Periprocedural Management with Therapeutic Tinzaparin for a Hemodialysis Patient with a Mechanical Heart Valve

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INTRODUCTION

Warfarin remains the mainstay for preventing thrombosis in patients with mechanical heart valves.[1] Inevitably, these patients require screening or interventional procedures at some point, during which the warfarin therapy must be held and a shorter-acting agent (e.g., low-molecular-weight heparin [LMWH] or unfractionated heparin) used to limit the duration of subtherapeutic anticoagulation.[2] Unfractionated heparin has typically been used for patients undergoing hemodialysis (HD). However, unlike the situation for LMWH, which can be administered in an ambulatory setting, administration and monitoring of IV unfractionated heparin require hospitalization. The LMWHs are primarily cleared by the kidney; therefore, the main concern about their use in this setting is the risk of accumulation in patients with creatinine clearance (CrCl) below 30 mL/min.[3] Tinzaparin is the largest LMWH and the least dependent on renal clearance.[3] Data suggest that accumulation does not occur with therapeutic doses of tinzaparin in patients with CrCl above 20 mL/min; hence, utilization of this drug is not recommended when CrCl is below 20 mL/min.[3]

Here, we describe an HD-dependent patient who was taking warfarin after mechanical heart valve replacement and who received therapeutic tinzaparin for periprocedural bridging related to hernia surgery, because there was a need to avoid hospitalization.

CASE REPORT

A 36-year-old man who was undergoing HD and was taking warfarin because of an On-X mechanical aortic valve replacement (Artivion) (with preferred international normalized ratio [INR] target of 2.0–2.5, as specified by the cardiology team) noted a swelling approximately the size of his palm in the right inguinal area.* The swelling caused enough pain to prematurely stop the HD sessions, and laparotomy was required to repair the right inguinal hernia.

*The patient provided verbal consent for publication of this case report.

At the age of 9 years, the patient had been given a diagnosis of congenital polycystic kidney disease, and he had been undergoing nocturnal intermittent HD 3 times weekly (duration 6 hours, blood flow rate 400 mL/min, dialysate flow rate 500 mL/min for all sessions). He had major depressive disorder, type 2 diabetes mellitus, and secondary hyperparathyroidism with parathyroid resection at the age of 33. Dermatological conditions were psoriasis and leukocytoclastic vasculitis. Gastrointestinal conditions were adenomyomatosis of the gallbladder and cholelithiasis. Cardiovascular conditions were dyslipidemia, hypertension, borderline aortic root/ascending aorta dilatation, pacemaker insertion for complete heart block, and *Staphylococcus aureus* infectious endocarditis of the bicuspid aortic valve. The aortic valve was initially replaced with a tissue valve at age 33; however, the patient experienced aneurysmal outpouching below the aortic valve with a fistula to the right atrium, necessitating re-operation 2 months later with implantation of the mechanical valve.

Outpatient medications were calcium carbonate 1000 mg 3 times daily, calcitriol 0.25 µg daily, darbepoetin alfa 150 µg administered intravenously every 14 days, insulin aspart administered subcutaneously twice daily, insulin glargine administered subcutaneously once daily, a general-purpose multivitamin daily, pantoprazole magnesium 40 mg daily, repaglinide 1 mg 3 times daily, warfarin daily as directed by the anticoagulation clinic, and acetylsalicylic acid (ASA) 81 mg daily.

The anticoagulation clinic, which managed the patient's warfarin therapy, was consulted for periprocedural anticoagulation management, in light of a strong preference to avoid hospitalization. The patient's recent laboratory results included body mass index 29.9 (height 182 cm, weight 99 kg), serum creatinine 606 µmol/L, estimated glomerular filtration rate 9 mL/min/1.73 m^2, and calculated CrCl 18 mL/min. Although data support a target INR of 1.5–2.0 for low-risk patients with a mechanical On-X aortic valve who are receiving ASA therapy, a collective decision was

made to target this patient's INR at 2.0–3.0, and preferably between 2.0 and 2.5, given the bleeding risk associated with HD.[3] The weekly warfarin requirement at 3 months before surgery was 35 mg (5 mg daily), with weekly INR results between 1.7 and 2.8. Three weeks before the procedure, the maintenance dose of warfarin was increased to 6 mg one day of the week, with 5 mg on all other days of the week.

The patient's periprocedural anticoagulation with tinzaparin is outlined in Figure 1. As per periprocedural guidelines,[2] ASA was continued throughout periprocedural management. No bleeding or clotting complications were noted during the procedure, and intraoperative blood loss was about 50 mL. Six days later, the INR was 1.8, whereupon the anticoagulation clinic implemented a higher daily warfarin maintenance dose of 6 mg on 2 days of the week, with 5 mg on all other days of the week. Fourteen days after the procedure, the patient's INR was 1.7, whereupon the anticoagulation clinic implemented a further weekly dose increase, to 6 mg on 3 days of the week, with 5 mg on all other days of the week. One week later, his INR was therapeutic, at 2.1. Notably, the postprocedure warfarin dose escalation was conservative, given data supporting a target INR of 1.5–2.0 (with ASA) for patients with an On-X aortic valve.[3]

DISCUSSION

Pharmacokinetic and pharmacodynamic studies of tinzaparin have outlined excellent bioavailability and predictable pharmacodynamic properties, and under ideal circumstances (CrCl > 20 mL/min) monitoring for accumulation of the drug is not needed.[4] The elimination half-life is 3–4 hours, with metabolism involving both the renal and reticuloendothelial systems.[4]

Evidence for the use of LMWH in HD patients requiring periprocedural management of warfarin is limited. A single randomized controlled trial (RCT) investigated anti-Xa levels 20–24 hours after administration of 3 therapeutic doses of either tinzaparin or dalteparin just before HD.[5] Notably, procedures were scheduled to occur the day after HD and were cancelled if repeat anti-Xa levels exceeded 0.2 IU/mL. Mean (standard deviation [SD]) predialysis trough anti-Xa levels suggested accumulation of both tinzaparin (n = 17 patients; 0.37 [SD 0.23] IU/mL) and dalteparin (n = 12 patients; 0.62 [SD 0.41] IU/mL). Other limited evidence for tinzaparin in HD patients is from settings outside of periprocedural management.[6-8] For example, the IRIS substudy, involving 87 patients with renal impairment who received therapeutic doses of tinzaparin (over a mean of 8.7 days), showed no statistically significant difference in accumulation between groups with moderate (CrCl 30–60 mL/min) and severe (CrCl ≤ 30 mL/min) renal impairment.[6] In these 2 groups, mean peak anti-Xa levels were 0.86 (SD 0.34) and 0.87 (SD 0.31), respectively. The Trivet study involved 148 patients, including 7 patients with CrCl below 20 mL/min and 25 HD-dependent patients who received daily therapeutic doses of tinzaparin for 7 days, with samples drawn for monitoring of anti-Xa levels before the third to fifth dose (first measurement) and before the fifth to seventh dose (second measurement).[7] The highest reported mean anti-Xa levels were 0.41 IU/mL and 0.35 IU/mL after the first and second measurements, respectively. Another study recommended against empiric dose adjustment of tinzaparin in those with moderate (which would have entailed a 25% dose reduction) or severe (which would have entailed a 50% dose reduction) renal insufficiency, as defined above, given that subtherapeutic peak anti-Xa levels could introduce the risk of treatment failure.[8]

In light of this evidence and to mitigate LMWH accumulation, we altered our typical periprocedural management strategy.[2] We chose tinzaparin as the anticoagulant because of its favourable pharmacokinetic properties and the need to avoid hospitalization. Weight-based dosing for this patient would have necessitated a total dose of 17 325 IU; using prefilled syringes and taking into account previous clinical experience, we

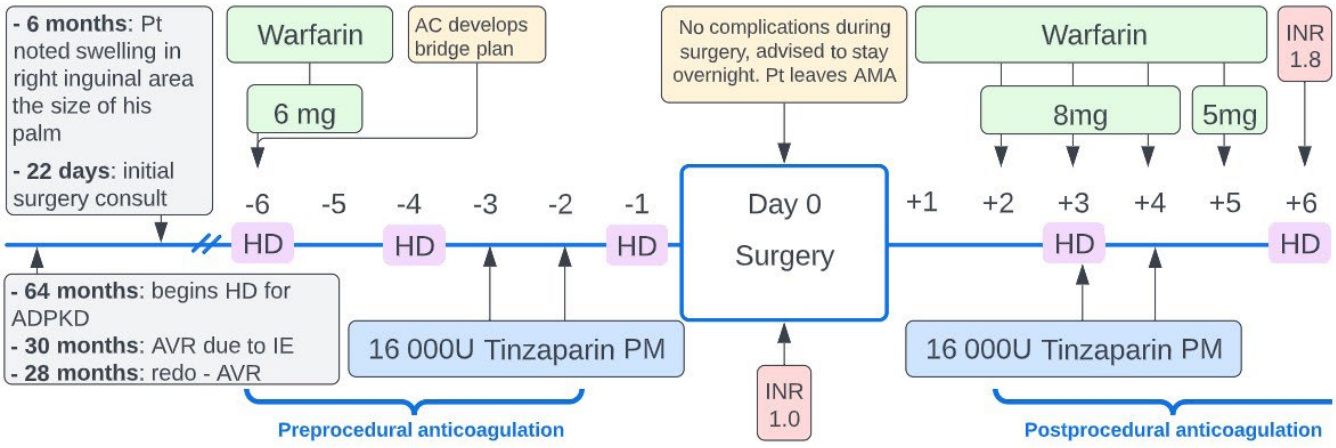

FIGURE 1. Case overview. AC = anticoagulation clinic, ADPKD = autosomal dominant polycystic kidney disease, AMA = against medical advice, AVR = aortic valve replacement, HD = hemodialysis, IE = infectious endocarditis, INR = international normalized ratio, PM = evening.

made the first of 3 empiric alterations by rounding the total dose down to 16 000 IU, instead of up to 18 000 IU. Second, in contrast to the RCT summarized above,[5] we administered 2 instead of 3 doses of tinzaparin before the procedure. Third, the final injection was administered at least 36 hours before the procedure. Given that the authors of the RCT[5] reported accumulation of LMWH, we aimed to limit drug accumulation by empirically reducing our patient's dose, providing fewer injections, and allowing more time between the last injection and the procedure. To monitor these modifications, a sample for measurement of anti-Xa level was to be drawn just before the procedure; however, because of a clinical error, this measurement was not performed.

Our patient had a good outcome, as did most patients in the RCT.[5] Of the 17 patients who received tinzaparin, only 1 experienced a major bleed (after a traumatic arteriovenous fistula puncture). Also in the RCT, prophylactic doses of tinzaparin were administered postoperatively until the INR value was above 2.0, with 63% of patients having undetectable predialysis anti-Xa levels and the remaining having a mean anti-Xa of 0.14 (SD 0.02) IU/mL, which suggested the absence of clinically relevant accumulation.[5] In our case, the surgeon recommended restarting therapeutic anticoagulation 72 hours after the procedure. Given the delayed impact of warfarin on INR, we restarted warfarin 48 hours after the procedure and administered therapeutic doses of tinzaparin for 72 hours after the procedure. To expedite re-establishment of therapeutic INR, our practice is to restart warfarin with 3 bolus doses (1.5 times the maintenance dose), as opposed to resuming maintenance dosing directly.[9] Two days after the second dose of tinzaparin in this case, anti-Xa levels were ordered during HD, but again the samples were not drawn. After 2 doses, the tinzaparin was discontinued because of concerns about potential accumulation with prolonged use, the lack of measurement of anti-Xa level, the increased risk of bleeding from the incision site, and the inherently increased risk of bleeding in HD patients.

Our analysis of this case is limited by the fact that despite being ordered, anti-Xa levels were not measured; this lack of data precludes any quantitative conclusions related to the accumulation of tinzaparin. We note, however, that the surgeon reported a typical amount of blood loss during the procedure, and the patient had no poor outcomes, arguably the most important observation in this case.

CONCLUSION

We have described a modified periprocedural management strategy for a patient undergoing HD, in which we endeavoured to mitigate tinzaparin accumulation by using a lower-dose prefilled syringe, ensuring a limited number of tinzaparin injections (2 before and 2 after the procedure), and lengthening the interval between the last tinzaparin injection and the procedure to at least 36 hours. Despite the lack of measurement of anti-Xa levels, we were reassured by the absence of adverse outcomes, with a typical amount of blood loss during the procedure itself. To our knowledge, no other case reports of this nature are available, and we propose that our case offers a thoughtful example of ambulatory-based periprocedural management for HD. Further investigation is needed before LMWH (specifically tinzaparin) can be recommended in this patient population.

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