Successful management of an acute subdural hematoma in a patient dependent on continuous treprostinil infusion therapy

Case report

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Treprostinil is a synthetic analog of prostacyclin, which is used for treatment of pulmonary arterial hypertension (PAH). Continuous subcutaneous administration of treprostinil has been proven in randomized controlled trials to improve quality of life, hemodynamics, and 5-year survival in patients with PAH. The efficacy of treprostinil has been attributed to its vasodilatory and antiplatelet effects. Unfortunately, the efficacy of treprostinil in the treatment of PAH is rapidly reversed upon cessation of the continuous infusion. Furthermore, cases of patients rapidly declining or succumbing to disease progression upon cessation of treprostinil have raised significant concern regarding discontinuation of this medication. To date, there are no reports of emergency craniotomies performed in the setting of continuous subcutaneous infusion of treprostinil. The authors report a case of a patient with PAH, treated with continuous administration of subcutaneous treprostinil as well as warfarin, who developed an acute subdural hematoma (SDH). Despite adequate INR (international normalized ratio) correction, the patient eventually underwent an emergency craniotomy for evacuation of the SDH while on continuous treprostinil administration. This case highlights the neurosurgical dilemma regarding the appropriate management of acute SDHs in patients receiving continuous treprostinil infusion.

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Key Words • treprostinil • Remodulin • subdural hematoma • anticoagulation • prostacyclin • traumatic brain injury

Abbreviations used in this paper: INR = international normalized ratio; PAH = pulmonary arterial hypertension; SDH = subdural hematoma.

Treprostinil is a synthetic tricyclic benzidine analog of prostacyclin. Similar to prostacyclin, it is both a vasodilator and a platelet aggregation inhibitor. Treprostinil’s primary therapeutic use is as an acute pulmonary vasodilator for the treatment of PAH. Before the introduction of prostacyclin therapy in the early 1990s, PAH was a fatal condition with a median life expectancy of 2.5 years.

Prostacyclin analog treatment has significantly improved outcomes in patients with PAH. Treprostinil has clearly demonstrated clinical pulmonary improvement in several studies in patients with PAH. It may also extend survival. Treprostinil has traditionally been administered via a continuous subcutaneous infusion and named Remodulin.

Although helpful as a vasodilator in the treatment of PAH, treprostinil may also cause undesirable side effects by impairing platelet aggregation. Prostacyclins activate platelet adenylate cyclase, raising platelet cAMP (cyclic adenosine monophosphate) levels. This increase leads to diminished fibrinogen binding to platelet surface fibrinogen receptors. As a result, platelet aggregation is inhibited and bleeding risk is increased.

Patients on anticoagulation medications present a clinical challenge during emergency neurosurgical operations. While reversing heparin or warfarin prior to craniotomy has been studied extensively, there is no literature on the management of treprostinil dur-
ing emergency neurosurgical procedures. Our literature search of “treprostinil” and “craniotomy” yielded zero results. While terminating the continuous treprostinil infusion prior to an emergency craniotomy seems intuitive from a surgical perspective, it carries significant risk of pulmonary demise for the patient. Because the medication serves as an acute pulmonary vasodilator, its effect is quickly lost with infusion termination.\(^{19}\) A patient with PAH dependent on treprostinil can experience a rapid pulmonary deterioration when the infusion is stopped. It can be difficult to bring patients back to their previous pulmonary status after any interruption of prostacyclin therapy.\(^ {17}\) In addition, cessation of prostacyclin analog infusion therapy has reportedly been fatal.\(^ {7,12}\)

The present case report illustrates the difficulties posed by treprostinil treatment during emergency craniotomy and calls for improved evidence/guidelines in managing this therapeutic agent during neurosurgical emergencies.

**Case Report**

**History and Examination.** This 77-year-old woman with a history of PAH while receiving continuous subcutaneous treprostinil infusion and warfarin presented to an outside institution after a mechanical fall. A head CT scan at the outside hospital demonstrated a 3-mm acute SDH overlying the right frontoparietal convexity. The patient’s initial INR was 3.0. This was corrected with 10 mg of vitamin K and 2 units of fresh-frozen plasma. Repeat CT at the outside institution 8 hours later demonstrated the thickness of the SDH had increased to 1.2 cm (Fig. 1A). The patient was then transferred to the intensive care unit at Tufts Medical Center. On arrival, her Glasgow Coma Scale score was 15 and she was neurologically intact. The INR at this point was 1.4, and the patient was treated with an additional unit of fresh-frozen plasma, which resulted in an INR of 1.3. The Tufts pulmonary service knew this patient’s PAH status as an outpatient and insisted upon continuing the treprostinil infusion to prevent deterioration in her pulmonary status. One day following her transfer to Tufts, the patient acutely became lethargic and developed a left hemiparesis. She was intubated and brought for an emergency head CT scan, which showed an increase in the thickness of the SDH to 1.8 cm (Fig. 1B), with an increase in midline shift. She was emergently brought to the operating room to undergo surgical evacuation of the clot. The pulmonary consult service continued to believe that there was a high likelihood of pulmonary deterioration if the Remodulin was stopped. Therefore, to support her pulmonary status, the treprostinil infusion was never interrupted.

**Operation and Findings.** A curvilinear incision was made and a large right frontotemporoparietal craniotomy was performed. The dura was opened and the subdural hematoma was removed using a combination of tumor forceps, suction, and irrigation. A pial vessel at the posterior aspect of the frontal lobe was bleeding briskly. This vessel was successfully coagulated with bipolar electrocautery. A subdural drain was placed, the bone flap was reapplied, and closure was performed in the standard fashion. We did not note any difficulty in achieving hemostasis at any point during the operation. There was no additional or unexpected bleeding. No blood replacement products were given.

**Postoperative Course.** The patient was transferred back to the intensive care unit in stable condition, had stable postoperative imaging findings (Fig. 1C), and continued receiving the subcutaneous treprostinil infusion. She had an uncomplicated postoperative course, although her mental status was slow to improve. At her 3-month postoperative visit, she was neurologically intact and back to her baseline mental status. Her 3-month postoperative CT scan showed continued resolution of the SDH (Fig. 1D).

**Discussion**

While its use has been shown to benefit PAH patients in multiple studies,\(^ {2,3,10,13,18}\) continuous treprostinil infusion in patients with intracranial hemorrhage has never been studied. Heparin and warfarin therapy can typically be rapidly reversed prior to an emergency craniotomy with a low likelihood of a deleterious thrombotic event. Interrupting a continuous treprostinil infusion, however, can lead to pulmonary demise that can even be fatal.\(^ {7,12}\) Therefore, continued infusion of the platelet aggregation inhibitor appears necessary even in the setting of an expanding SDH.
Subdural hematoma and continuous treprostinil infusion

In the patient in our present case, SDH expansion was observed both before and after the INR was normalized by fresh-frozen plasma and vitamin K. The SDH expansion from 1.2 cm to 1.8 cm took 32 hours. We theorize that this progression may have been from partial or intermittent thrombosis of this pial vessel that ultimately failed to permanently thrombose secondary to the platelet aggregation inhibition by treprostinil.

When the patient was transferred to our institution, we elected to observe her in the intensive care unit rather than evacuate the SDH. This is a controversial decision, as some reports in the literature support evacuating any SDH greater than 10 mm. Furthermore, many neurosurgeons likely would have evacuated the SDH on the basis of its expansion from 3 mm to 12 mm. We probably would have undertaken surgery based on this hematoma expansion if the situation had not been complicated by the treprostinil infusion. Her dependence on the infusion swayed us away from surgery and toward observation because we were worried about the possibility of uncontrolled intraoperative bleeding. As previously mentioned, we did a search and could not find any literature to guide our decision-making process.

After the patient suffered clinically deterioration and the SDH expanded to 1.8 cm, the patient clearly needed an emergency craniotomy to evacuate the SDH. We considered a platelet transfusion but felt it would not be helpful because the continuous infusion would inhibit all the infused platelets. We were pleasantly surprised to find no difficulty achieving intraoperative hemostasis during any stage of the craniotomy.

It is difficult to base future management decisions on the experience of treating just one patient. However, if we encountered this situation again, we feel we would likely manage the patient differently. In the present case, it appears the platelet aggregation inhibition of the treprostinil may have been enough to lead to SDH expansion, but it was not enough to complicate the craniotomy. Early craniotomy based on the SDH expanding from 3 mm to 12 mm before the patient’s acute neurological deterioration would have probably been in her best interest.

Conclusions

We think this report shows that performing a craniotomy in a patient on treprostinil infusion is not an absolute contraindication and should be considered in the setting of an expanding or life-threatening intracranial hemorrhage. We hope to further study patients admitted to our hospital who have an intracranial hemorrhage and are on treprostinil infusion. We also encourage other centers to report their experiences managing such cases. We clearly need a larger cohort to determine how to best manage these challenging patients.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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