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Case Report

Continuous Vasopressin Infusion for the Management of Central Diabetes Insipidus - Ⓜ

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ABSTRACT

Central Diabetes Insipidus (CDI) is a common complication of Traumatic Brain Injury (TBI). One option for CDI management is a Continuous Vasopressin Infusion (CVI). However, evidence of efficacy for this regimen is lacking. We present a case series evaluating the effect of CVI on urine output and possible adverse effects related to renal function and tissue perfusion.

We retrospectively identified subjects at the University of New Mexico Hospital between January 2008 to November 2013 who had received CVI and had been declared dead by neurological criteria. Our analysis included time to decreased urine output and compared changes in creatinine (paired t-test), lactate, and systolic blood pressure (repeated measures ANOVA) before and after infusion of vasopressin. Thirty-two subjects met inclusion criteria. Urine output declined from a median of 345 ml/hour (IQR 178-500) to 222 ml/hour (IQR 114-273) within an hour of starting CVI. Urine output had declined to 50% goal by a median time of 90 minutes (IQR 60-123) with goal urine output at a median of 120 minutes (IQR 84-210). Our results also indicate that systolic blood pressure (repeated measures ANOVA), creatinine (paired t-test) and lactate after infusion of vasopressin were not statistically different compared with values prior to CVI. CVI appears to be an effective means of decreasing urinary output without adverse effects on renal function and tissue perfusion in patients on the donor service with CDI.

Keywords: Central DI; Continuous vasopressin infusion; Traumatic brain injury; Pituitary dysfunction; Death by neurologic criteria

INTRODUCTION

Central Diabetes Insipidus (CDI) is a common complication of Traumatic Brain Injury (TBI) and occurs in approximately 15% of all severely head injured patients [1]. In a prospective study of 436 head injured patients, 387 of which had isolated head injury, DI was identified to be an independent risk factor of death and was associated with five-to-six times higher mortality (74% mortality) [1].

Native vasopressin is a useful alternative treatment for CDI in the acute critical illness phase due to its shorter duration of action and ability for close dose adjustment. Unfortunately, in prior studies vasopressin has been shown to cause concomitant stimulation of V1 receptors leading to development of anti-vasopressin antibodies, thus causing a lack of response to treatment [2]. Our practice has been to use Continuous Vasopressin Infusion (CVI) to control CDI. However, evidence of efficacy for this regimen is lacking. In this retrospective analysis, we evaluated the effect of CVI on the timing and efficiency for control of urine output and monitored for adverse effects on renal function or tissue perfusion.

MATERIALS AND METHODS

We retrospectively identified subjects at the University of New Mexico Hospital Health Sciences Center between January 2008 to November 2013 who were retrospectively identified as having received CVI as ordered via the organ donation order set. Subjects had been declared dead by neurological criteria and had received CVI for CDI in the ICU. The order set for CVI was activated when urine output exceeded 250 mL per hour for two consecutive hours, serum sodium exceeded 145 mg/ dL, and/or urine specific gravity < 1.005. The CVI was titrated to obtain a urine output of less than 125 mL/ hour or until time of organ donation.

The primary endpoint was the duration from initiation of CVI to the time of control of polyuria, defined as a urine output of less than 125 mL/ hour. Secondary endpoints were systolic blood pressure (mmHg), kidney function measured as serum creatinine, and tissue ischemia using serum lactate as a surrogate marker.

We evaluated time to decreased urine output, including time to 50% of goal and time to goal urine output. We also compared changes in creatinine (paired t-test), lactate, and systolic blood pressure (repeated measures ANOVA) before and after infusion of vasopressin.

RESULTS

32 subjects met the inclusion criteria with a mean age of 45+/-16 (mean+/-SD). Subjects had declared brain dead with TBI being the most common injury type (Table 1).

Our results also indicate that systolic blood pressure (repeated measures ANOVA), creatinine (paired t-test), and lactate after infusion of vasopressin were not statistically different compared with values prior to CVI (Table 2).

Blood pressures were stable throughout 6 hours of infusion of vasopressin with no significant increase in systolic blood pressures noted ($p = 0.1192$ repeated measures ANOVA). Similarly, serum creatinine remained stable with no significant changes between before and after vasopressin infusion ($p = 0.5770$ paired t-test). Importantly, there also was no significant increase in serum lactate, highest recorded lactates were 2.90 +/- 2.3 (Mean +/- SD). This was not significantly different from lactates before infusion ($p = 0.0887$ paired t-test) (Table 2).

Median vasopressin dosing was 0.5 Units/hour. Doses of vasopressin ranged from 0.04 to 4.8 units/ hour, however most doses

Table 1: Inclusion criteria

Patients (n= 32)	
Age, Mean +/- SD	45 +/- 16
Gender, n (%)	
Male	17 (53%)
Female	15 (47%)
Declared Brain Dead, n(%)	
28 (88%)	
Injury Characteristics	
Traumatic Brain Injury	15 (47%)
Subdural Hematoma	11(34%)
Traumatic Subarachnoid	10 (31%)
Spontaneous Subarachnoid	9 (28%)
Intraparenchymal Hemorrhage	7 (22%)
Intraventricular Hemorrhage	5(16%)
Anoxic Brain Injury	3 (9%)
Cerebrovascular Accident	1 (3%)
Meningitis	1 (3%)

were 0.5 units/ hour or less. Median doses at 50% urine output goal and output goal were 0.5 units/ hour (Table 3). Vasopressin dosing typically started at 0.5 units/ hour with varied levels of titration.

Urine output rapidly declined in most subjects from a median of 345 ml/hour (IQR 178-500) to 222 ml/hour (IQR 114-273) within an hour (Figure 1). Urine output had declined to 50% goal by a median time of 90 minutes (IQR 60-123) with goal urine output at a median of 120 minutes (IQR 84-210) (Figure 1).

DISCUSSION

Central Diabetes Insipidus is a common problem for providers taking care of patients with severe traumatic brain injury (15%) [1]. It is most often associated with direct mechanical impact, acceleration-deceleration effect, and/or cerebral consequences of trauma (ie., ischemia, hypoxia, alterations in cerebral vascularization or metabolism, or intracranial hypertension [3]. The stretching or tearing of small vessels or neuronal structures can lead to hemorrhages or infarction to the stalk, the hypothalamic nuclei, or the in fundibular regions thus causing an ADH deficiency due to impaired synthesis [3]. This hormone deficiency can be transient, most likely secondary to small vessel damage of inflammatory edema, or permanent and

leads to the inability to concentrate urine. ADH deficiency leads to the loss of large amounts of dilute urine (polyuria), which then triggers an increased thirst mechanism (polydipsia) [3]. Unfortunately, in patients with TBI, who are critically ill, many have the inability to express their feeling of thirst or may have concomitant damage of the thirst osmoreceptors in the hypothalamus [3]. In these cases, high volume inappropriate dilute urine results in a state of hypovolemic hypernatremia. This profound dehydration can lead to tachycardia, hypotension, decreased renal perfusion and poor cerebral perfusion pressures, a scenario that can be catastrophic to a severely injured TBI patient. Furthermore, the signs of symptoms of hypernatremia include confusion, disorientation, hyperreflexia, seizures, lethargy, and coma, all of which are difficult to differentiate in patients with neurologic injury [3].

Unrecognized CDI, delayed treatment, and/or overtreatment may have significant effects on morbidity and mortality [4]. Diagnosis of CDI is not always straightforward for a number of reasons. Many TBI patients require hyperosmolar therapy in an effort to temporize intracranial hypertension. Additionally, many suffer from other traumatic injuries leading to high volume blood loss and require aggressive volume resuscitation [1]. Providers should be vigilant in monitoring hourly urine output (UOP) and if > 250 ml/ hour, a urine osmolality or urine specific gravity and serum sodium should be obtained. Diagnosis can be confirmed by a urine osmolality of < 200 mOsm/ L or a urine specific gravity of < 1.003 and a rapidly rising or above normal sodium (> 145 mEq) [5].

Medical management of CDI is aimed at the replacement of fluids to avoid hypovolemia, maintenance of electrolyte balance, and if necessary, Antidiuretic Hormone (ADH) replacement [6]. There are various options for the treatment of CDI including: chlorpropamide, carbamazepine, thiazide diuretics, nonsteroidal anti-inflammatory drugs, and diet control. However, in most hospitalized/ ICU patients, Desmopressin (DDAVP), a synthetic analog of vasopressin with minimal pressor effect, is the preferred drug [1]. DDAVP is typically administered as a single oral, intranasal, subcutaneous, or parenteral dose rather than as a continuous intravenous infusion [7]. In the critical care setting, parenteral desmopressin is the route of choice [5]. Unfortunately, the duration of action for DDAVP is 12 hours which limits the ability of additional dosing and carries a significant risk of overtreatment which can lead to Cerebral Salt Wasting Syndrome (CSW) and rapid hyponatremia [6].

Native vasopressin has offered us an alternative treatment for CDI in the acute, critical illness phase due to its shorter duration of action and ability for close dose adjustment. Unfortunately, in prior studies vasopressin has been shown to cause concomitant stimulation of V1 receptors leading to development of anti-vasopressin antibodies, thus causing a lack of response to treatment [2]. Vasopressin delivered via continuous infusion can be an efficient method of gaining rapid control of a patient’s urine output and therefore decreasing the risk of hypotension, hypoperfusion, and/or hypernatremia. Additionally, given the medication is being titrated to urine output the risk of overcorrection is minimized, avoiding hyponatremia which can be detrimental in maintaining lower ICP and therefore impairing cerebral perfusion pressures.

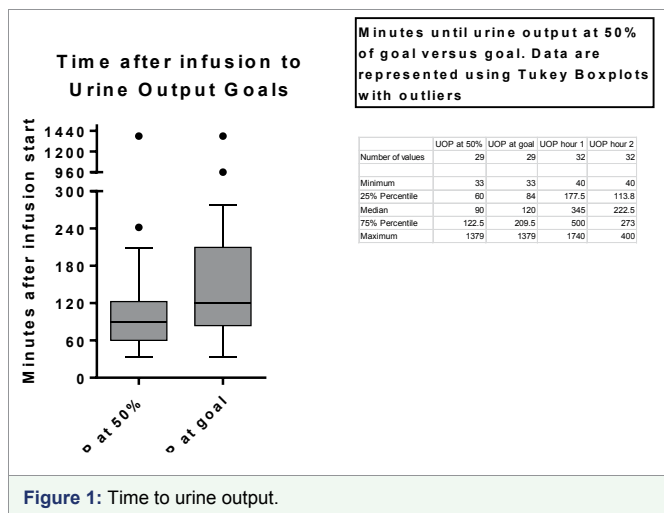
Our findings indicate that the use of CVI in the context of CDI is an effective method to control urine output. Our data also indicate that can be accomplished without significant effects on systolic blood pressure, lactate levels, and creatinine levels. This study is limited due

Table 2: Clinical criteria

Systolic Blood Pressure (mmHg)	Mean +/- SD
Before infusion	120 +/- 20
1 hr after infusion	124 +/- 22
6 hrs after infusion	130 +/- 22
Creatinine (mg/dL)	Mean +/- SD
Before infusion	0.97 +/- 0.29
After infusion	0.94 +/- 0.28
Lactate (mmol/L)	Mean +/- SD
Before Infusion	2.50 +/- 1.3
Highest	2.90 +/- 2.3

Table 3: Vasopressin dose

	n	Median	IQR	Min-Max
Starting dose	32	0.50	0.50 - 0.50	0.04 - 4.80
Dose at 50% Urine output goal	31	0.50	0.50 - 0.75	0.00 - 4.80
Dose at Urine output goal	30	0.50	0.50 - 0.56	0.00 - 4.80



to the fact that we studied only patients who had been declared dead by neurologic criteria. However, it is still unclear as to whether this is applicable in non-brain dead patients.

In conclusion, we have reported the first case series of patients with CDI successfully managed with CVI. Our case series demonstrates that CDI is a safe and effective treatment modality in this context.

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