selective injury to islands of neurons with relative sparing of white matter [65].

Elliott and colleagues [24] directly compared transluminal balloon angioplasty and intra-arterial papaverine therapy for treatment of cerebral vasospasm. They found transluminal balloon angioplasty to be superior to intra-arterial papaverine because of greater sustained improvements in TCD velocities, greater improvement in cerebral perfusion as demonstrated by SPECT scanning, and fewer treatment failures. Transluminal balloon angioplasty resulted in permanent reversal of

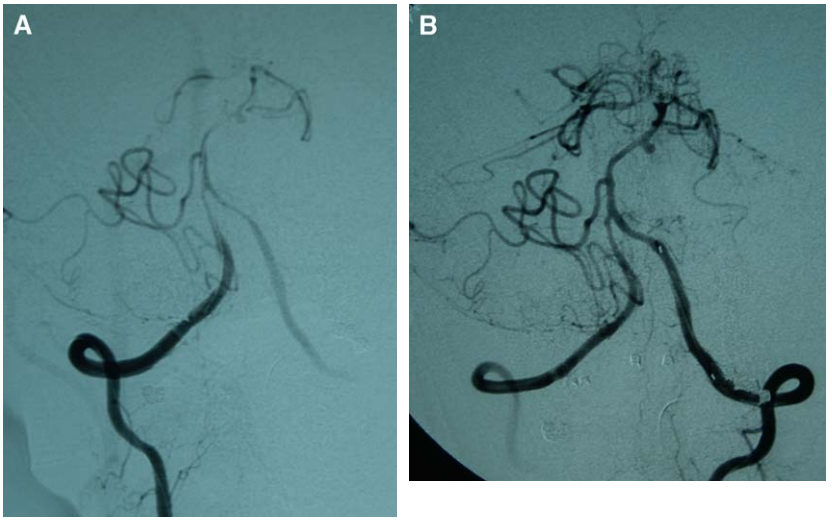

Fig. 2. Intra-arterial nicardipine infusion for cerebral vasospasm. (*A*) AP right vertebral artery (VA) injection digital subtraction angiography (DSA) demonstrating severe vasospasm of the vertebrobasilar system. (*B*) Post-intra-arterial nicardipine AP left VA injection DSA demonstrating angiographic reversal of vasospasm in the vertebrobasilar system.

vasospasm in the cerebral vessels, whereas patients treated with intra-arterial papaverine often required retreatment [24].

Intra-arterial nicardipine

For a number of reasons, including the significant number of complications we encountered using intra-arterial papaverine at the Massachusetts General Hospital in the 1990s [50], the lack of sustained treatment effect of papaverine, the need for multiple treatments, and the associated increases in ICP [43,46,52], we have abandoned using papaverine and have used nicardipine as our intra-arterial vasodilating agent for the endovascular treatment of cerebral vasospasm (Fig. 2).

Nicardipine is a dihydropyridine calcium antagonist with an apparent selective dilatation effect on vascular smooth muscle over cardiac muscle. Initially, it was studied as an intravenous agent for prophylactic treatment against the development of cerebral vasospasm and was shown to have beneficial effects in lowering the incidence of angiographic and clinical vasospasm [66–69].

We have previously reported our initial experience with intra-arterial nicardipine therapy for cerebral vasospasm at the Massachusetts General Hospital [70]. In a 12-month span, we treated 48 vessels in 24 patients with intra-arterial nicardipine alone or in addition to transluminal balloon angioplasty. We reported on 18 patients who underwent only intra-arterial nicardipine treatment in 44 vessels. There was angiographic and TCD improvement in all cases. Clinical improvement occurred in 8 patients (42%). Mean TCD velocities were significantly improved before to after intra-arterial nicardipine treatment from 268.9 $\pm$ 77.8 cm/s to 197.6 $\pm$ 74.1 cm/s ($P <$ .001) and were sustained for 4 days after treatment. The only adverse effect occurred in 1 patient in whom there was an increase in ICP, which necessitated termination of the intra-arterial nicardipine infusion. There were no hemodynamic changes with nicardipine infusion.

Based on this experience, we have adopted a current treatment protocol of transluminal balloon angioplasty or intra-arterial nicardipine therapy as endovascular treatment for medically refractory cerebral vasospasm.

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