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Abstract

Background: Treprostinil is a prostacyclin analog used to treat portopulmonary hypertension (PPHTN) and is one of several drugs shown to increase survival, but results in platelet dysfunction. Little is known about the management of patients on treprostinil who present with an acute subdural hematoma (aSDH). We describe such a case and offer our recommendations on management based on our experience and review of the literature.

Case Description: A 63‑year‑old, right‑handed female with a history of PPHTN presented with severe headache and was found to have a large left aSDH with midline shift on imaging. She was admitted to the neurosurgical intensive care unit (ICU) where she developed hemiparesis and subsequently underwent emergent decompression. Postoperatively she improved, but several hours after became obtunded and imaging showed reaccumulation of the aSDH, which required reoperation. At 6 months postoperatively she had only a mild hemiparesis and was being reconsidered for treprostinil therapy as a bridge to liver transplant. Only one paper in the literature thus far has reported a patient with an aSDH managed with treprostinil. The authors achieved adequate intraoperative hemostasis without the use of platelet transfusion and lack of complications intraoperatively.

Conclusion: While concerns related to the risk of bleeding in surgery are valid, intraoperative hemostasis does not appear to be profoundly affected. Surgical intervention should not be delayed and prostanoid therapy discontinued, if possible, postoperatively. Patients should be placed in an intensive care setting with assistance from pulmonary specialists and close monitoring of neurological status and blood pressure.

Key Words: Acute subdural hematoma, portopulmonary hypertension, prostanoid therapy, pulmonary arterial hypertension, treprostinil

INTRODUCTION

The patient with acute subdural hematoma (aSDH) often constitutes a neurosurgical emergency; however, many cases are managed conservatively.² Patients who present with an aSDH less than 1 cm in maximum thickness, less than 5 mm of midline shift and no neurologic deficit...
can be managed without immediate surgery. Those who develop a diminished level of consciousness or other neurologic deficit should receive surgical intervention. It has been estimated that by 2050 aSDH evacuation will be the most common neurosurgical procedure due to shifts in demographics and the number of people taking oral anticoagulants or affected by coagulopathy. More frequently, neurosurgeons are faced with complex decision making due to intracranial hemorrhage, particularly in patients with aSDH. This case report and brief literature review serve as an introduction to portopulmonary hypertension (PPHTN), its proposed pathophysiology, common treatments, and our experience in the neurosurgical treatment of a patient with aSDH and PPHTN.

CASE PRESENTATION

History
A 63-year-old, right-handed female presented with new complaints of shortness of breath, nausea, vomiting, and severe progressive headache over the course of 3 weeks. Her past medical history was complicated with a longstanding history of hepatitis C acquired from a blood transfusion in the 1970s. Unfortunately, she developed end-stage liver disease, cirrhosis, PPHTN, and coagulopathy. Her neurologic examination was grossly intact. A computed tomography (CT) scan of the head demonstrated a 13-mm, left-sided lentiform-shaped hyperdensity suggestive of subdural hematoma with midline shift of 7 mm and minimal transtentorial herniation [Figure 1a]. She had an international normalized ratio (INR) of 1.55 and a platelet level of 47,000/μL. At the time of our consultation, she was undergoing a continuous treprostinil infusion and taking oral sildenafil for PPHTN. The patient was admitted to the intensive care unit (ICU) and medical, hepatology, and pulmonary consultations were sought. Fresh frozen plasma (FFP) and platelets were administered, and she was monitored closely. According to our critical care colleagues, the treprostinil could not be discontinued. Repeat laboratory studies yielded an INR of 1.50 and a platelet level of 90,000/μL. Over the ensuing 10 h, her level of consciousness diminished and she acquired mild right-sided hemiparesis. Most concerning was the development of an enlarged left pupil. Repeat head CT at that time revealed the SDH had increased to a maximum width of 16 mm and midline shift of 9.5 mm [Figure 1b].

Operative findings
She was taken to the operating room for a left frontotemporoparietal craniotomy and evacuation of the subdural clot. A small, bleeding pial artery that had coagulated was the likely source of the hematoma. Treprostinil infusion and sildenafil were continued throughout the surgery. Intraoperatively, hemostasis was obtained in routine fashion without undue burden from excessive bleeding. The brain was nicely pulsatile at the conclusion of surgery, a patch duraplasty loosely sewn, and the bone flap replaced. Tack-up sutures were used, and a subgaleal drain was left behind. Postoperatively she had an INR of 1.45 and a platelet count of 136,000/μL. She awoke immediately and began following commands. Her anisocoria and weakness improved. She became obtunded several hours after the operation and showed signs of hemiatrophy (Glasgow Coma Scale 4). A head CT scan demonstrated a large extra-axial hyperdense fluid collection with a midline shift of 19 mm in the same location as the SDH [Figure 1c]. She was taken emergently to the operating room for reopening of the craniotomy and evacuation of the hematoma. On repeat operation hemostasis was more challenging. The scalp, temporalis muscle, and external dural surface were hemorrhaging diffusely. The hematoma was found in the epidural space, and it was evacuated. There was no significant blood in the subdural space. The coagulopathy was felt to be qualitative, and cryoprecipitate, FFP, and additional platelets were administered in an effort to obtain hemostasis. Various techniques and products including bipolar electrocautery, irrigation, thrombin-soaked Gelfoam® (Pfizer), Gelfoam Powder® (Pfizer), Avitene™ (Davol, Inc.), and Floseal Hemostatic Matrix (Baxter BioSurgery) were utilized to stop the bleeding. At the conclusion of the case the brain was again found to be pulsatile and the decision was made not to replace the bone flap. Subdural and subgaleal drains were placed and the wound was closed using a 2-0 Vicryl™ (Ethicon) on a CT-1 needle and then stapled. In the first hours postoperatively, she began to

![Figure 1: Initial CT findings of left frontoparietal extra-axial hyperdensity and accompanying left-to-right shift of the ventricular system representing an acute SDH and its resultant mass effect (a) with subsequent progression (b). Following craniotomy and bone flap replacement there is recurrence (c). After reoperation for craniectomy, ventricles assume a more midline position (d). 2 months postoperatively, the brain has a sunken appearance and residual postoperative fluid has disappeared (e). Following cranioplasty the brain assumes its normal appearance (f).](http://www.surgicalneurologyint.com/content/8/1/161)
follow commands and move all of her extremities with strength. Her treprostinil and sildenafil were continued.

**Postoperative course**

A postoperative CT scan demonstrated resolution of midline shift and some persistent fluid within the operative bed [Figure 1d]. Her INR measured between 1.4 and 1.7 throughout the remainder of her hospital stay, which lasted just over 1 month. Platelet counts remained between 45,000 and 225,000/µL. Multiple platelet function assays demonstrated dysfunctional platelets while on treprostinil infusion therapy. She was weaned from the ventilator and began to eat. Given her acute medical condition she was no longer a candidate for liver transplant. Over the course of several weeks in the hospital she was weaned from the treprostinil infusion and the tunneled infusion catheter removed. She was transferred to inpatient rehabilitation and eventually was discharged home. Her 2-month postoperative scan showed resolution of fluid in the operative bed [Figure 1e]. She underwent cranioplasty roughly 6 months after the initial surgery [Figure 1f]. At that time, she had stable mild right hemiparesis and was ambulatory with a walker. Currently, she is being considered for rechallenge with treprostinil therapy as a bridge to liver transplant.

**DISCUSSION**

The common pathophysiology in idiopathic pulmonary arterial hypertension (iPAH) and PPHTN results from diminished levels of endogenous eicosanoids produced in pulmonary vascular endothelial cells, which contributes to a high mean pulmonary arterial pressure and increased pulmonary vascular resistance.[7,5] Because of this prostanoid therapies have been studied since the 1980s and approved by the Food and Drug Agency (FDA) for the treatment of PAH in the mid 1990s.[3,7] Epoprostenol has been shown to improve exercise capacity, lower pulmonary artery pressure (PAP), and improve survival as well as reduce all-cause mortality in prospective randomized trials of PAH.[4,5] Subsequent research focused on subcutaneous and intravenous treprostinil — a more stable pharmacologic analog of epoprostenol — that likewise demonstrated improved quality of life and survival (91–72% over 1–4 years).[5] Trials of prostanoid therapy in PPHTN patients have also demonstrated improved hemodynamic and functional responses with treatment.

Prostacyclin analogs function primarily via the prostaglandin receptor on vascular smooth muscle cells.[3,7] This leads to elevated levels of cyclic adenosine monophosphate via activation of intracellular adenylate cyclase which, in turn, induces smooth muscle relaxation. The inhibition of thromboxane-mediated platelet activation and nitric oxide- and endothelin-receptor-mediated vasodilation of pulmonary and systemic vascular endothelium are other notable effects.[6,9]

In the literature abrupt cessation of prostanoid therapy has been associated with rebound systemic and pulmonary hypertension.[7,14,17,39] This results in increased right ventricular afterload and subsequent decreased pump function borne out by echocardiogram demonstrating right heart dysfunction and mitral valve regurgitation. Clinically, patients may manifest a triad of decreased PAP, increased central venous pressures, and profound hypotension.[11] Severe dyspnea and chest discomfort are often seen in the nonintubated patient. Rebound pulmonary hypertension leading to right heart failure usually responds to inotropes, sedation, and resumption of prostanoid therapy. However, other treatments have been shown to be effective including digoxin, inhaled nitric oxide, high frequency ventilation with minimization of positive end-expiratory pressure (PEEP), and treatment with oral (bosentan, ambrisentan) and intravenous (tezostentan) endothelin receptor antagonists (ERAs). High-dose phosphodiesterase-5 (PDE5) inhibitors like sildenafil and angiotensin II-receptor antagonists have all been shown to significantly ameliorate the effects of rebound pulmonary hypertension or right heart failure.[11,6,12,13,20] Additionally, cessation of beta-blocker therapy and avoidance of calcium channel blockers should be encouraged as they decrease inotropicity and diminish preload, respectively.[11,14,17] All patients should have vital signs, electrolytes, and arterial blood gas (if ventilated) closely monitored to prevent hypothermia (increases pulmonary vascular resistance), hypotension (decreases preload), hypercarbia, hypocalcemia, hyperkalemia, and acidosis.[17]

Even if rapid prostanoid cessation is not an option we recommend treating these patients aggressively — meaning limited unnecessary delay in reversal of coagulopathy prior to operative intervention. Safain et al. successfully treated a patient with iPAH on treprostinil surgery and concluded that intraoperative hemostasis was not problematic, a finding we corroborate.

Specific steps can be taken during surgery to minimize the risk of reaccumulation requiring reoperation. The use of a subdural and subgaleal drain with consideration of craniectomy during the first operation may ameliorate the need to return to the OR if bleeding continues after initial surgery. We placed tack-up sutures in the first operation; however, the duraplasty was not closed at all the edges and a potential space remained between the bone and duraplasty that allowed blood to accumulate. It would have been safer to sew a watertight patch duraplasty with enough room for some expansion of the brain. With a duraplasty, aggressive tacking of the dura to the bone flap for obliteration of any potential epidural space would have made it more difficult for
epidural hematoma formation. Placement of both subdural and subgaleal drains may have saved our patient from a repeat operation. During the second operation, we found the use of 2-0 Vicryl™ (Ethicon) on a CT-1 needle helped to ensure deep galeal, hemostatic stitches were placed in a swollen scalp, thus limiting the risk of epidural hematoma. The use of irrigation with a thrombin solution at the time of surgery for SDH has been described in patients with liver cirrhosis and is also an option as the technique resulted in an absolute risk reduction for recurrence of 20%. 18 Blood pressure control and adequate postoperative sedation also play important roles in the prevention of rebleeding.

CONCLUSION

This report now represents the second published case of a surgically treated aSDH in a patient on prostanoid therapy and the first such case in end-stage liver disease and PPHTN. While concerns related to the risk of bleeding in surgery are valid, intraoperative hemostasis does not appear to be profoundly affected in patients taking prostanoid medications. Therefore, these patients should be operated on like any other patient with aSDH requiring surgery. If prostanoid therapy can be discontinued, we recommend careful monitoring in an ICU setting with assistance from neurocritical care and pulmonary specialists. There are a variety of critical care steps and technical nuances that can be employed to maximize patient care in this setting. The authors encourage other physicians to share their experiences with difficult cases so that patients may benefit.

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Conflicts of interest
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REFERENCES


