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CASE REPORT

Peri-operative DDAVP Use Leading to Severe Hyponatremia after Total Shoulder Replacement in a Patient with von Willebrand's Disease

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Introduction

The estimated prevalence of von Willebrand's disease (vWD) worldwide has been widely reported as near 1%. This makes vWD the most common inherited bleeding disorder. Although the condition can present with varying degrees of severity, it is usually mild and its presence often goes undiagnosed until significant hemorrhagic stress is placed on the patient, such as during major orthopedic surgical procedures. Given the heightened prevalence of the disorder in the general population, it is very important for all surgeons to be aware of its presentation, treatment options, and the side effects of these treatments in order to effectively reduce hemorrhagic and other medical complications related to vWD. von Willebrand's disease is categorized as a disorder of primary hemostasis involving platelet dysfunction and the inability to produce sufficient plasma concentrations of von Willebrand factor (vWF). It is also associated with qualitative deficits in the structure of vWF which prevents normal function during the clotting cascade. Normal levels and structure of vWF act not only to initiate primary hemostasis but also to stabilize factor VIII. In more clinically significant cases of vWD, recombinant factor VIII protein may be needed in addition to replacement vWF to address all deficiencies in both primary and secondary hemostases [3].

There are three major pharmacologic treatment modalities available to address the clinically significant bleeding risks of vWD. They include the following: vWF/factor VIII replacement (Humate-P*), DDAVP (desmopressin), and antifibrinolytic treatment using estrogen-progesterone hormone therapy [4]. All therapies are associated with their own benefits and possible side effects. DDAVP carries no risk of transmitting infection or immunologic complications, is relatively inexpensive, and should be the preferred prophylactic treatment when possible. The drug acts by increasing endogenous release of vWF from circulating platelets. This maximizes all available circulatory system vWF into the plasma. One of the most significant potential side effects of desmopressin is severe water intoxication and concomitant hyponatremia. This unwanted effect may trigger severe physiologic consequences including seizure and death [6]. The drug acts as a synthetic form of anti-diuretic hormone (ADH), increasing the number of aquaporin channels in the collecting duct of the renal nephron, resulting in heightened free-water absorption, decreased urine output, and potential serum electrolyte dilution. This can become especially true if a patient's fluid intake is not carefully observed. Excess free-water ingestion should be limited while on DDAVP, and IV fluid use meticulously scrutinized to ensure serum electrolyte concentrations remain at physiologic levels. If IV fluids are necessary, normal saline is preferred over lactated ringers due to its higher concentration of sodium per unit volume which should decrease the potential for DDAVP-induced hyponatremia. Despite the increased susceptibility and association with hyponatremia in the vWD pediatric population [4], the phenomenon can also present suddenly in the adult surgical patient as this case study demonstrates.

Case Report

The patient, a 67-year-old female with past medical history of vWD, presented with a lengthy 2-year history of disabling left shoulder pain refractory to conservative treatment modalities including activity modification, physical therapy, anti-inflammatory treatments, and intra-articular steroid

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injections. Diagnostic imaging with plain radiographs revealed bone-on-bone contact consistent with end-stage osteoarthritis of the left shoulder. The patient was considered a candidate for total shoulder arthroplasty.

The patient had a well-documented history of clinically significant bleeding following operative procedures secondary to her von Willebrand's disease. This included a tonsillectomy in 1955, childbirth in 1965 and 1975, and a hysterectomy in 1985, all of which were associated with significant but not life-threatening bleeding. Our patient had no past history of spontaneous bleeds unassociated with surgery. She was not actually diagnosed with vWD until 1997, following an elective cholecystectomy procedure. Following her correct diagnosis with vWD, she did undergo a major spine surgery in 2012, which included multilevel hardware insertion and segmental vertebral fusions. For this surgery, she was prophylactically treated with DDAVP perioperatively and reported no significant problems with excessive bleeding post-operatively. Our patient never had major bleeds that required specific replacement of factor VIII or vWF for adequate hemostasis.

Preoperative shoulder exam showed severe pain with any shoulder movement. Range of motion was limited in forward flexion, adduction, abduction, and internal/external rotation. Muscle weakness was marked with rotator cuff and deltoid testing. Neurovascular status and exam were intact. Following approval from her cardiologist and hematologist, our patient was scheduled to undergo total shoulder arthroplasty in June 2014. Due to the potential bleeding risk posed by her vWD and her previous successful treatment with DDAVP after her spine operation, the patient received 0.5 mcg/kg DDAVP 30 min prior to surgery. The dosing strategy was to repeat 0.5 mcg/kg DDAVP every 8 h for the initial 48 h following surgery.

Management and Outcome: Left total shoulder arthroplasty was completed without clinically significant bleeding or complication following preoperative DDAVP treatment. The procedure was performed under general anesthesia by the senior author. Severe osteoarthritic change and bone-on-bone grinding were noted as well as partial rotator cuff tear and biceps tendon tenosynovitis. Total shoulder replacement using standard implants and a biceps tenodesis was performed. Trial and final reductions showed stable and full range of motion. Blood loss during the procedure was 75 mL, and at no time was bleeding clinically worrisome or excessive. Post-operative imaging revealed satisfactory alignment and position of both the cemented glenoid component and the cementless humeral implant. (Fig. 1)

The initial 24-h post-operative period was uneventful. The patient's baseline sodium was noted to be 139 mmol/L preoperatively in a specimen drawn 1 week before the operation. It should be noted that this patient was on chronic thiazide diuretic therapy for hypertension. Post-operative serum sodium drawn on the morning after surgery was noted as 125 mmol/L. The patient was asymptomatic at this time, but free-water ingestion was restricted to 1 L in 24 h. On the morning of post-op day 2, the patient was being prepared for discharge when she began vomiting. Serum sodium on post-op day 2 was 120 mmol/L. Symptomatic hyponatremia was suspected, and the hospital-based critical care team was consulted. Later in the afternoon of post-op day number 2, repeat serum sodium was found to be 117 mmol/L and the patient was transferred to the ICU for medical management. Her hyponatremia was hypothesized to be acute on chronic in nature, reflecting both her routine thiazide diuretic usage for hypertension and the addition of peri-operative DDAVP for bleeding prophylaxis. On the afternoon of post-op day 2, the DDAVP was discontinued and a complete restriction of oral water was instituted. Her symptomatic hyponatremia was initially supported with continuous infusion of isotonic normal saline. That afternoon, the patient was producing dilute urine and it was hoped that she was beginning to spontaneously correct the hyponatremia. She remained in the ICU for continued observation with seizure precautions.

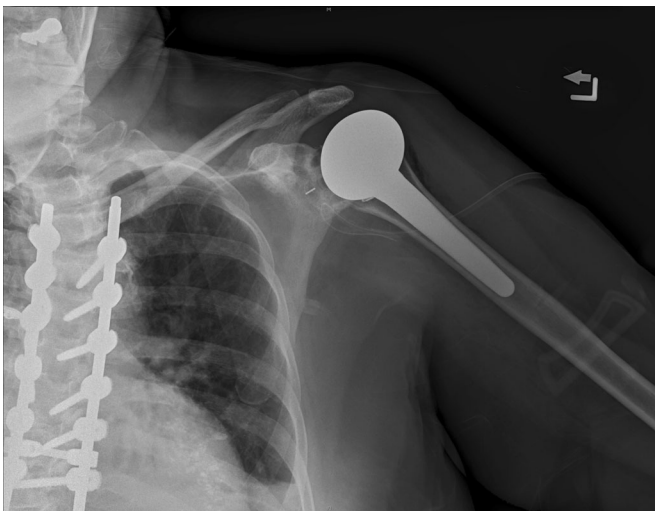

Fig. 1. This AP radiograph of the left shoulder documents satisfactory alignment and position of both the cemented glenoid component and the cementless humeral implant.

The following morning on post-op day 3, morning labs indicated a serum sodium level of 114 mmol/L with a urine osmolality of 599 mOsm/kg. Treatment now included a 3% hypertonic saline intravenous drip, and nephrology consultation was obtained. Despite the worsening hyponatremia, the patient felt well, remained alert, and had no obvious alternations in mental status. Serial serum sodium levels and urine osmolalities were tracked in the ICU, and nephrology concluded the DDAVP effect would soon wear off leading to normalization of serum sodium. From an orthopedic standpoint, the patient was progressing routinely well without any complications. She had satisfactory pain relief and had good range of motion with occupational therapy in the shoulder and elbow. Repeat serum sodium values showed improvement. The patient was discharged on post-op day 5 with a serum sodium in the normal range and the presence of dilute urine indicating improved renal function. It was concluded that the hyponatremia side effects of DDAVP had resolved. Clinically, the patient continued to do well after shoulder replacement and had substantial gains in strength, motion, and improvement in quality of life.

Discussion

Given the heightened prevalence of von Willebrand's disease in the general population of approximately 1%, it is important that all surgeons be familiar with its presentation and understand the risks of post-operative bleeding in untreated individuals. Surgeons must also be familiar with the prophylactic treatments to prevent bleeding and the potential side effects of these treatments.

This case highlights the need for more information on this common disorder and the potential side effects of its prophylactic treatment in surgical patients. Although our patient made an excellent clinical recovery, serious complications related to unrecognized hyponatremia could occur in other patients treated with DDAVP. More severe vWD disease patients may require direct factor VIII or vWF replacement for bleeding prophylaxis. Recently, the senior author has treated a hip replacement patient with vWD using antihemophilic factor/von Willebrand factor complex (Humate-P). This form of treatment is associated with other possible side effects including immunologic or hypersensitivity reactions, thrombotic reactions, and transmission of blood-borne pathogens [7]. The hip patient did not bleed excessively post-operatively but developed confusion and mental status changes, even with the use of a regional anesthetic. His confusion disappeared soon after stopping the Humate-P treatments, leading the senior author to reconsider the relative benefits of prophylaxis with DDAVP.

On review, there are other factors which may have predisposed our case report patient to DDAVP-induced hyponatremia. One published article recommends the DDAVP dose start at 0.3 mcg/kg [2] as opposed to the 0.5 mcg/kg administered in the peri-operative period of this case. DDAVP has also been shown to be associated with the phenomenon of tachyphylaxis, in which repeated doses of the drug become less effective thus meriting an increased dose if the concern for blood loss is great [4]. The potential for tachyphylaxis must also be taken into consideration when prolonged usage of the drug is indicated, such as after major orthopedic joint replacement cases. Of interest, the patient recalled in retrospect that her previous spine surgeon also communicated to her that he had concerns about lowered serum sodium levels after surgery that utilized the same dose of DDAVP. Another factor which must be evaluated in all patients receiving intravenous DDAVP is the pharmacokinetics of the drug related to renal function The creatinine of the patient in this case was within normal range (1.16) a week prior to surgery. Her estimated GFR preoperatively was 48. This baseline level of renal concentrating ability may have been secondary to mild hypertensive nephropathy. Agerso et al. noted that moderate-to-severe renal impairment may significantly prolong the half-life of DDAVP from 3.7 h in patients with normal renal function to 10 h in patients with severe renal impairment [1]. Knowledge of this becomes especially important when continuous or repeated DDAVP dosing is used. Repeated dosing is the standard practice for patients with significant vWD undergoing major surgical procedures. Standard q8-h dosing over an extended period may lead to higher than expected serum concentrations of DDAVP if there is altered renal function, thus further increasing the risk for hyponatremia.

Not to be overlooked are the drug-drug interactions that may have played a role in this patient's hyponatremia. One such interaction is the potentiation of DDAVP's water intoxicating effects in the presence of nonsteroidal anti-inflammatory drugs (NSAIDs) [8]. This is an important finding to highlight as NSAIDs are used commonly in the peri-operative setting of orthopedic procedures. While the mechanism behind this interaction is still largely unknown, one theory based on findings in animal models postulates that the anti-prostaglandin effects of NSAIDs increases the fraction of aquaporin channels in the plasma membrane as opposed to storage vesicles within the tubular cell. This would augment the water absorbing capacity of the distal nephron increasing the likelihood of developing water intoxication and hyponatremia [8]. The patient in this case had been taking celecoxib 200 mg daily post-operatively, and her arthritis pain had been partially controlled with naproxen 500 mg twice daily prior to surgery. At discharge, all NSAIDs were discontinued to mitigate bleeding risk.

A final factor which may have played a role in this case was the patient's chronic use of a thiazide diuretic for hypertension. Thiazide diuretics are known to cause modest to severe drops in serum sodium concentrations [5]. Preoperative lab draws in our patient noted a serum sodium baseline of 139. This would suggest that her diuretic usage did not play a significant role in her development of hyponatremia. Nevertheless, extra caution is warranted in regard to the risk of hyponatremia in patients taking DDAVP while on concurrent thiazide diuretics. In fact, unless deemed necessary for other reasons, simple blood pressure control in patients on repeated DDAVP dosing should be obtained via means other than diuretics. This would allow DDAVP's effect on serum and urine electrolyte levels to be more accurately interpreted.

In conclusion, von Willebrand's Disease is a common inherited disorder predisposing those affected to clinically significant bleeding especially after surgical procedures. It is vital that surgeons be aware of this condition and the side effects of prophylactic treatments available to prevent bleeding. Careful consideration as to which treatment to utilize is advisable. Hematology and or renal consultation may be prudent before surgery. Careful attention to historical information from the patient concerning prior bleeding episodes may indicate a heightened risk of bleeding and adverse effects from prior treatments of their vWD.

Disclosures

Conflict of Interest: James S. MacKenzie, BS and Stuart C. Kozinn, MD have declared that they have no conflict of interest.

Human/Animal Rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

Informed Consent: Informed consent was waived from all patients for being included in the study.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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