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Case report

Paradoxal Diuresis after Vasopressin Administration in Hemodialysis Patient with Bleeding

Selma Ajanovic[1], Halima Resic[1], Amela Beciragic[1], Aida Coric[1], Nejra Prohic[1], Fahrudin Masnic[1] and Lejla Burazerovic[2]

[1]Clinic for Haemodialysis, [2]Clinic 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 fin diabetes insipidus. Oral form of desmopressin was used for treatment of haematoma in the right upper thigh in hemodialysis patient. Residual urine output was 100-200 ml/24 hours in the past couple of years. The second day after desmopressin administration, patient experienced suprapubic painful distension. Urinary catheter was placed and 900 ml of clear liquid was collected?.
In the following days, duiresis continued between 600-800 ml per day. Scientific explanation for this phenomenon is not found. This question can be answered by a prospective trial of the effect of vasopressin in dialysis patients.

Keywords: uremic bleeding, desmopressin, diuresis

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 caused by Bright's disease (the term is no longer used, but it is described as acute or chronic nephritis) who experienced severe and generalized bleeding [2]. It has been known for many decades that uremic bleeding and platelet dysfunction increases the risk of general bleeding in these patients. The exact mechanism for this emains largely unknown, aldo it seems to be multifactorial.
Important factors contributing to uremic bleeding are dysfunctional vonWillebrand factor (vWF), increased levels of cyclic AMP (cAMP), increased levels of cyclic GMP (cGMP), uremic toxins and anaemia [3-6]. 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]) [10-12].

Case report

Twenty eight years old female patient has been on haemodialysis from July 2007. The primary cause for renal failure is unknown. As ayoung 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 start of dialysis treatment, creation of arterio-venous fistula (AVF) was repeatedly attempted, but it was not successful. Over the years, a central venous catheter was used as a vascular access. In 2010, she received living kidney transplantation from her father. On the second postoperative day, there was an acute humoral rejection. Further in the postoperative period an extensive gastrointestinal bleeding and multiple organ dysfunction developed, and the patient was put on artificial ventilation for a month.
Aftherwards a graft nephrectomy was performed and she was reinstated on intermittent haemodialysis three times per week. Anticoagulant therapy used was low molecular weight heparin (LMWH), Enoxaparin in dose 0.7 mg/ kg before hemodialysis. Residual urine output was100-200 ml/24 hours over the past couple of years. She did not use diuretic therapy. Rutine ultrasound showed small kidney, size 6 cm, modified by type of chronic renal insufficiency. The bladder was with echosonographic normalm features. The patient remained stable until December 2015, when her wellbeing was complicated with pain and swelling in the right upper thigh.
CT scan was performed and showed voluminous musculature of the rear lodge of the right leg as a whole, in

Correspondence to: Selma Ajanovic, Clinic for hemodialysis, Clinical Center of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Hercegovina; E-mail: selmaajanovic@yahoo.com

comparison with the left side, and small fluid collections that had extended the muscle fibres (hematoma). The hematoma was punctured and 50 ml of coagulated blood was evacuated. She remained hemodinamicly stable and mobile, without any decrease in the level of hemoglobin. In February 2016, swelling and pain in the right thigh occurred again. The patient was hospitalized in the Department of Orthopaedics and Traumatology of the Clinical Centre in Sarajevo. Urgent ultrasound was performed and the computed tomography angiography (CTA) verified a large hematoma in the same or similar location as before, located in the m. 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 was recorded in the central and peripheral trace forms. Laboratory findings were as follows: WBC 9.0 x 10^9/L, RBC 2.34 x 10^{12}/L, HGB 7.6 g/dL, HCT 21.4%, PLT 186 x 10^9/L 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), 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 givenconcentrated filtered red cells and fresh frozen plasma, 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 evacuated. Later she developed acute compartment syndrome and was surgically treated, by ligature of artery femoris profunde (APF).

The 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 certain 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 legand to the right (Figure 1).

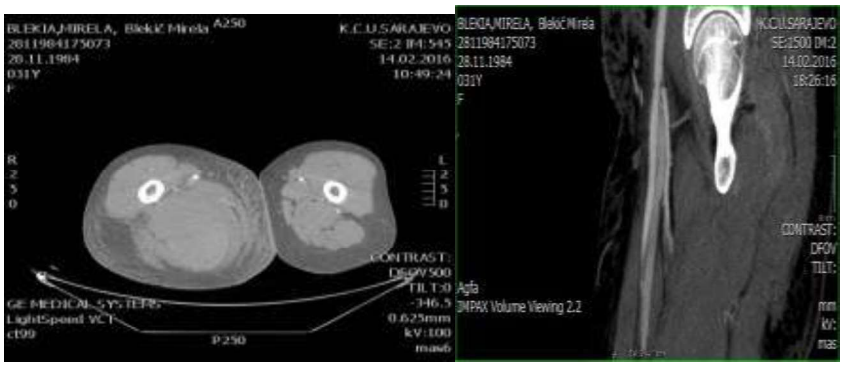

Fig. 1. CTA showed progression in the size of the hematoma with propagation to the distal third of the back of the leg, to the right

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 4% citrate lock in the cathether. 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; also pain and swelling of the left upper arm and left breast. Ultrasound was performed in the left axilla and it verified polycyclic liquid collection, located next to the artery, 54x25 in diameter. In the superolateral caudal quadrant of the breast there was a hematoma withliquid and sediment component, about 44x17 mm in diameter. The ultrasound of the leg showed a slight regression in the size of the hematoma. The size of the liquid component was about 8 x 30 x 3 cm.Since coagulation factor inhibitors were suspected, during the fourth day of hospitalization, plasmapheresis was performed with plasma volume of 2500 ml of FFP. In the afternoon, there was a further decrease in haematological findings: RBC 2.2 x 10^{12}/L, HBG 6,8 g/dL, HCT 0.20, PLT 222 x 10^9/L, WBC 10.6 x 10^9/L.

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 of dezmopresin, Minirin tablets, 3x2 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, 900 ml of clear liquid was collected in the urinary bag. 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 were: 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 was 1042 ?mmol/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 dose of 3 x 2 mg.

Laboratory findings showed further decline:WBC 7.42 x 10^9/L, RBC 2.72 x 10^{12}/L, HGB 8.72 g/dL, haematocrit 25.7%, PLT 409 x 10^9/L, Na 137 mmol/L, K 6.8 mmol/L, Ca 2.18 mmol/L, CI 105mmol/L, BUN 20,9 mmol/L, creatinine 1007 ?umol/L, LDH 295, INR 0.99, aPTT 32.7.

The patient continued to have dieresis in the following days, between 600-800 ml per day. After one month, her diuresis is between 300 and 400 ml per day.

Discussion

Desmopressin (DDAVP) is a synthetic analogue 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) in the central nervous system in disorders where there is decreased production of 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 r in diabetes insipidus, and range from 0.3 ug/kg to 0.4 ug/kg administered intravenously or subcutaneously as a single injection. Desmopressin should not be administered for more than three days [10,11]. To our knowledge, no trial has ever evaluated the oral use of 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 administered desmopressin orally 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 showed a paradoxical increase in diuresis in patients with diabetes insipidus after using DDAVP. After an immediate and transient antidiuresis, a single intravenous bolus injection of lysine vasopressin was given during treatment with chlorpropamide. Followed by continuous intravenous infusion of chlorpropamide with lysine vasopressin, carbamazepine or clofibrate and 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 multi-centre 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 *et al*, showed 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 by 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.

Conclusions

To conclude, in this case, vasopressin was administered for uremic bleeding which resulted in increased

urine output in previously oliguric patient on haemodialysis. Safe scientific explanation of this phenomenon was not found. This question can be answered by a prospective trial of the efffect of vasopressin in dialysis patients.

Conflict of interest statement. None declared.

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