Intraoperative Urokinase Infusion for Embolic Stroke during Carotid Endarterectomy

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EMBOLIC STROKE IS an infrequent complication of carotid endarterectomy. Somatosensory evoked potential monitoring detected delayed acute neurological deterioration during endarterectomy performed on a 71-year-old woman. Intraoperative arteriography performed via an indwelling shunt revealed thrombus within the middle cerebral artery and distal branches. A microcatheter was placed into the internal carotid artery via the arteriotomy and advanced into the middle cerebral artery. Urokinase was infused into and around the thrombus until almost complete thrombolysis had been achieved. The patient recovered quickly and was discharged without neurological deficit. (Neurosurgery 36:606–611, 1995)

Key words: Carotid, Cerebral embolism and thrombosis, Endarterectomy, Fibrinolysis, Thrombolytic therapy, Urokinase

CASE PRESENTATION

A 71-year-old woman was admitted for the evaluation of cerebrovascular disease after a left hemisphere transient ischemic attack. One week before admission, the patient experienced a sudden onset of right hemiparesis, worse in the upper extremity, right central cranial nerve VII palsy, and expressive dysphasia. All deficits cleared within 20 minutes, except for the dysphasia, which persisted slightly longer. Sonographic evaluation performed at an outside institution suggested bilateral high-grade carotid stenoses, worse on the left than on the right. A physical and neurological examination was remarkable only for bilateral cervical bruits.

Angiography demonstrated occlusion of the left internal carotid artery (ICA). The left external carotid artery was widely patent. The left middle cerebral artery (MCA) distribution filled via the posterior communicating artery during the injection of the left vertebral artery; the left anterior cerebral artery distribution filled via the anterior communicating artery during the injection of the right common carotid artery. The right ICA had more than 90% proximal stenosis (Fig. 1).

Stable xenon-computed tomography (CT) cerebral blood flow examinations (Fig. 2) were performed before and 20 minutes after an acetazolamide challenge to evaluate cerebral hemodynamic reserve (20). These studies showed both low baseline flows and severely diminished cerebral blood flow augmentation. In a study of 68 patients at our institution, Yonas et al. (29) reported a significantly increased risk of stroke associated with these findings. The baseline CT demonstrated a right putamen and caudate infarction that had not been present on CT performed 10 months earlier.

Although the clinical presentation of the patient was most likely caused by a left ICA embolus that occurred either before or at the time of the occlusion of the left ICA, the identification of a high-grade right ICA stenosis and a new right side infarction provided additional evidence that the right ICA lesion was symptomatic. The decision was made to proceed with a right carotid endarterectomy. An intravenous heparin infusion was started 6 hours after angiography and continued throughout surgery, which was initiated 38 hours later.

OPERATIVE PROCEDURE

Median and peroneal nerve somatosensory evoked potential (SEP) monitoring, as well as two electroencephalograph (EEG) leads per hemisphere, was performed after the induction of general anesthesia with nitrous oxide, isoflurane, and fentanyl. The carotid bifurcation was exposed with minimal manipulation of the artery. An additional 5000-U intravenous bolus of heparin was given; 5 minutes later, the superior thyroid artery, the ICA, the common carotid artery, and the external carotid artery were occluded, in that order. An

![FIGURE 1. Preoperative right common carotid artery arteriogram (lateral view) revealed a severe proximal ICA stenosis.](image-url)
management and for the pathophysiology of brain tumors.

Concerning management, it is important to continue observing the "edema" around a meningioma in the first postoperative year; if it enlarges, a biopsy is indicated. This is an unusual event, but it does occur. In a personal series of 300 meningiomas, it occurred once in a 71-year-old woman with an anterior temporal meningioma and temporal lobe "edema" that turned out to be an anaplastic astrocytoma 6 months later.

The pathophrenology of this phenomenon is fascinating. Is this a coincidental occurrence, or is there a growth factor such as platelet-derived growth factor in meningioma cells that leads to a transformation of astrocytes? Several authors have demonstrated that platelet-derived growth factor subunits are expressed in meningiomas, and Westermark et al. have postulated a paracrine mechanism for platelet-derived growth factor within astrocytomas (1, 2). In a paracrine mechanism, there is secretion of growth factor into the medium around the cell inducing the change. Is there such an induced transformation of cells of different origin in this situation? As well as paracrine mechanisms, juxtacrine mechanisms have been recently proposed; they differ from paracrine effects in that the molecule inducing the change remains associated with the cell membrane of the cell of origin (3). Are they operative here? The coexistence of meningiomas and astrocytomas again emphasizes the importance of cell biology in understanding the phenomena we observe in the clinical world.

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In this article by Davis et al., three well-documented cases of patients with concurrent adjacent meningioma and astrocytoma are presented. Although the simultaneous occurrence of different primary intracranial tumors is rare, the authors have discussed the need for the careful interpretation of preoperative radiographs and intraoperative flexibility in terms of the approach to the tumors. It is clear that the lesion causing the neurological symptoms should be removed first and foremost, whether it is a meningioma or an astrocytoma. However, close follow-up and staged surgery may be necessary if the former lesion is thought to be an astrocytic neoplasm. From the biological standpoint of the tumor, the authors have identified the most important aspect of their three cases. That is, whether the tumors of different histopathological origin are so situated because of chance alone or because of an underlying genetic predisposition to forming multiple tumors. In this regard, it would be extremely valuable to study cases such as those presented by the authors by molecular genetic techniques in the future.

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ANNOUNCEMENT

Future Meetings—Congress of Neurological Surgeons

The following are the planned sites and dates for future annual meetings of the Congress of Neurological Surgeons:

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<tr>
<td>1995</td>
<td>San Francisco, CA</td>
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arteriotomy was made in the common carotid artery approximately 2 cm below the bifurcation; this was extended into the ICA until a normal lumen was visualized approximately 4 cm above the bifurcation. Because no alteration of electrical activity was observed, the endarterectomy was initiated without a shunt.

Four minutes after the vascular clamps were placed, the right cortical SEP P30 wave began to show a reduction in amplitude with no latency shift (Fig. 3). This amplitude reduction rapidly progressed to over 50% within 2 minutes. No changes in the contralateral N20 or P30 waves were noted. A Brenner T shunt (CR Bard, Inc., Billerica, MA) was placed to establish flow to the right hemisphere again. Despite the establishment of flow through the shunt, the SEP P30 wave did not recover. The endarterectomy was rapidly completed. The blood pressure of the patient was maintained in a high-normal range as she was given mannitol and albumin and placed into thiopental burst suppression under EEG and SEP monitoring (80% burst suppression and bilateral SEP P30 wave suppression). A single-shot plain film arteriogram obtained by the injection of contrast through the side arm of the shunt revealed an occlusive intraluminal thrombus within the proximal MCA (Fig. 4).

A portable digital angiography unit (OEC-Disons, Salt Lake City, UT) was moved into the operating room. A Tracker-18 high-flow microcatheter (Target Therapeutics, San Jose, CA) was inserted into the original arteriotomy, alongside the shunt, and advanced into the MCA using the arterial roadmap function. The microcatheter was advanced through the proximal MCA thrombus and into the superior division of the MCA, beyond the thrombus. The distal arterial branches were seen to be patent, but with slow runoff (Fig. 5A). Fifty thousand units of urokinase (Abbott Laboratories, North Chicago, IL) was infused into these distal branches. The microcatheter was then slowly withdrawn through the thrombus into the proximal MCA as 100,000 U of urokinase was infused; follow-up arteriography showed the restoration of...
flow to the superior division of the MCA, but the inferior division remained occluded (Fig. 5B). By the use of gentle probing of the guidewire at the MCA bifurcation, the occluded inferior division of the MCA was entered with the microcatheter. An arteriogram showed patent distal branches with slow runoff (Fig. 5C). Three hundred fifty thousand units of urokinase was infused into the thrombus as the microcatheter was slowly withdrawn into the proximal M1 segment. After a total of 500,000 U of urokinase was infused, almost complete thrombolysis was achieved approximately 2.5 hours after the onset of SEP signal changes. A follow-up ICA arteriogram showed only minimal, nonocclusive thrombus within the inferior division of the MCA (Fig. 5D). A few distal MCA branches had slightly slow flow.

With the patient fully anticoagulated, we thought that further infusion of urokinase to attempt absolute thrombolysis would have an excessive risk of hemorrhage in the operative site. The catheter and shunt were removed, and the arteriortetomy was closed. Heparin was continued at 500 U per hour intravenously for 8 hours. During skin closure, approximately 4 hours after the decrease of SEP signals, the SEP responses of the patient recovered to 50% of baseline.

**POSTOPERATIVE COURSE**

A stable xenon-CT cerebral blood flow examination obtained immediately after the patient was taken from the operating room showed hyperemia of the right hemisphere and a small focal flow defect corresponding to the previously identified right basal ganglia infarction (Fig. 2). The patient's bilateral median nerve SEPs were monitored continuously in the intensive care unit. The patient was slow to awaken because of the thiopental. She was extubated on postoperative Day 2, and her SEPs had returned to baseline by that time. Her neurological examination at that time was remarkable only for a new, mild, right upper extremity pronator drift and right side strength of 4/5. She was discharged on POD #8 with a normal neurological examination.

**DISCUSSION**

Intraoperative SEP and EEG monitoring is widely used during carotid endarterectomy to determine tolerance for carotid occlusion (7, 10, 18, 24). Although monitoring requires additional set-up time and expense, there is no risk to the patient and the potential for identifying the need for shunting or a treatable complication justifies the minimal investment.

Ischemic complications occur in up to 7.9% of carotid endarterectomies, with permanent, nonfatal deficits occurring in 0 to 4.2% and death caused by stroke occurring in 0 to 1.2% of cases (1–3, 7, 8, 23, 25, 27, 28). Ischemic complications
may be either embolic or related to poor collateral circulation. Because of possible embolization and arterial injury, routine shunt use to avoid inadequate perfusion is controversial (1–3, 7, 8, 10, 24, 25, 27, 28). Intraoperative monitoring may identify those patients with poor vascular reserve who will require shunt placement, while sparing the remainder any increased risk (24, 25). SEP and EEG can identify individuals in whom a dramatic decrease in cerebral blood flow (<20 ml/100 g per min) occurs with ICA occlusion (4, 24). Continuous intraoperative transcranial Doppler recordings may also reveal large changes in blood flow or the passage of microemboli (12, 13, 19, 22). These studies are also sensitive to a sudden reduction of flow, which can occur with a more distal embolic event, typically within the MCA territory.

In our patient, the abrupt decrease in SEP signal amplitude 4 minutes after carotid occlusion suggested a sudden loss of MCA flow, more consistent with an embolic event than insufficient flow as the result of ICA occlusion, which usually causes more gradual changes during the initial minutes after occlusion. The lack of evidence of improvement after shunt placement also strongly suggested that a major embolic event had occurred.

When monitoring suggests the possibility of intraoperative embolization, emergent arteriography should be performed to confirm the presence and location of emboli. An intraoperative single-shot plain film arteriogram may be readily obtained via the side arm of the shunt, with the shunt maintaining antegrade arterial flow. The maintenance of antegrade flow is important to minimize additional ischemic injury, which could occur if the ICA flow were arrested at any time. If available, intraoperative digital arteriography will provide more information and is more likely to show subtle changes caused by microemboli.

Local intra-arterial fibrinolysis (LIF) was first performed for vertebrobasilar occlusion. It was thought that the dismal outcomes of patients receiving conservative therapy for vertebrobasilar occlusion justified the potential risk of intracranial hemorrhage. In 1983, Zeumer et al. (31) reported the successful treatment by superselective streptokinase infusion of three (60%) of five patients with vertebrobasilar occlusion. Because the risk of intracranial hemorrhage and other complications seemed acceptably low, these encouraging initial results led to the treatment of carotid territory strokes. In 1984, Zeumer et al. (32) reported the successful treatment of two patients with distal ICA occlusions. Five small series describing the results of carotid territory strokes in 98 patients treated with LIF were reported between 1987 and 1993 (5, 6, 17, 26, 30). Selective infusions of fibrinolytic agents (proximal to thrombus) were performed in 46 patients, and superselective infusions (intratherombotic or perithrombotic) were performed in 52 patients. Urokinase was infused into 80 patients, streptokinase was infused into 16, and tissue plasminogen activator was infused into 22. Most patients were treated within 8 hours of ictus.
logical improvement was noted in 53 patients (54%), with good neurological outcome in 40 (41%). Symptomatic hemorrhages occurred in five (5%) patients.

A patient in the operating room, where the immediate recognition of a stroke by intraoperative monitoring is possible, should be an excellent candidate for LIF. In addition, cerebral protection with mannitol (to improve rheology) and thiopental burst suppression, with attention to maintaining or elevating blood pressure, may be readily achieved in the operating room.

The direct intrathrombus infusion of either urokinase or tissue plasminogen activator via a microcatheter is thought to be the optimal method of LIF (15, 16). This may be performed either by a transfemoral approach or, as in this case, a direct carotid approach via the arteriotomy. The availability of intraoperative digital arteriography and roadmapping is essential for this technique. If a neurointerventionalist trained in the use of microcatheters is not available, the infusion of the thrombolytic agent into the ICA may be performed via the shunt in the ICA. Although the infusion of the thrombolytic agent proximal to the thrombus is less effective than direct instillation, it still has had reasonable efficacy (6, 17).

Both urokinase (40,000–1,440,000 IU) (5, 6, 11, 17, 26, 30) and tissue plasminogen activator (20–100 mg) (14, 21, 30) have been used for LIF. Although no large comparison studies have been reported, the available data suggest that urokinase and tissue plasminogen activator have similar efficacies when infused directly into the thrombus (9, 30). Urokinase is, however, less expensive. Typical doses of urokinase to achieve successful thrombolysis are 500,000 to 1,000,000 U infused over 1 to 2 hours. Larger doses may be required with proximal ICA infusion. Peripheral hemorrhage, including hemorrhage into the operative site, is more likely to occur with cumulative doses of more than 10⁶ U (15, 17).

CONCLUSION

This case illustrates the utility of rapid intraoperative endovascular intervention when neurophysiological monitoring detects an embolic event during carotid endarterectomy. Immediate recognition of an MCA embolus allowed successful thrombolysis to be performed with the prevention of severe permanent neurological deficit. The use of a Brenner T shunt provided ready access for intraoperative angiography and thrombolysis while maintaining antegrade blood flow during the procedure. Thrombolytic therapy is an important new addition to the armamentarium of the surgeon when an intraoperative embolic event occurs.

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REFERENCES

The Avoidance of Surgery in the Treatment of Subarachnoid Cutaneous Fistula by the Use of an Epidural Blood Patch: Technical Case Report

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IN THIS REPORT, we present two cases of subarachnoid-cutaneous fistula. In both of these cases, an epidural blood patch, a technique frequently used by anesthetists and radiologists, was successfully used to treat the fistulae, thus avoiding the need for open closure. (Neurosurgery 36:612–614, 1995)

Key words: Cerebrospinal fluid leak, Epidural blood patch, Subarachnoid-cutaneous fistula

The use of an epidural blood patch in anesthesia and radiology has been well established for many years. In anesthesia, an epidural blood patch can be used to treat a cerebrospinal fluid (CSF) leak from the dura after an inadvertent dural puncture for epidural anesthesia or after the insertion of a spinal needle for spinal anesthesia during obstetric care. In radiology, an epidural blood patch is used after a spinal needle has been inserted to introduce contrast for myelography (4, 10). The presenting symptom is usually headache, a result of intracranial hypotension (3, 11, 14). Unusually neurological signs may present resulting from transtentorial herniation (5–7, 13). A variety of techniques have been used to demonstrate the leakage of CSF, including retrograde radio-cruor study (2, 6, 8). One dramatic presentation and confirmation of this CSF leak are those in which the leak occurs at the skin, thus forming a subarachnoid cutaneous fistula. We report two cases that developed CSF leaks after the insertion of intrathecal catheters in the lumbar spine and their successful treatment with an epidural blood patch.

CASE REPORTS

Patient 1

A 23-year-old man who has cerebral palsy and is wheelchair bound had a Cordis Baclofen pump to treat spasticity. The thecal end of the 14G silicone catheter was placed using a Tuohy needle at the L4–L5 intervertebral level. The catheter was tunneled to an incision over the left anterior chest wall, where the Baclofen-filled pump was placed in a subcutaneous pouch. One month after the insertion of this pump, the patient was admitted with the complaint of a 9-cm fluctuant swelling at the site of the pump on the anterior chest wall and a 4-cm swelling over the L4–L5 intervertebral level where the silicone catheter was inserted into the lumbar theca.

The anterior wound was opened, and a cavity filled with CSF around the pump was found. The pump was removed, and gentle traction was applied to the lumbar catheter. By the 2nd postoperative day, the patient had recurrence of the swellings at both sites. It was thought that CSF was continuing to leak from the puncture site in the lumbar theca and was tracking along a fibrous tunnel. To prevent further CSF leakage, an epidural blood patch was performed. Twenty milliliters of the patient’s blood, taken under aseptic conditions, was injected into the L4–L5 epidural space, under local anesthesia, using a 16-gauge Tuohy needle. The patient was kept on strict bed rest overnight. After he was mobilized the next day, the swellings reappeared. A second epidural blood patch was applied with 30 ml of blood injected, using the same technique. The patient was kept on bed rest for an additional 18 hours before being allowed to get up. No further recurrence of these swellings was observed during the remainder of his stay or at the 6-week follow-up.

Patient 2

A 54-year-old woman had a lumbar peritoneal shunt inserted for postsubarachnoid hemorrhage hydrocephalus. Subsequent to insertion, she was experiencing low-pressure headaches. The lumbar peritoneal shunt was removed 4 months after insertion through a dorsal approach through the existing lumbar scar, under general anesthesia. Postoperatively, the patient had continuing low-pressure headaches. Five days after the removal of the lumbar peritoneal shunt, the lumbar wound started to leak CSF between sutures. An epidural blood patch was performed at L4–L5 intervertebral level, with 20 ml of the patient’s blood (taken under aseptic conditions) injected through a 16-gauge Tuohy needle. The patient was on bed rest overnight. After the application of the patch, the leak stopped and the patient described having characteristic high-pressure headaches, which she had been complaining of prior to shunt insertion; it was assumed that the epidural patch had succeeded in stopping the CSF leak. At follow-up, the patient continued to complain of high-pressure headaches and is now awaiting insertion of a ventriculoperitoneal shunt.

DISCUSSION

When a catheter is inserted into the dura, it traverses the layer by producing a hole. This hole, as with any living...
Urokinase Infusion during Endarterectomy


COMMENTS

This case report offers a glimpse into what promises to be an ever-expanding field of the therapeutic fibrinolysis of embolic clots arising from carotid endarterectomies. Hopefully, this report will stimulate both clinical trials and basic research that would lay the foundation for a standardized treatment protocol for embolic strokes.

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This is a case report of an intraoperative embolus that was rapidly detected because of intraoperative evoked potential monitoring. The presence of the embolus was confirmed by an intraoperative arteriogram. Thiopental was used to decrease the metabolism of the brain during this time, and then urokinase was placed into the middle cerebral artery beyond the site of the embolus through a microcatheter. The thrombus was dissolved, and flow was restored with a good clinical outcome. Extreme vigilance and careful monitoring during endarterectomy, then aggressive detection and treatment of complications, such as an intraoperative embolism, will very likely reduce the incidence of complications in this condition. This case report must be read by all surgeons who perform carotid endarterectomy. The clinical management by the authors of this case is exemplary. Their management serves as the standard to which all other surgeons performing this procedure should aspire.

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LEGACY ANSWERS

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RAYMOND VIEUSSENS 1641-1716

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