Successful Use of a 20% Lipid Emulsion to Resuscitate a Patient after a Presumed Bupivacaine-related Cardiac Arrest

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THE infusion of a lipid emulsion has been shown to increase the survival rates of both rats and dogs that have been resuscitated after an overdose of bupivacaine.1–3 We report the first successful use of a 20% lipid infusion to resuscitate a patient from a prolonged cardiac arrest that immediately followed the placement of an interscalene block with bupivacaine and meperidine.

Case Report

The patient was a 58-yr-old, 82-kg, 170-cm male who presented for arthroscopic repair of a torn rotator cuff in the right shoulder. His medical history was significant for coronary artery bypass graft surgery at age 43 yr. He gave a history of angina upon exertion and occasionally at rest. He declined further preoperative cardiac workup but was considered by his cardiologist to be stable on medical therapy. This included nitroglycerine as needed, lisinopril, atenolol isosorbide mononitrate, and clopidogrel and enteric-coated aspirin, both of which had been discontinued 1 week previously. His preoperative electrocardiogram revealed a right bundle-branch block, a left anterior hemiblock, and evidence of an old anterior wall myocardial infarction.

The patient arrived at the operating room holding area, where standard monitors were applied. Blood pressure was 120/80 mmHg, heart rate was 60 beats/min. Supplemental oxygen was delivered at 3 l/min via a nasal cannula. A 20-gauge intravenous catheter was placed in the dorsum of his left hand, through which 2 mg midazolam and 50 µg fentanyl were administered. A 50-mm, 22-gauge Stimuplex® insulated needle was connected to a Stimuplex® DIG nerve stimulator (both B. Braun, Inc., Bethlehem, PA), and the interscalene groove was identified at the level of C6. The brachial plexus was identified by eliciting biceps stimulation (0.1-ms duration, 2 Hz) at 0.34 mA, following which 40 ml local anesthetic solution (20 ml bupivacaine, 0.5%, and 20 ml meperidine, 1.5%) were injected slowly (over approximately 2.5 min) in 5-ml increments with gentle aspiration between doses. The patient was awake and conversant during the performance of the block. At no time was any blood aspirated, nor did he report pain or paresthesias.

Approximately 50 s after removal of the block needle, the patient became incoherent and then developed a tonic–clonic seizure. Oxy-
lipid infusions not only increase the dose of bupivacaine required to produce asystole in rats but also improve survival in rats resuscitated after receiving intravenous bolus doses of bupivacaine. They then applied this observation to dogs, as a model of a species closer in size to humans, and found that lipid infusions during resuscitation from bupivacaine-induced cardiac arrests improved survival. Specifically, 12 dogs were given 10 mg/kg bupivacaine. All of the dogs developed circulatory collapse, and internal cardiac massage was delivered. Six of these dogs received 20% lipid infusion and 6 received saline as a 4-ml/kg bolus given over 2 min, followed by a continuous infusion of 0.5 ml · kg⁻¹ · min⁻¹. All of the dogs treated with the intralipid solution were successfully resuscitated, whereas none of the saline-treated animals survived.² While it would have been preferable to infuse the lipid via a central venous catheter, the initial absence of such access necessitated the use of the peripheral intravenous line. Although recommendations for specific doses of intralipid have been suggested, we chose to administer 100 ml of a 20% lipid emulsion. While this is in excess of the suggested initial bolus of 1 ml/kg,³ we wanted to ensure that an adequate volume of lipid would reach the central circulation during cardiac compressions. Immediately after this administration, 1 mg each of atropine and epinephrine were administered, and sinus rhythm returned, where similar efforts had been unsuccessful before infusion of the lipid emulsion. Our maintenance infusion of 0.5 ml · kg⁻¹ · min⁻¹ was consistent with those used in the canine experiments but likely excessive. The specific recommendations of Weinberg et al. entail the use of a bolus infusion of 20% lipid emulsion, 1 ml/kg over 1 min while continuing chest compressions. This dose could be repeated every 3–5 min to a maximum of 3 ml/kg. At the point of conversion to sinus rhythm, Weinberg⁶ recommends that an infusion of 20% intralipid, at a rate of 0.25 ml · kg⁻¹ · min⁻¹, should be continued until hemodynamic recovery. Fortunately, there was no deleterious effect from this dose of intralipid. Since this event, a 100-ml bag of 20% lipid emulsion has been made immediately available in all areas in which peripheral nerve blocks are performed at our institution.

Levsky and Miller⁷ recently reported cardiovascular collapse from a bupivacaine dose of less than 1.1 mg/kg administered during a lumbar sympathetic ganglion radiofrequency ablation in a patient who previously sustained non-Q-wave myocardial infarction and whose preoperative electrocardiogram showed first-degree atrioventricular block. Although our patient had significant cardiac risk factors, he had been evaluated preoperatively by his cardiologist, who deemed him to be medically optimized to undergo this surgical procedure. His preoperative electrocardiogram revealed both a right bundle-branch block and a left anterior hemiblock. A significant preoperative conduction deficit may predispose to the development of local anesthetic induced cardiac toxicity at lower mg/kg basis than expected, and although no recommendations currently exist, in this group of patients, the use of levo-isomeric local anesthetics may offer some advantage. We have added ropivacaine to our hospital formulary specifically for the use in patients with significant cardiac histories who are undergoing peripheral plexus blockade.

We report the first use of a lipid emulsion as part of the successful resuscitation efforts in a patient who most likely sustained a local anesthetic-induced cardiac arrest. We concur with Picard,⁸ who considers a lipid emulsion, like dantrolene, a “crucial antidote” (which is both inexpensive and has a long shelf life) that should be routinely kept in areas in which peripheral nerve blocks are being performed.

References

A Case of Severe Diffuse Venous Thromboembolism Associated with Aprotinin and Hypothermic Circulatory Arrest in a Cardiac Surgical Patient with Factor V Leiden

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COMPLEX cardiac operations and reoperative cardiac surgery have a documented risk of excessive perioperative bleeding and increased transfusion requirements. To minimize hemorrhagic complications associated with complex surgical procedures, the literature supports the use of prophylactic antifibrinolytic therapy.1,2

Massive intravascular thrombosis in cardiac surgery is a rare but catastrophic occurrence. We previously reported two cases of massive thrombosis in the left ventricle and arterial circulation3 in two patients undergoing thoracic aortic surgery requiring hypothermic circulatory arrest. Both of these patients had received ε-aminocaproic acid therapy. Blood from one of these patients was retained for postmortem testing, revealing a heterozygous factor V Leiden genotype. We now report a separate case of massive thrombosis involving the venous system and right heart in a patient with unsuspected factor V Leiden mutation.

Case Report

A 61-yr-old man presented for aortic valve replacement for severe calcific aortic stenosis with mild aortic insufficiency. He had undergone myocardial revascularization 10 yr previously and had bilateral patent internal mammary artery grafts. The surgical plan was aortic valve replacement through a limited sternotomy using cardiopulmonary bypass. Immediately preoperatively, his vital signs were normal; his coagulation, hematologic, and biochemical profiles were all normal; and he was taking the following medications: ramipril, aspirin, atenolol, hydrochlorothiazide, and amlodipine. He had a history of minor allergic reactions to penicillin and sulfa drugs. Anesthesia and neurovascular blockade were achieved using 100% oxygen, etomidate, midazolam, sufentanil, and vecuronium and maintained using inhalational isoflurane and infusions of midazolam, sufentanil, and vecuronium. Clindamycin, 600 mg, was administered for antibiotic prophylaxis. Monitoring included standard anesthesia monitors, a radial intraarterial line, a pulmonary artery catheter, and a transesophageal echocardiography probe. The transesophageal echocardiography examination confirmed the severe nature of the aortic stenosis with a peak instantaneous transvalvular gradient of 102 mmHg and a calculated aortic valve area of 0.47 cm². The examination results were also notable for diffuse atherosclerosis of the ascending aorta, transverse arch, and descending thoracic aorta. Before skin incision, a test dose of 10,000 kallikrein inhibiting units aprotinin was well tolerated; a 2,000,000-kallikrein inhibiting unit loading dose was infused, followed by an infusion of 500,000 kallikrein inhibiting units per hour. Aprotinin, 2,000,000 kallikrein inhibiting units, was also added to the cardiopulmonary bypass priming solution (full-dose Hammersmith regimen).3

Kaolin-activated clotting time was maintained at greater than 500 s with bovine lung heparin, and heparin concentration was maintained at greater than 2.7 U/ml. The initial dose of heparin was calculated using an in vitro heparin dose–response curve generated using the patient’s own blood. Kaolin-activated clotting time testing was performed at least every 30 min thereafter.

Because of the high risk of disrupting the bilateral internal mammary arterial grafts with sternotomy, femoral arterial and venous cannulation was performed, and cardiopulmonary bypass was instituted before limited median sternotomy. The limited median sternotomy and the initial mediastinal dissection were conducted without difficulty during a 37°-min period of normothermic cardiopulmonary bypass. The patient was weaned from cardiopulmonary bypass for several minutes for relocation of the arterial cannula to a region of the ascending aorta with minimal atherosclerosis under epiaortic ultrasonic guidance. Cardiopulmonary bypass was reinstituted, the aortic cross clamp was placed with epiaortic ultrasonic guidance, cardioplegia was administered, and aortic valve replacement was performed using a Hewlett-Packard St. Jude (St. Paul, MN) prosthesis. After rewarmed and resuscitation of the heart were remarkable for ventricular arrhythmias controlled with amiodarone and ventricular pacing.

The patient was weaned from cardiopulmonary bypass using moderate doses of epinephrine and norepinephrine by continuous infusion. A vasopressor infusion was added. Moderate pulmonary hypertension was treated with inhaled nitric oxide, 40 parts per million. The venous cannula was removed from the right femoral vein, and a slow protamine infusion was begun. Hypotension and worsening pulmonary hypertension required discontinuation of the protamine infusion after administration of 120 mg—approximately 50% of the calculated dose. Large reticular thrombi that nearly filled the inferior vena cava and extended into the right atrium, right ventricle, and pulmonary arteries were noted on transesophageal echocardiography. The patient was reheparinized, aprotinin was discontinued, and cardiopulmonary bypass was reinstituted.

The thrombosis extended inferiorly into the left femoral vein and was evacuated upon replacement of the femoral venous cannula. Using moderately hypothermic perfusion, the right atrium and pulmonary artery were opened, and massive quantities of friable thromboembolic material were removed. After rewarmed, the patient did not wean from cardiopulmonary bypass due to severe biventricular failure. He could not be adequately oxygenated despite a fractional inspired oxygen concentration of 1.0, high levels of positive end-expiratory pressure, and inhaled nitric oxide therapy, presumably because of distal
pulmonary embolization of the friable thromboembolic material. Extra
corporeal membrane oxygenation was instituted, but severe hem-
orrhage from the aortic cannulation site was present. The ascending
aorta was replaced using a Hemashield (Medi-Tech, Natick, MA) graft
during a second period of hypothermic circulatory arrest.

Massive bleeding ensued intraoperatively. The patient developed a
consumptive coagulopathy that was diagnosed by persistent increase
of the Kaolin-activated clotting time to greater than 1,000 s, despite
heparin concentrations less than 2.0 U/ml in the face of continued
heparin administration. The patient received further extracorporeal
membrane oxygenation support and massive transfusion of packed
cells, platelets, fresh frozen plasma, and cryoprecipitate. He died in the
operating room.

The family underwent counseling and testing for hypercoagulable
states. The patient’s two sons both tested positive as heterozygotes for
the Leiden mutation of factor V (FV:R506Q), and their biologic mother
(the patient’s wife) tested negative for this mutation. We conclude that
the patient was a carrier of the factor V Leiden mutation.

Discussion

Reoperative cardiac surgery is associated with a more
complex and prolonged surgical intervention that results in a higher incidence of pathologic bleeding and periop-
erative requirement for allogeneic transfusions. The in-
flammatory, coagulation, and fibrinolytic cascades are activated to a greater degree than in primary cardiac
surgery due to incision through the thromboplastin-rich
mediastinal scar, extensive tissue dissection, and pro-
longed cardiopulmonary bypass duration. To minimize
hemorrhagic complications associated with complex surgical procedures, data support the use of prophylac-
tic antifibrinolytic therapy.5–8 The risks of hypercoagu-
lability or overt thrombosis in association with antifi-
brinolytic therapy are theoretical, at best. The mechan-
isms of activity of these agents are not “proco-
agulant,” but are “antifibrinolytic,” in a population of
patients who are hypocoagulable and have active fibrino-
lysis. However, a small subset of patients experience
thrombosis after cardiopulmonary bypass despite stand-
ard care. We previously reported two cases of com-
plete aortic thrombosis after aortic repair and deep hy-
perthermic circulatory arrest in which e-aminocaproic
acid was used.3 Perimortem blood samples were drawn,
and one patient was found to have a factor V Leiden
gene mutation (FV:R506Q). It seems reasonable to pro-
pose that patients with known predispositions to throm-
botic disease should not receive prophylactic antifibrino-
lytic therapy, even in association with cardiopulmonary
bypass. However, in patients with a heterozygous muta-
tion or a subclinical presentation of such an illness,
preoperative recognition would be impossible to detect
by clinical history and examination.

In operations requiring deep hypothermic circulatory
arrest, antifibrinolytic therapy is frequently used, al-
though its efficacy in this population has not yet been
demonstrated. There are early reports of renal failure and
thrombosis when using antifibrinolytic therapy in
deep hypothermic circulatory arrest, but many of these
reports are retrospective, anecdotal, or both.5–14 Aortic
surgery is itself associated with a risk of renal dysfunc-
tion, and this is not increased by the concomitant use of
aprotinin.15 The retrospective nature of these studies
cannot identify those patients with thrombosis who had
presumed inadequate heparin levels during cardiopul-
monary bypass because the threshold diatomaceous
earth (Celite) kaolin-activated clotting time was main-
tained at only 480 s. Nor can retrospective reporting
identify which patients may have received two different
antifibrinolytic agents in combination.5 The risks of
thrombosis in deep hypothermic circulatory arrest have
prompted some investigators to avoid the use of apro-
tinin. Others recommend using the drug after deep hypo-
thermia and circulatory arrest have been completed.16
Most other clinicians continue to use the drug without a
change in practice.17

High concentrations of aprotinin inhibit many serine
proteases, including kallikrein and protein C.18 Factor V
Leiden mutations, which occur in 3–5% of the popu-
lation, yield a resistance to activated protein C, which
results in impaired signaling for anticoagulation and fi-
brinolysis. Using a clot-based assay, in vitro analyses
evaluating the response to activated protein C in cardiac
surgical patients indicate that aprotinin does induce a
factor V Leiden–like defect in normal plasma. In vitro
analyses from factor V Leiden patients suggest that apro-
tinin further exacerbates this defect in the plasma.19
Corroborating clinical data demonstrate that factor V
Leiden patients have lesser amounts of mediastinal tube
drainage and allogeneic transfusions.20,21 A case report
describes a patient with factor V Leiden who experi-
enced thrombosis of coronary artery revascularization
grafts within a month of surgery.22

In the current case, the patient experienced a throm-
botic event before the overt consumptive coagulopathy
to which he succumbed was diagnosed. The inherited
factor V Leiden mutation and abnormality of the protein C
anticoagulant pathway predisposed this patient to hy-
péroagulability, which became evident when the pro-
tective effects of heparin were reversed with protamine.
After the consumptive coagulopathy ensued, the patient
would certainly have been at high risk for further throm-
botic and bleeding complications. The thrombus in the
inferior vena cava at the same anatomical site occupied
by the venous cannula (from the femoral vein to the
right atrium) is rare and suggests that endothelial integ-
rity disruption provided a nidus for thrombus formation.
Therefore, the possible etiologies for this thrombotic
event include endothelial injury, disseminated intravas-
cular coagulation after hypothermic cardiopulmonary
bypass and deep hypothermic circulatory arrest, factor V
Leiden mutation, and the use of an antifibrinolytic agent.
Elimination of just one of these risk factors might have
avoided this outcome.
Factor V Leiden mutation has been associated with an increased risk for venous thrombosis, although large-scale observational studies have not demonstrated the presence of factor V Leiden as an independent risk factor for the development of arterial atherosclerotic cardiovascular disease. In population-based studies, the elderly seem to have no increased risk of arterial thrombosis due to factor V Leiden, whereas women and, specifically, obstetric patients do have significant thrombotic risks. Although no direct link between factor V Leiden and atherosclerosis has been shown, resistance to activated protein C has been identified as a laboratory marker that is linked to an increased risk of advanced atherosclerosis.

Screening for subclinical procoagulant states such as factor V Leiden abnormality may be considered in patients undergoing deep hypothermic circulatory arrest in which the use of antifibrinolytic therapy is planned. The benefits of reduced blood loss due to pharmacologic therapy need to be carefully weighed against the cost of testing in any population. Because no causative agents or clinical conditions have been definitively identified, the potential risk of intravascular thrombosis is not currently known.

At our institution, we have had four fatal thrombotic events in cardiothoracic surgical patients in a 3-yr span. The common factors include antifibrinolytic therapy (aprotinin or e-aminocaproic acid), a period of hypothermic circulatory arrest, and documented predisposition to hypercoagulable state (factor V Leiden mutation in two cases and antiphospholipid antibody in one). Based on this experience, we have begun screening elective surgical procedures requiring hypothermic circulatory arrest for factor V Leiden mutation at a cost of $175 per patient. We plan to withhold antifibrinolytic therapy in any patient testing positive for factor V Leiden mutation despite the absence of scientific evidence of a causal relation between antifibrinolytic therapy and adverse outcomes, in patients with this genetic trait.

References

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