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CASE STUDY

Parathyroidectomy in a patient treated with emicizumab

Helen Hupston

Experience of surgery during prophylaxis with emicizumab is currently limited, but the information available suggests that it is associated with a low risk of complications. This case study describes the surgical management of a patient with haemophilia A and inhibitors, managed with emicizumab prophylaxis, who underwent parathyroidectomy. The plan to manage bleeding risk during surgery involved prophylaxis with oral tranexamic acid 1g six-hourly and recombinant Factor VIIa (rFVIIa), prescribed at the discretion of the consultant haematologist. Preoperatively, rFVIIa 45 mcg/kg (3 mg) was administered immediately, and repeated every three to four hours after surgery depending on clinical presentation. There was no unexpected or excessive bleeding during surgery and no clinical need for additional haemostatic medication. Postoperatively, rFVIIa 3 mg was administered at three and ten hours after the first dose. Two further doses were administered on the morning and evening of the first postoperative day. There was no unexpected or excessive bleeding requiring additional treatment, and satisfactory haemostasis resulted in optimal wound healing. The patient reported no bleeding episodes and also an improved quality of life. This case study demonstrates the successful use of emicizumab in conjunction with rFVIIa.

Keywords: *Emicizumab, surgery, Factor VIIa, tranexamic acid, parathyroidectomy*

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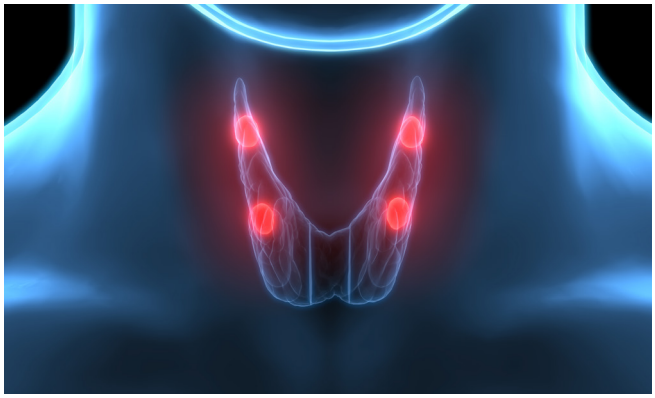

A patient with haemophilia A and inhibitors undergoing parathyroidectomy continued a standard maintenance dose of emicizumab, with bleed risk managed intra- and postoperatively with recombinant Factor VIIa (rFVIIa) and tranexamic acid. Despite the risk of hypercoagulability with the combination of emicizumab and rFVIIa, no postoperative complications were reported.

Emicizumab has greatly improved the outlook for people with haemophilia A who have inhibitors, compared with prophylaxis or on-demand treatment with a bypassing agent. Experience of continuing prophylaxis with emicizumab during surgery is relatively limited [1], but published evidence in people undergoing minor or major surgery is encouraging to date. In one series of seven patients, two developed mild bleeding complications that resolved after a single dose of recombinant Factor VIIa (rFVIIa) [2]. The emicizumab HAVEN clinical trial programme involved 29 procedures in 22 participants; no bypassing agents were prescribed in 20 procedures [3]. Of these, six were associated with postoperative bleeds (including three minor procedures), four of which were managed with a bypassing agent. Of the nine procedures in which a bypassing agent was used prophylactically, one was associated with a bleed. Although there is an increased risk of thrombosis with

concurrent emicizumab and rFVIIa, no cases have been reported [4]. In most cases, a single dose of bypassing agent was effective in stopping bleeding [2,3]; treatment with rFVIIa for 14 days has been reported, though this appears to have been driven by a protocol or bleeding history rather than current clinical need [5,6].

The case study reported here describes the perioperative management of a 53-year-old patient with severe haemophilia A and inhibitors.

CASE PRESENTATION

The patient was admitted for an elective parathyroidectomy (removal of the right superior parathyroid gland) following a diagnosis of hypercalcaemia contributing to calcium phosphate renal stones. A CT scan confirmed the presence of parathyroid adenoma. On admission, the patient's serum calcium level was 2.9 mmol/L; his parathyroid hormone level had been as high as 12.5 pmol/L (normal range 1.6–6.9 pmol/L).

The patient had been infected with HIV by contaminated blood; this was managed with antiretroviral medication. He had also contracted hepatitis C, but this had been cleared with eradication therapy. He had significant haemophilia-related arthropathy resulting in reduced mobility; he was restricted the use of a wheelchair, and required assistance when transferring from this. He had previously been using prophylaxis with Factor VIII Bypassing Activity (FEIBA) at 3,000 IU on alternate days, but had experienced one to two breakthrough bleeds per month. In February 2019, he began treatment with emicizumab, and at the time of admission was taking the standard maintenance dose of 1.5 mg/kg once weekly. Emicizumab had reduced his bleeds more effectively than prophylaxis with bypassing agents (activated prothrombin complex concentrate (aPCC) and rFVIIa).

MANAGEMENT AND OUTCOME

There is limited experience of surgery in patients treated with emicizumab, though in clinical trials patients have undergone surgery without discontinuing prophylaxis. In this case, there was little point in discontinuing emicizumab as its effects can persist for up to six months and there was insufficient time before the procedure. The manufacturer warns that the combination of emicizumab and rFVIIa may cause hypercoagulability, though this is based on experimental data rather than clinical evidence. The dose of rFVIIa should therefore be lower than otherwise recommended. There is also little experience of using systemic antifibrinolytic agents with emicizumab. The consultant haematologists prescribed rFVIIa based on clinical judgement and experience.

The plan to manage bleeding risk during surgery involved prophylaxis with tranexamic acid and rFVIIa. Oral tranexamic acid 1g four times daily was initiated on the day before surgery and continued for seven days postoperatively. rFVIIa 45 mcg/kg (3 mg) was administered immediately preoperatively; this dose was scheduled to be repeated every three to four hours after surgery depending on clinical presentation.

During surgery there was no unexpected or excessive bleeding and no clinical need for additional haemostatic medication; no tests for haemostasis were carried out. Postoperatively, rFVIIa 3 mg was administered at three and ten hours after the first dose. Two further doses were administered on the morning and evening of the first postoperative day. There were no postoperative bleeding complications and no further rFVIIa was administered.

On the second postoperative day, the patient's calcium level was 2.19 mmol/L (normal range 2.20–2.60 mmol/L). He received one dose of iron intravenously, and oral calcium was administered for three days, after which serum levels of thyroid hormone and calcium were within the normal range. The patient reported paraesthesia of the face, left arm and chest.

There was no unexpected bleeding and satisfactory haemostasis resulted in optimal wound healing. This resulted in a shorter hospital stay than might have been the case if the patient's haemophilia had been managed with rFVIIa or aPCC.

Following intensive physiotherapy, the patient is now able to walk short distances independently with no assistance. His level of pain has reduced and the burden of treatment is less. His hypercalcaemia is now rectified and he does not require ongoing treatment. The patient's haemophilia is better managed, he has had no reported bleeding episodes, and administration of treatment has significantly improved. The patient has also reported a more active social life and generally improved quality of life.

The risks associated with surgery and the postoperative experience were discussed with the patient. Before surgery, he expressed concern about the "unknown elements of using emicizumab for surgery, in particular the risk of thrombosis," noting that clinicians had "a more positive outlook than my own." However, he expressed trust that the medical team would involve him in decision-making and address his needs holistically. His experience of treatment with emicizumab had been reassuring and he felt optimistic, saying:

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"Twelve months on, I have been largely bleed- free. I have noticed possibly two to three bleeds in the past 12 months, but they haven't resulted in anything... I have in my small joints experienced occasional pain, but without the usual fluid feel or stiffness of a bleed. They never amount to being a bleed."

He added that treatment with emicizumab had "changed [his] life dramatically."

Postoperatively, the patient expressed satisfaction with his management and was reassured about the risk should he ever need surgery again. He had wanted prophylaxis with rFVIIa in addition to emicizumab as he would have "rather been safe than sorry," but with hindsight acknowledged that it had not been necessary and had increased the risk of thrombosis. Asked if he now felt more confident given the lack of evidence on treatment with emicizumab during surgery, he commented:

"I would still feel better going forward if there was more research available. I could have just been fortunate and, with the expertise of surgeons, had minimal bleeding along with emicizumab and rFVIIa."

DISCUSSION

The purpose of this case study is to provide nurses, physicians and other healthcare professionals with guidance on the management of patients with haemophilia on prophylaxis with emicizumab undergoing similar surgery. This patient's management was a success from the perspectives of the patient, the surgical and medical teams, and other healthcare professionals who were involved, all of whom are now more confident about carrying out surgery in a patient treated with emicizumab.

In the HAVEN trials, perioperative rFVIIa was prescribed at the discretion of the physician; a similar procedure was followed in the case reported here [3]. Consistent with published experience, the patient did not require readmission for any postoperative complications [2]. He experienced minimal blood loss intraoperatively and no bleeding after surgery, and did not require transfusions of blood products. His requirement for rFVIIa was less than anticipated. In contrast with published case reports describing experience with orthopaedic surgery, where rFVIIa was continued for up to 14 days postoperatively [5,6], the patient required no additional treatment after the first postoperative day.

Experience of minor and major surgery in patients using emicizumab prophylaxis is limited. However, our experience has been consistent with published cases, and we encountered minimal bleeding and no postoperative complications. Our findings demonstrate the successful use of emicizumab in conjunction with rFVIIa, and the clinical value of exercising clinical judgement based on experience.

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