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Considerations for epidural anesthesia in a patient with type 1 von Willebrand disease

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Abstract
Epidural anesthesia, combined with general anesthesia, was performed in a patient with type 1 von Willebrand disease (VWD). VWD is a common inherited bleeding disorder, and an anesthetic concern in patients with VWD is susceptibility to postoperative bleeding and epidural or spinal hematoma associated with neuraxial block. After confirming the patient's responsiveness to 1-desamino-8-D-arginine vasopressin (DDAVP) and obtaining informed consent, epidural anesthesia was performed to avoid the use of analgesics that inhibit platelet function. The patient's postoperative course was uneventful. Epidural anesthesia could be one of the choices of treatment for postoperative pain in those patients with type 1 VWD for whom the conditions discussed are fulfilled, to ensure safe usage of this technique.

Key words Bleeding disorder · Desmopressin · Neuraxial block

Introduction

von Willebrand disease (VWD) is an inherited bleeding disorder that is caused by the deficiency or dysfunction of von Willebrand factor (VWF), a protein that mediates the initial adhesion of platelets at sites of vascular injury and that also binds and stabilizes blood clotting factor VIII [1]. VWD is classified into three major categories: partial quantitative deficiency (type 1), qualitative deficiency (type 2), and total deficiency (type 3). Type 2 VWD is divided further into four variants based on phenotype. VWD is a relatively common cause of bleeding, with an estimated prevalence of up to 1% [1], and type 1 VWD affects approximately 75% of symptomatic persons who have VWD [2].

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Despite VWD being a quite common bleeding disorder, very few reports describe the anesthetic management of VWD patients. Because most anesthesiologists consider bleeding disorders to be contraindications for neuraxial block, very little is known regarding the use of neuraxial block in VWD patients.

Here, we report the successful use of epidural anesthesia in the management of a patient with type 1 VWD undergoing an anterior cruciate ligament reconstruction. In our patient the anticipated advantages of epidural anesthesia for relieving postoperative pain included minimizing the requirement for postoperative analgesics with antiplatelet actions and facilitating early rehabilitation.

The conditions required for the safe use of neuraxial blocks in type 1 VWD patients are discussed.

Case report

A 15-year-old woman, weighing 73 kg and 167 cm in height, suffered a recurrent injury of her right anterior cruciate ligament and was scheduled for reconstruction surgery. In a previous surgery 1 year prior to presentation, difficulty in hemostasis during the operation and prolonged postoperative bleeding were noted. Based on laboratory tests, she was diagnosed with type 1 VWD. She had few or no symptoms in daily living, although she had experienced prolonged bleeding after skin injury.

Preoperative laboratory tests showed that her bleeding time was 330 s, and prothrombin time (PT) and activated partial thromboplastin time (APTT) were 12.9 s (PT%, 77.5; PT-INR, 1.09) and 38.2 s (control, 30.0 s), respectively. The activity and antigen levels of VWF were 43% and 48%, respectively. The activities of VWF ristocetin cofactor and factor VIII (FVIII) were 42% and 47%, respectively. The patient's VWF multimer pattern was normal. Plasma levels of fibrino-

gen (201 mg·dl^{-1}) and the platelet count ($24.7 \times 10^3 \cdot \mu l^{-1}$) were within normal limits. Two weeks before the operation, 20 μg (0.28 μg·kg^{-1}) of 1-desamino-8-D-arginine vasopressin (DDAVP) was administered intravenously, as a trial. The activities of VWF and FVIII were elevated to 230% and 185%, respectively, and her bleeding time was shortened to 60 s. On the morning of the surgery, a second dose of DDAVP (16 μg) was administered preoperatively. Consequently, the activities of VWF and FVIII reached 198% and 165%, respectively, just before epidural catheterization. Third and fourth doses of DDAVP (16 μg) were administered on postoperative day (POD) 1 and POD 2, respectively. She had type O, Rh-positive blood. No electrolyte abnormality was observed preoperatively.

In the previous operation, continuous intravenous infusion of fentanyl had been employed first to treat her postoperative pain. However, she suffered from intractable nausea and vomiting due to an adverse action of fentanyl. Eventually, the fentanyl infusion was discontinued and the pain had become exacerbated. She and her parents therefore refused opioid analgesia this time. According to her responsiveness to DDAVP, we carefully explained the risk of epidural hematoma and the benefits of analgesia via epidural catheterization. She and her parents ultimately requested epidural anesthesia. After obtaining informed consent, we planned epidural anesthesia in combination with general anesthesia.

No premedication was given. In the operating room, standard American Society of Anesthesiologists (ASA) monitors were prepared. An epidural catheter (Smiths Medical Japan, Komaki, Japan) was gently inserted through an 18-gauge Tuohy needle into the L3/4 interspace prior to the induction of general anesthesia. No bleeding was observed around the catheter. An aspiration test produced neither blood nor cerebrospinal fluid. General anesthesia was induced with fentanyl (100 μg) and propofol (80 mg), administered intravenously. Rocuronium 50 mg was then administered and her trachea was intubated uneventfully. Her lungs were ventilated mechanically throughout the operation. General anesthesia was maintained with sevoflurane (end-tidal concentration, 1.3%–1.5%) and oxygen/air. An initial dose of 8 ml of 0.375% ropivacaine was injected into the epidural space approximately 20 min before the first incision, and then ropivacaine 0.375% was administered continuously at a rate of 6 ml·h^{-1}. Her heart rate and blood pressure were stable, and her bladder temperature ranged from 36.3°C to 35.9°C. End-tidal carbon dioxide level was maintained at 33–40 mmHg throughout anesthesia. The operation and extubation proceeded uneventfully. Bleeding volume was 40 ml during the operation. Total anesthetic time was 280 min, and the patient felt no pain at emergence. Ropivacaine (0.2%) was administered through the epidural catheter for 48 h postoperatively, at a rate of 5 ml·h^{-1}, and postoperative pain was well controlled. She resumed walking on POD 1. The epidural catheter was removed on POD 2, at which time the activities of VWF and FVIII were 136% and 100%, respectively. Little wound bleeding was observed postoperatively. No unexpected event was observed throughout the patient's postoperative course.

Discussion

Generally, bleeding disorders are contraindications for neuraxial block. Prior to performing neuraxial block, alternative techniques that include continuous intravenous infusion of opioids and peripheral nerve block should be considered for postoperative pain control in patients with bleeding disorders. As mentioned above, in the previous operation, continuous fentanyl infusion had been stopped postoperatively due to its adverse effects, and we did not plan to use it this time. On the other hand, presumably, continuous peripheral nerve blocks can be performed more safely than neuraxial blocks for VWD patients. We had only limited experience in the use of femoral nerve blocks, and could not ensure satisfactory pain relief for our patient after the first operation.

To our knowledge, very few reports have described epidural anesthesia in VWD patients. Three cases of Cesarean section were conducted uneventfully in patients with VWD, using epidural anesthesia [3, 4]. Because VWF increases three- to fivefold over baseline in pregnant women in their final trimester, neuraxial block would be feasible for parturients who have mild VWD, without any treatment. However, bleeding disorder can present after delivery and the epidural catheter should be removed as soon as possible. In this regard, subarachnoid block may be preferable to epidural block for parturients. The greatest advantage of epidural anesthesia for persons with VWD is the avoidance of additional analgesics, such as aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and other platelet-inhibiting drugs. Indeed, our patient felt comfortable without any other drugs during the postoperative period, and began rehabilitation on POD 1. The National Heart Lung and Blood Institute, National Institutes of Health, recommends that for severe bleeding or major surgery, initial target VWF and FVIII activities should be at least 100% and subsequent dosing should maintain levels of more than 50% for at least 7–10 days, and for minor surgery, levels of VWF and FVIII activities of at least 30% and preferably more than 50% should be maintained for 1–5 days [1]. Consequently, we think that the target nadir levels of VWF and FVIII activities

seem to be 50% at insertion and removal of the epidural catheter; however, they should be preferably more than 100 % and maintained at more than 50% during the period of catheter placement.

The decision to provide epidural analgesia should be dependent on the type and severity of VWD, and the patient's responsiveness to DDAVP. DDAVP stimulates the release of VWF from endothelial cells, thus increasing plasma VWF and FVIII two- to fivefold over baseline levels [5–7]. The standard dose of DDAVP is 0.3 $\mu g \cdot kg^{-1}$, given intravenously, which is sufficient to elicit maximal VWF release. A previous study showed that patients with type 1 VWD showed a response rate (defined as a twofold increase in VWF and FVIII activity) of 91% in response to DDAVP administration, whereas patients with type 3 VWD almost never showed a clinically relevant rise in VWF or FVIII activity [8]. In patients with type 2 VWF, proteins that are released by DDAVP do increase in concentration, but show intrinsic molecular dysfunction [1]. Thus, DDAVP is less efficacious in most patients with type 2 VWD. Patients with type 1 VWD are the most promising candidates for DDAVP therapy. DDAVP is contraindicated in patients at very high risk for cardiovascular or cerebrovascular disease and in patients under the age of 2 years [1]. Persons with VWF activity below 10% and FVIII activity below 20% are less likely to demonstrate clinical or laboratory response to DDAVP. However, a DDAVP trial should still be considered in these individuals [1]. An epidural puncture must be avoided if the patient is unresponsive to DDAVP (VWF and FVIII activities <50%).

Of note, evidence shows that the response to DDAVP diminishes with repeated doses, probably due to the depletion of VWF in the storage compartment [5, 9]. In a previous report [10], no significant change in response was observed with the second to fourth doses, as given in our patient. Consequently, the epidural catheter can be placed safely within 3 days after surgery. In our patient the epidural catheter was removed on POD 2 upon confirming that VWF and FVIII activities were more than 100%. Plasma VWF has a half-life of approximately 12 h. After stimulation with DDAVP, released VWF and FVIII circulate with a half-life of approximately 8–10 h in normal individuals [1]. Because peak increases in VWF and FVIII are observed between 30 and 90 min after DDAVP infusion [4–6], the epidural catheter should be removed during this period. The VWF and FVIII activities should be measured just before insertion and withdrawal of the epidural catheter, and daily monitoring seems to be advisable during the period of catheter placement. It is important for anesthesiologists to adequately discuss the timing of DDAVP administration and the timing of removal of the epidural catheter with hematologists.

Replacement therapy, using a VWF concentrate, is indicated for significant bleeding events or major surgery in patients with type 1 VWD in whom either DDAVP is ineffective or contraindicated, as well as for patients who have type 2 and type 3 VWD. If the responsiveness to DDAVP is markedly and unexpectedly attenuated by repeated administration during the period of catheter placement (VWF and FVIII activities <50%), the VWF concentrate should be given to the patient before removal of the epidural catheter. The VWF concentrates currently available are blood products, and a risk of infection remains. Therefore, information concerning blood transfusion should be provided for the patient even if DDAVP is proven effective by the trial.

ABO blood types have a significant effect on plasma VWF concentrations. As in our patient, individuals who have blood type O show VWF concentrations about 25% lower than those with other ABO blood types. The survival of VWF appears to be reduced in individuals with blood type O [11]. When neuraxial block is performed, the plasma concentrations of VWF should be higher in type O patients than in patients with other blood types.

Taken together, our findings suggest that epidural anesthesia may be a useful technique for the patient with VWD under certain conditions: i.e., the patient has type 1 VWD with confirmed responsiveness to DDAVP, the timing of the anesthetic procedures and DDAVP administration is synchronized, and appropriate informed consent is given. Our patient was diagnosed with mild type 1 VWD and showed a good response to DDAVP (more than fivefold increase in VWF activity at the first administration). In this patient, the VWF activity remained at more than 100% throughout the period of epidural catheterization. It is assumed that the incidence of hematoma after neuraxial blocks in patients with type 1 VWD whose VWF and FVIII activities are normalized by DDAVP is almost the same as that in unaffected individuals. However, anesthesiologists must provide a thorough explanation regarding the possibility of epidural or spinal hematomas to the patient and his/her family, because the profession has very little experience in epidural analgesia for VWD patients. In addition, the patient should be kept under careful observation during the postoperative course to monitor for early symptoms of hematoma such as backache and neurological impairment.

Here, we have reported successful anesthetic management with epidural anesthesia in a patient with VWD. In patients with VWD for whom the conditions discussed are fulfilled, epidural anesthesia may be a useful technique.

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