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CLINICAL REPORT

Intraoperative hypernatremia and polyuric syndrome induced by dexmedetomidine

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Abstract Hypernatremia and polyuria are the main symptoms of diabetes insipidus. Polyuria is characterized by a 24-h urine volume in excess of 40–50 ml/kg in adults. Dexmedetomidine, a highly selective, short-acting intravenous alpha-2 agonist, is used as a component of anesthesia, and has been suspected to induce polyuric syndrome. We report a patient who presented with severe hypernatremia and polyuria after intravenous infusion of dexmedetomidine.

Keywords Hypernatremia · Polyuric syndrome · Dexmedetomidine · Diabetes insipidus

Introduction

Polyuria is characterized by a 24-h urine volume in excess of 40–50 ml/kg in adults. The release of arginine vasopressin (AVP) increases in response to surgical stress that stimulates the pituitary–adrenal axis. Therefore, oliguria is common during surgery. Oliguria is also associated with a pronounced release of AVP during spinal surgery [1]. Dexmedetomidine, a highly selective, short-acting intravenous alpha-2 agonist, has been used as a component of anesthetics due to its imidazoline receptor affinity, which provides analgesic, anxiolytic, and antinociceptive effects without respiratory depression [2]. Hypotension and bradycardia are the common adverse reactions to this agent [3]. In an animal model involving general anesthesia, dexmedetomidine increased urinary output while decreasing urine osmolality and increasing free water clearance. However, increased urine output, or DI, is not considered to be a common complication in humans [4]. We report a critical case that is significant due to the severity of polyuria and hypernatremia.

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Case description

A 71-year-old female patient presented for an elective posterior L3–5 decompression, posterior spinal fusion (PSF) from L2 to the sacrum, placement of autograft and allograft for the PSF, posterior instrumentation, and transforaminal lumbar interbody fusion of L3–4 and L4–5. Her medical history included lumbar radiculopathy, hypertension, hypothyroidism, glucose intolerance, and osteoporosis. Her past surgical history included a total abdominal hysterectomy, appendectomy, and surgeries for strabismus and cataracts. The patient did not experience any sodium or urine output complications in her previous surgeries. She reported getting up 1–2 times per night to urinate, but this has been the case for many years. There was no complaint of polydipsia prior to her hospitalization. Her medications included felodipine, levothyroxine, and aripiprazole. Her preoperative laboratory tests were all normal, including renal function and urine analysis. She was allergic to erythromycin and tetracycline. Her height was 145 cm, she weighed 74 kg, and she was graded ASA physical classification III.

On the day of surgery, the patient received 2 mg of midazolam as preoperative medication. Standard monitors

were applied. The patient was intubated after inducing general anesthesia with fentanyl (100 μg), propofol (150 mg), and rocuronium (100 mg). Volume-controlled ventilation (8 ml/kg) with a positive end-expiratory pressure (PEEP) of 5 cm H_2O was used to achieve an end-tidal CO_2 of 30–40 mmHg by adjusting respiratory rate. Anesthesia was maintained with sevoflurane, dexmedetomidine infusion at 0.42 μg/kg/h without bolus, and remifentanil infusion at 0.1 μg/kg/min. A left radial artery catheter was placed and connected to a FloTrac/Vigileo system (Edwards Lifesciences, LLC, Irvine, CA, USA) that enabled the continuous monitoring of blood pressure (BP), stroke volume (SV), stroke volume variation (SVV), cardiac output (CO), and cardiac index (CI). During the surgical procedure, patients were managed in accordance with our institution's standard of care. Patients received fluid intraoperatively at the discretion of the anesthesiologists. Intravenous (IV) solution bolus (250 ml) was given when stroke volume variation (SVV) was above 13 % and repeated if necessary until SVV returned to below 13 % during surgery. CO was used concomitantly to ensure that there was an increase in CO each time the preload (IV fluid bolus) was increased and to avoid volume overload. The procedure lasted 7 h and patient received 4 l Lactated Ringer's (LR) solution, 500 ml hydroxyethyl starch 130/0.4 (HES130/0.4), 400 ml packed red blood cells (PRBCs), 200 ml fresh frozen plasma (FFP), and 300 ml of cell saver blood. The estimated blood loss was 850 ml and urine output was 3950 ml.

During surgery, her urine output increased to 300 ml/h within the first hour and climbed to 700 ml/h by the second hour. The highest urine output was reached, 970 ml/h, by the third hour. The patient's hemodynamic parameters (BP 120/60 mmHg, HR 60 beats/min, CO 2.5 l/min, SVV 9 %) were stable with intravascular volume replacement therapy and a phenylephrine infusion. Her urine output reached 600 ml/h by the fourth hour and 705 ml/h during the fifth hour. During this period, SVV slightly increased above the baseline, but blood pressure was still stable (Table 1). At the same time, it was also noted that she had hypernatremia, with sodium increasing from 138 to 151 mEq/l, and her urine gravity reduced from 1.017 to 1.006 (Fig. 1), her urine osmolality was 108 mOsm/kg, and her serum osmolality was 311 mOsm/kg. Blood urea nitrogen (BUN) and creatinine (Cr) were normal. Endocrinology was consulted for possible DI. The dexmedetomidine infusion was reduced to 0.3 μg/kg/h and discontinued at the end of surgery.

Intraoperatively, the sodium level corrected itself to 147 mEq/l and subsequently decreased to 142 mEq/l postoperatively (Fig. 1). The urine output decreased to 275 ml/h at the end of surgery. The patient was brought out to the post-anesthesia care unit (PACU) intubated due to delayed emergence and severe respiratory acidosis on arterial blood gas. Urine output decreased further (to <200 ml/h) during the PACU stay. The hypernatremia resolved with 5 % D5W at 100 ml/h and fluid boluses. The patient received 3 l of crystalloids and 500 ml of HES prior to discharge to the intensive care unit for further observation and treatment. Over the next 24 h, all laboratory values returned to their normal ranges and the patient was extubated. There were no changes in the cognitive and neurologic examinations from baseline. Postoperative urine osmolality was 450 mOsm/kg with a urine sodium of 106 mEq/l, and serum osmolality was 290 mOsm/kg with a serum sodium 142 mEq/l. Urine specific gravity increased to 1.021 (Fig. 2). The patient was subsequently discharged home on postoperative day 4 without further complications.

Discussion

Although there was no evidence of either decreased AVP releases (central DI) or impaired AVP responsiveness (nephrogenic DI), the patient presented with severe hypernatremia, low urine specific gravity, and high plasma osmolality, which were consistent with a polyuric syndrome and perhaps DI. She denied any history of brain and kidney diseases and had a normal preoperative renal function test. She had a total abdominal hysterectomy under general anesthesia with identical anesthetics, except for dexmedetomidine, ten years ago. Therefore, it is suggested that dexmedetomidine is relevant to the hypernatremia and polyuric syndrome seen in this case. Studies have reported that α_2-agonists (clonidine and/or dexmedetomidine) produced diuretic responses in both anesthetized and conscious animals and humans by decreasing both central AVP release and peripheral AVP sensitivity [4, 5]. There is no previous report of a case of severe polyuric and hypernatremia syndrome caused by dexmedetomidine in a human.

In 1999, the Food and Drug Administration approved dexmedetomidine for sedation during surgery [6]. Now dexmedetomidine is widely used for anesthetic premedication, sedation, anxiolysis, and analgesia in unite states. A clinical study found 17 % of non-cardiac surgery patients received dexmedetomidine preoperatively or intraoperatively between 2007 and 2008 [7]. In a meta-analysis, dexmedetomidine improved surgical outcomes by reducing all-cause mortality, non-fatal MI, and myocardial ischemia in patients undergoing non-cardiac surgeries [3]. However, attention must also been paid to the adverse reactions of dexmedetomidine. In addition to hypotension and bradycardia, urine output increase following dexmedetomidine use has been reported in the perioperative period [3, 8].

Table 1 Perioperative laboratory values, fluid balances, and hemodynamic parameters

	Pre-op	Intra-op. hr 1	Intra-op. hr 2	Intra-op. hr 3	Intra-op. hr 4	Intra-op. hr 5	Intra-op. hr 6	Intra-op. hr 7	Post-op. hr 2	Post-op. hr 4	Post-op. hr 6	Post-op. hr 18
pH	7.42	7.43	7.45	7.43	7.43	7.37	7.41	7.25	7.26	7.32	7.34	7.37
Hb	11.3	10.7	10.6	10.0	10.1	11.7	11.3	10.9	11.2	8.6	9.7	10.9
HCT	34.3	33.1	32.8	30.9	31.2	36	34.8	33.6	33.5	25.2	30.4	32.9
GLU	100	110	117	121	125	144	121	269	201	147	142	137
Lac	1.5	1.0	0.9	0.8	0.8	1.9	1.9	2.6	2.1	1.1	1.2	1.4
Na_P	138	141	145	148	148	150	151	147	148	142	141	142
Na_U						48						106
Ca_i	1.18	1.16	1.16	1.18	1.19	1.04	1.83	1.28	2.11	1.92	1.83	2.2
Spec. $grav._i$	1.017					1.006			1.008	1.014	1.017	1.021
Osm_U						108						450
Osm_P						311						294
BUN	17					9				9		9
Cr	0.61					0.68				0.61		0.62
BP	124/62	125/65	110/65	120/60	121/63	119/67	105/55	105/60	113/50	107/61	111/71	
HR	69	59	65	60	62	65	63	78	84	79	69	
CO		1.8	2.4	2.5	2.0	2.5	2.2	2.5				
SVV		6	5	9	14	14	12	9				
EBL			200	200	200	100	50	100				
UOP	100	300	700	970	600	705	275	300	<200/h	<200/h	<200/h	NR
AR		1000		1000		500	300					
NS						500						
6 %HS (130)				500								
PRBC						400						
FFP						200						
D5W						100						
Autologous blood						300						

Hr hour, *Hct* hematocrit (%), *Cr* serum creatinine (mg/dl), Ca_i ionized serum calcium (mg/dl), Na_U urine sodium (mEq/l), Na_P plasma sodium (mEq/l), $Spec.\ grav._U$ urine specific gravity, Osm_U urine osmolality (mOsm/kg H_2O), Osm_P plasma osmolality (mOsm/kg H_2O), *BUN* blood urea nitrogen, *Cr* blood creatinine, *BP* arterial blood pressure (mmHg), *HR* heart rate (beats/min), *CO* cardiac output, *SVV* stroke volume variation, *EBL* estimated blood loss (ml), *UOP* urine output (ml), *AR* Ringer's acetate solution, *NS* normal saline, *HES* hydroxyethyl starch, *PRBC* packed blood red cells, *FFP* fresh frozen plasma, *D5W* 5 % dextrose solution, *NR* not recorded, *POD* postoperative day

Patients receiving dexmedetomidine as an adjunctive medication to epidural analgesia after thoracotomy had significantly greater cumulative postoperative urine output and significantly better-preserved perioperative renal function compared with the control group [6]. α_2-adrenoreceptor agonists induce diuresis, possibly by suppressing the secretion of AVP or by attenuating its effect on the renal tubules, by inhibiting the release of rennin, or by releasing atrial natriuretic peptide [9, 10].

The paraventricular nucleus (PVN) is dense in α_2-receptors and participates in the control of AVP secretion. Cabral's study suggested that xylazine (α_2-agonist) activates α_2-adrenergic receptors in the PVN and thereby inhibits vasopressin secretion [11]. They also found that the subsequent microinjection of yohimbine (α_2-antagonist) into the PVN reduced urine flow rate by 50 % by preventing the inhibitory action of xylazine on vasopressin secretion and thus increasing circulating levels of this hormone. This finding is supported by the reduction in urine observed upon yohimbine administration and the reversal of this effect upon the subsequent intravenous administration of a vasopressin receptor antagonist. Dexmedetomidine inhibits AVP release from isolated rat hypothalamic PVN and paraventricular magnocellular neurons [12, 13], theoretically through a decrease in neuronal firing rate secondary to hyperpolarization by a G-protein-coupled, inwardly rectifying potassium channel mediated by α_2-adrenergic receptors. In addition to its central effect, dexmedetomidine can directly attenuate sodium reabsorption in tubular cells [14]. Dexmedetomidine caused a diuretic

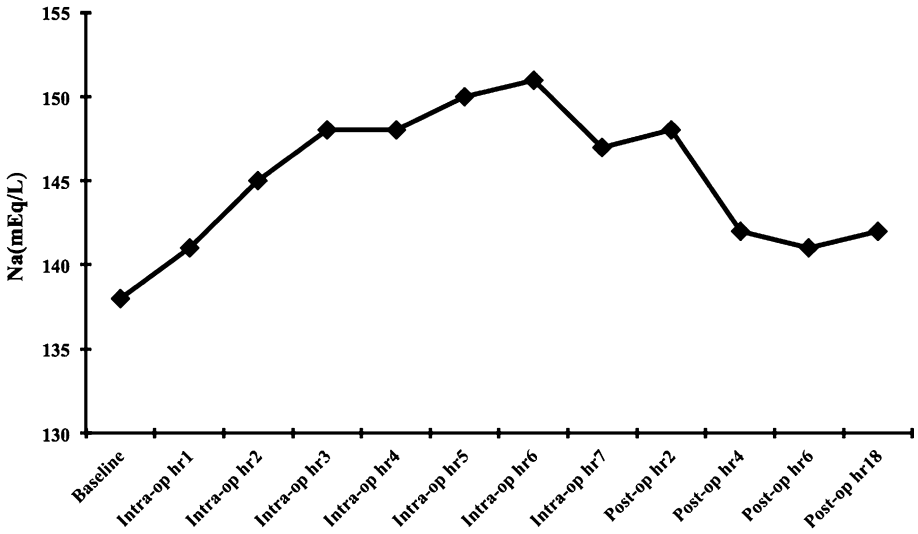

Fig. 1 Perioperative levels of serum sodium. Intraoperative and postoperative times are plotted (*x*-axis) against the level of serum sodium (*y*-axis). *Intra-op* intraoperative, *hr* hour, *Post-op* postoperative; *hr1*, *hr2*, *hr3*, … indicate the number of hours that have elapsed during or since surgery

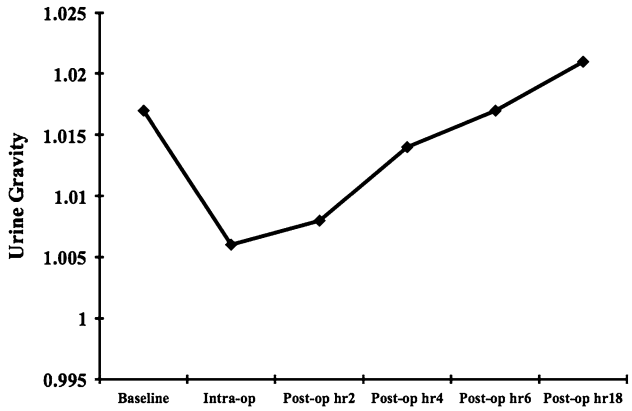

Fig. 2 Perioperative urine gravity. Intraoperative and postoperative times are plotted (*x*-axis) against urine gravity (*y*-axis). *Intra-op* intraoperative, *hr* hour, *Post-op* postoperative, *hr1*, *hr2*, *hr3*, … indicate the number of hours that have elapsed since surgery

effect and a dose-dependent increase in the frequency of voiding [15].

Although dexmedetomidine-induced polyuria and hypernatremia may be explained by the previously stated mechanisms, studies in human are still sparse. To our knowledge, such high magnitudes of polyuria and hypernatremia have not been reported so far. In addition to dexmedetomidine, the following factors may have also contributed. First, the type of surgery may make a difference. Several studies have reported that patients undergoing spine surgery or spinal cord trauma patients developed excessive urine output [16]. Second, it has been reported that calcium channel antagonists enhance the diuretic activity of dexmedetomidine in rats by directly inhibiting renal tubular water and electrolyte reabsorption and blocking the inhibitory actions of angiotensin and vasopressin on renin secretion [15]. In the present case, the patient had taken a calcium channel antagonist (felodipine) for hypertension. Finally, thyroid hormone is associated with urine output and changes in electrolyte excretion. The patient also took levothyroxine, which is thought to cause polyuria in humans, for hypothyroidism [17]. However, the polyuria resolved after discontinuing the use of dexmedetomidine. Moreover, although the patient took felodipine, levothyroxine, and aripiprazole, there was no complaint of polydipsia prior to her hospitalization. Finally, the patient did not experience any sodium or urine output complications in her previous surgeries, during which she underwent general anesthesia brought on by various anesthetics, but not dexmedetomidine. This evidence strongly supports the hypothesis that dexmedetomidine is relevant to the polyuria and hypernatremia.

In summary, this case brings attention to the possible risk of severe polyuria and hypernatremia resulting from the use of dexmedetomidine, especially when combined concomitantly with calcium channel antagonists, levothyroxine, and spinal surgery. The mechanisms for this remain unclear, so further investigation is needed.

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