Paradoxal Diuresis After Vasopressin Administration To Hemodialysis Patients With Bleeding

Selma Ajanović¹, Halima Resić¹, Amela Bećiragić¹, Aida Ćorić¹, Nejra Prohić¹, Fahrudin Mašnić¹,
Lejla Burazerović²

¹Clinic for Haemodialysis, University Clinical Centre Sarajevo, Bosnia and Herzegovina
²Clinic for Hematology, University Clinical Centre Sarajevo, Bosnia and Herzegovina

Abstract

Uremic bleeding is a well-recognized complication in patients with renal failure. The most common agent used in uremic patients with active bleeding is desmopressin. Desmopressin doses for uremic bleeding are approximately 10-fold higher than doses used for diabetes insipidus. We use desmopressin in oral form in treatment of haematoma in the right upper thigh in haemodialysis patients. Residual urine output amounted to 100-200 ml / 24 hours during the past couple of years. The second day after the introduction of desmopressin to the treatment, patient complained about suprapubic tension, clinically verified as painful distension. The urinary catheter was placed and the patient received 900 ml of clear liquid. The patient continued to wet diuresis in the following days, between 600-800 ml per day. Scientific explanation for this phenomenon is not found.

This question can only be answered by a prospective trial of vasopressin in dialysis patients.

Introduction

Uremic bleeding is a well-recognized complication in patients with renal failure [1]. It was described by Reisman almost 100 years ago, in two patients with renal failure resulted from Bright’s disease (the term is no longer used, but it is described as acute or chronicnephritis) who experienced severe and generalized bleeding [2]. It has been known for many decades that uremic bleeding and platelet dysfunction put patients at increased risk of general bleeding. The exact mechanism of risk increase remains largely unknown, but seems to be multifactorial.

Important factors contributing to uremic bleeding are dysfunctional vWF, increased levels of cyclic AMP (cAMP), increased levels of cyclic GMP (cGMP), uremic toxins and anaemia [3, 4, 5 , 6] . Patients with uremic bleeding typically present ecchymosis, purpura, epistaxis and bleeding from venepuncture sites. These patients can also present gastrointestinal or intracranial bleeding [7, 8]. Treatments for uremic bleeding target the various factors that seem to have a role in platelet dysfunction.

The most common agent used in uremic patients with active bleeding is desmopressin (1- deamino-8-D-arginine vasopressin [DDAVP]) [10, 11 and 12].

Case Presentation

The patient, aged 28, is on haemodialysis since July 2007. Kidney disease is unknown. As a young girl, she had frequent urinary infections. When she was 6, she was wounded by shrapnel in the abdomen and right thigh, and by a bullet in her right shoulder. From the very start of dialysis treatment, construction of AVF was repeatedly attempted, but it was not successful. Over the years, a vascular access was used a central venous catheter. In 2010, she
received living kidney transplantation (donor father). On the second postoperative day, there was an acute humoral rejection. In the postoperative period comes to an extensive gastrointestinal bleeding and multiple organ dysfunction, and the patient was on artificial ventilation for a month. We performed the graft nephrectomy. Residual urine output amounted to 100-200 ml / 24 hours over the past couple of years. The patient remained stable until December 2015, when the situation was complicated by the appearance of pain and swelling in the right upper thigh. CT verifies voluminous musculature of the rear lodge of the right leg as a whole, in comparison with the left side, and small fluid collections that have extended the muscle fibres (hematoma). Hematoma was punctured and 50 ml of old blood removed. The patient was stable, mobile, without falling into the haematological data. In February 2016, swelling and pain in the right thigh again occurred. The patient was hospitalized in the Department of Orthopaedics and Traumatology of the Clinical Centre in Sarajevo. Urgent ultrasound was performed and the CTA verified a large hematoma in the same or similar location as before, located in the adductor Magnus semimembranosus and semitendinosus in the right leg, polycyclic in form; the dimension of the transverse cross section was about 83X55 mm, and length about 160 mm. The main blood vessels were in order. In the delayed post-contrast stage, extravasation of contrast central and peripheral trace forms was recorded.

In laboratory findings:

WBC 9.0, RBC 2.34 , HGB 7.6 g / dL, HCT 21.4%, PLT 186 prothrombin time 0.72% (0.64-1.20), prothrombin time PT 1.17 (INR 0.90 - 1.40), APTT 51.85 sec (22-38), APTT ratio 1.67 (0.84-1.46) TT thrombin time 16.9 sec (14.0 to 24.0), activity of fibrinogen 4.1 g / l (1.5 - 4.0) , ECLT> 2 h (> 2), factor VIII 0.52 (0.50 1.80), adhesion PLT 7.7 (> 7.5) aggregation and adhesion PLT 630 (> 900).

The patient was supported by doses of concentrated filtered red cells and fresh frozen plasma doses, and was treated with antibiotic Clindamycin 600 mg every 6 hours.

The emergency radiologist performed punctuation of the hematoma and 400 ml of fresh blood was extracted.

In the evening, due to the acute compartment syndrome, the patient was surgically treated, and the ligature of artery femoris profunde was performed.

Next day, the patient suffered less pain, leg circumference was smaller and there was no further decline in haematological data.

Control CTA showed the state after ligation: APF right with visible air collection of postoperative nature. APF directly distal to the ligation was filled with contrast and well opacified, including its branches. No safe CTA signs of extravasation of HP from blood vessels were recorded. There were signs of cellulitis with a distinct progression in the size of the hematoma compared to the previous CT, with propagation to the distal third of the back of the leg, to the right.

Regular haemodialysis treatments were carried out at regular times, 3 times per week in duration of 4 hours, with controlled ultrafiltration, without anticoagulation and with lock 4% citrate. After each dialysis, beta erythropoietin was administered at a dose of 4000 IU iv.

During the third day of hospitalization, the patient again felt strong pain in the upper thigh, with an increase in the scope of the same; pain and swelling of the left upper arm and left breast. The ultrasound performed in the left axilla verified polycyclic liquid collection, located next to the artery, of 54x25 in diameter. In the superolateral caudal quadrant of the breast there was a hematoma of liquid and sediment component, of about 44 x 17 mm in diameter.

Thigh echo showed a slight regression in the size of the hematoma. The size of the liquid component of the anechoic was about 8 x 30 x 3 cm.

Since coagulation factor inhibitors were suspected, during the fourth day of hospitalization, we acted with plasmapheresis plasma volume of 2500 ml FFP. In the afternoon, there was a further fall in haematological data: RBC 2.2, HBG 6.8 g/dL, HCT 0.20, PLT 222, WBC 10.6.
Since we did not have desmopressin in parenteral form, we decided to parenterally administer tranexamic acid in a dose of 10 mg/kg, and the same dose was repeated after 48 hours.

Due to the severity of the general condition and the further decline in haematological data, the next day we introduced an oral preparation dezmopresina Minirin, tablets, 3 x 2 mg (the fifth day of hospitalization), although oral administration of desmopressin is not included in the guidelines for treatment of uremic bleeding. The second day after the introduction of desmopressin, the patient complained of suprapubic tension, clinically verified as painful distension. After placement of the urinary catheter, the patient received 900 ml of clear liquid. Since the patient was practically anuric over the last few years, analysis of the resulting content was performed, which showed that it was urine. Analysis of the content: yellow, pH 7.0, the relative density of 1.010, 1 g protein/L, glucose negative, negative ketones, bilirubin negative, negative nitrites; the sediment showed 6-8 leukocytes, erythrocytes 20-25, epithelial cells plates and some bacteria. Creatinine in the sample amounted to 1042 umol/L, BUN 24.0 mmol/L, calcium 1.57 mmol/L.

During the seventh day of hospitalization, the patient was stable, with slight pain in the upper leg and hand. Ultrasound showed no further progression of the hematoma and the hemogram was stable. Laboratory findings verified thrombocytosis, with a slight increase in LDH. A small dose of LMWH Enoxaparin 20 mg was administered before haemodialysis treatment, while desmopressin was excluded. Desmopressin therapy was orally administered over three days, at daily a dose of 3 x 2 mg.

Laboratory findings-WBC 7.42, RBC 2.72, HGB 8.72 g/dL, haematocrit 25.7%, Tr 409, Na 137, 6.8 K, Ca 2.18, CI 105, BUN 20.9 mmol/L, creatinine 1007 umol/L, LDH 295, INR 0.99, aPTT 32.7.

The patient continued to wet diuresis in the following days, between 600-800 ml per day. After one month, the patients still has diuresis, between 300 and 400 ml per day.

**Discussion**

Desmopressin (DDAVP) is a synthetic replacement of vasopressin, the hormone that reduces urine production. It may be taken nasally, intravenously or as an oral or sublingual tablet. There are certain benefits of desmopressin in adults who have problems with night time urination and in treatment of central diabetes insipidus (DI). It is used to replace endogenous antidiuretic hormone (ADH) missing in the central nervous system type of this disorder (decreased production of ADH from the posterior pituitary). The most common agent used in uremic patients with active bleeding is desmopressin (1-deamino-8-Darginine vasopressin [DDAVP]). Desmopressin doses for uremic bleeding are approximately 10-fold higher than doses used for diabetes insipidus, and range from 0.3 ug/kg to 0.4 ug/kg administered intravenously or subcutaneously as a single injection. Do not administer desmopressin for more than three days [10, 11]. To our knowledge, no trial ever evaluated oral DDAVP in uremic bleeding. Oral administration of DDAVP might be as beneficial as intravenous therapy, but there are currently no data to support this [13, 14].

Although not in accordance with treatment guidelines, due to lack of parenteral medication, we orally administered desmopressin to our patient, in total duration of three days.

After examining the available literature, we did not find a case in which urine output in haemodialysis patients was increased after treatment with desmopressin. The study Meinders and associates from 1975 shows a paradoxical increase in diuresis in patients with diabetes insipidus after using DDAVP. After an immediate and transient antiureasis, a single intravenous bolus injection of lysine vasopressin was given during treatment with chlorpropamide; chlorpropamide with a continuous intravenous infusion of lysine vasopressin, carbamazepine or clofibrate, resulted in increased water diuresis for 12-24 h or longer. It is suggested that the antidiuretic action of chlorpropamide, carbamazepine and clofibrate is localized at the receptor site for ADH in the distal renal tubular cell [15]. In a large multicentre study of 778 patients who had septic shock,
Gordon et al. found that vasopressin compared to norepinephrine was associated with a trend to reduced creatinine over time, reduced progression to renal failure/loss and reduced mortality. As a result, fewer patients treated with vasopressin in comparison with norepinephrine required renal replacement therapy. These results are consistent with previous small studies, showing that vasopressin compared to norepinephrine increased urine output and creatinine clearance [16]. Study Holmes CL at all show that vasopressin markedly and significantly increased MAP, did not change PAP, markedly increased urine output and decreased pressor dosage significantly in this retrospective case series of patients receiving vasopressin for severe septic shock [17]. Urine output significantly increased at 4 h, but this effect was not sustained over 24 and 48 h. The paradoxical diuretic effect of vasopressin has been observed in patients with Hepatorenal syndrome and congestive heart failure [18], yet the mechanisms remain unexplained.

There are three possible explanations of vasopressin’s diuretic effect. Firstly, the renal vasculature seems to be relatively resistant to the vasoconstrictor effects of vasopressin [19]. At low doses, there is some renal efferent arteriolar vasoconstriction, relatively sparing the afferent renal arterioles, which therefore increases renal perfusion pressure [20]. A vasodilatory effect of vasopressin on the renal vasculature is present at low doses (0.02 U/mil), which can be blocked by L-NAME [21], suggesting that the effect is mediated by nitric oxide. Secondly, oxytocin has a natriuretic and diuretic effect, due to inhibition of sodium reabsorption at the proximal and distal tubules [22]. Vasopressin may be directly activating oxytocin receptors, causing natriuresis and diuresis. Thirdly, vasopressin releases atrial natriuretic peptide [23], which may be an indirect mechanism of its diuretic effect.

To conclude, in this case, vasopressin for uremic bleeding and increased urine output in previously oliguric patients on haemodialysis was administered. Safe scientific explanation of this phenomenon was not found. This question can only be answered by a prospective trial of vasopressin in dialysis patients.

References


