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Prospective Study to Evaluate the Role of Vasopressin in Hypernatremia Treatment in Brain Dead Patients

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Abstract

Brain dead patients are potential organ donors but the pathological changes associated with braindeath can affect graft survival. Among various effects of braindeath endocrine and autonomic changes are noteworthy. Central diabetes insipidus characterized by reduced level of anti-diuretic hormone in brain dead patients can result in hypernatremia which inturn may affect the survival of the transplanted liver graft. Managing hypernatremia with exogenous vasopressin replacement improves the liver graft function.Vasopressin also maintains haemodynamic stability and reduce excessive free water loss as urine. It is given as intravenous infusion at 0.01-0.04 U/min or maximum 2.4U/hour.

Keywords: Braindeath; Endocrine dysfunction; Anti-diuretic hormone (vasopressin); Central diabetes insipidus; Hypernatremia; Liver transplantation; Liver graft survival; Vasopressin infusion.

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Introduction

Traumatic brain injury or other physiological change to the brain (e.g. cerebral hemorrhage, CVA) may result in irreversible loss of brain stem function, leading to brain death. These patients can donate viable organs to those who in need of them.

Brainstem dysfunction causes many changes in normal physiology. These alterations in the cell homeostasis may adversely affect the viability of donated organs which can affect the graft function. Understanding the brain death pathophysiology helps us managing the adverse sequele reasonably, which inturn improves the viability of the transplanted organs.

Of the major changes autonomic and endocrine malfunctions are significant. Central Diabetes insipidus as a result of failure of posterior pituitary to secrete adequate anti-diuretic hormone (vasopressin) is a common endocrine dysfunction seen in the brain-dead patients.

Diabetes insipidus is characterized by high serum osmolarity and hypematremia. Hypernatremia is serum sodium level > l45 mEq/L[3].

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Organs usually donated are cornea, liver, kidneys, heart/heart valves. Organs sensitive to hypematremia are kidney, liver, heart. Donor liver grafts with hypernatremia are prone to rejection on transplantation. Adverse ouycome is more likely when the sodium level is more than 155 mEq/L, in particular when the hypernatremia duration is longer before organ harvesting.[3]

Various studies have highlighted the effect of high serum sodium level on liver graft survival. So administering exogenous vasopressin as intravenous infusion to replace its deficiency to treat hypernatremia can improve the of the transplanted organs especially the liver. Which is the aim of our study.

In this study we have attempted to treat hypematremia using vasopressin in clinically brain-dead patients who were waiting for apnoea test and brain death certification, by assessing the serum sodium levels before and after starting the vasopressin therapy. Vasopressin also improves the blood pressure, as hypotension is a known and frequent complication of brain stem injury and brain death.

Aim of the Study

To evaluate the role of vasopressin in the treatment of hyperatremia in clinically brain-dead patients using intravenous vasopressin infusion at a dose of 0.01-0.04 U/min or maximum 2.4 U/hr in 40 clinically brain-dead patients.

Materials and Methods

It is a prospective study of vasopressin in the management of hypermatrmia in clinically brain-dead patients, conducted in Government General Hospital, Chennai, during the period 2010–2011.

Study Design

Prospective, interventional. After obtaining institutional ethical committee clearance, 40 clinically brain-dead patients with hypermatremia were selected using following criteria:

Inclusion Criteria

- Clinically brain-dead patients (ASA PS 6), diagnosed by neurosurgeon or neurophysian using brainstem reflex tests, waiting for apnoea test and brain death certification.
- Traumatic injury
- Serum Na^+ level > 145 meq/L
- Urine output > 4 ml/kg/hr

Exclusion Criteria

- Brain-dead patients with serum Na+ < 1 46 meq/L
- Urine output < 1 .5-2m 1/kg/hr
- Patients with known renal pathology
- Allergy to vasopressin group of drugs

Outcome Measures

- Serum Na^+ level (by venous or arterial sample)
- Urine output
- Blood pressure
- Pulse rate
- Serum potassium
- Serum creatinine

Monitoring Interval

Blood pressure- 1st hour — every 15 mins, 2nd & 3rd hour — every 30 mins, subsequent hours — hourly monitoring (if stable with supports) for 6 hours.

All other parameters were monitored second hourly.

Materials

1. l8G venflon
2. Heparin
3. ABG analysis source
4. Intra venous fluids (5%D, RL, 1/2NS)
5. Monitors-Monitors: ECG, Pulse oximetry, Capnography, NIBP
6. Vasopressin injection

Study Method

After receiving information about a clinically braindead patient information from any ward or ICU, patients were examined and clinical brain death certification was confirmed twice at 4-6 hours interval. Investigations were evaluated to rule out other possibilities of unconciousness like intoxication.

After verifying the inclusion criteria and confirming the diagnosis of hypermatremia, written

consent was obtained from patient's attenders and intravenous vasopressin infusion was started at a dose range of 0.01-0.04 U/min. 20 units (1 ampoule) vasopressin is diluted in 500m1 NS to get 0.04U/ ml.

The parameters mentioned above were monitored at specified time intervals for 6-hours.

Single blinded study where the patient was blind.

Results

1. Serum Na+ reaches the target value (<145 mEq/L)
2. Decreased but not to the target level
3. No change in serum Na^+ level
4. Persistently increasing levels noted

Interpretation of results

Response to vasopressin

1. ***Present:*** If there was decrease in serum Na+ level (to target level <145 mEq/L or decrease >10 to 15% from baseline).
2. ***Not Present:*** If there was no change or increasing levels.

Statistics

Statistical analysis was done to determine the significance (friedman test and paired t test were used).

Observation and Results

Male, Female distribution in this study was 75%, 25% respectively. In this study 85% cases were road traffic accident, 15% cases were fall from height. Mean age was – 33.3. There was a consistent decrease in serum sodium level in every hour. There was significant decrease in serum sodium at the end. There was a consistent decrease in urine output. There was a definite increase in mean arterial pressure at the end of 6 hrs. There was no significant difference, in serum sodium control, among the male and female population. Mode of injury didn't produce any significant difference in sodium control and blood pressure variation in this study.

Table 1: Frequency Table: Demographic profile: Sex

Sex	Frequency	Percent
Male	30	75.0
Female	10	25.0
Total	40	100.00

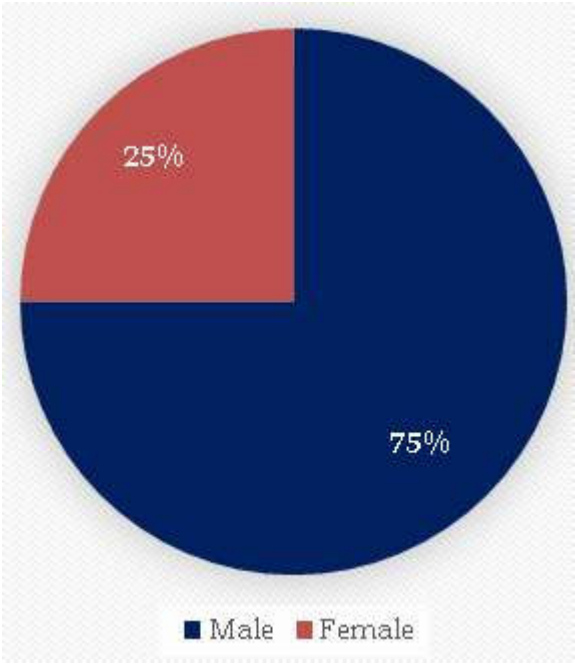

Fig. 1: Sex distribution

Table 2: Frequency Table: Mode of Injury

Mode of Injury	Frequency	Percent
RTA	34	85.0
Fall from Height	6	15.0
Total	40	100.00

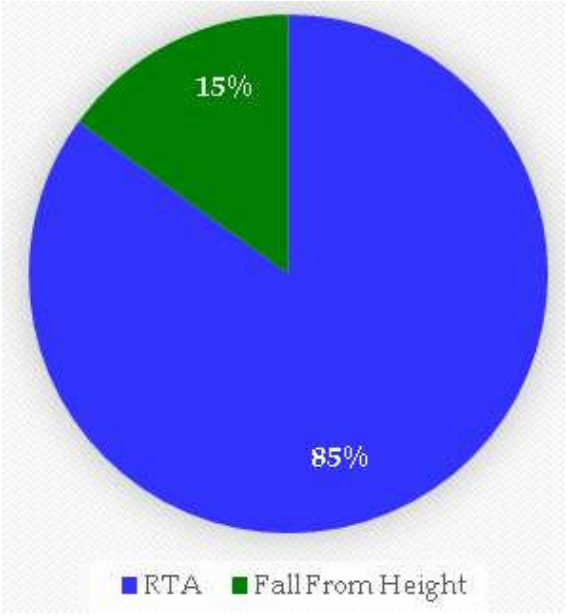

Fig. 2: Mode of injury

Table 3: Descriptive statistics: Age

	N	Minimum	Maximum	Mean	Std.Deviation
Age in years	40	15	60	33.30	12.041

Table 4: Descriptive Statistics, Freidman Test – to compare the hourly serum sodium values.

Serum Sodium

Serum sodium	N	Mean	Std. Deviation	Minimum	Maximum	P-value
Initial	40	160.10	8.041	146	179	
1 hr	40	158.28	7.582	146	175	
2 hrs	40	154.77	7.026	142	170	
3 hrs	40	151.15	7.145	138	166	
4 hrs	40	147.98	7.767	135	166	<0.001**
5 hrs	40	145.12	9.030	132	171	
6 hrs	40	142.48	10.195	130	174	

Table 5: Paired Samples Statistics

Paried T-Test to compare the initial and final serum sodium values.

Serum sodium	Mean	N	Std. Deviation	Std Error Mean	P –value
Initial	160.10	40	8.041	1.271	<0.001**
6 hrs	142.48	40	10.195	1.612	

Fig. 3: Hourly serum sodium level

Table 6: Friedman Test – to compare the hourly urine output values

Descriptive statistics

Urine output	N	Mean	Std. Deviation	Minimum	Maximum	P-value
Initial	40	240.50	31.861	180	320	
1 hr	40	222.38	31.297	165	300	
2 hrs	40	205.50	32.715	160	290	
3 hrs	40	188.25	33.846	140	290	
4 hrs	40	174.50	35.225	130	280	<0.001**
5 hrs	40	162.50	38.213	125	290	
6 hrs	40	149.88	42.115	110	280	

Fig. 4: Hourly urine output

Table 7: Mean arterial pressure Descriptive Statistics

Friedman Test – to compare the MAP values

Mean arterial pressure	N	Mean	Std Deviation	Minimum	Maximum	p-value
Initial	40	74.97	4.633	66	88	
15 mins	40	77.10	6.515	67	105	

30 mins	40	77.70	4.603	68	88	
45 mins	40	78.70	4.575	70	90	
1 hrs	40	79.63	4.436	70	91	
1.30 hrs	40	81.68	4.305	74	89	<0.001**
2 hrs	40	83.33	4.486	75	94	
2.30 hrs	40	85.60	4.301	78	97	
3 hrs	40	87.43	4.069	80	99	
4 hrs	40	91.48	4.309	84	101	
5 hrs	40	95.60	4.361	87	104	
6 hrs	40	98.50	4.546	92	108	

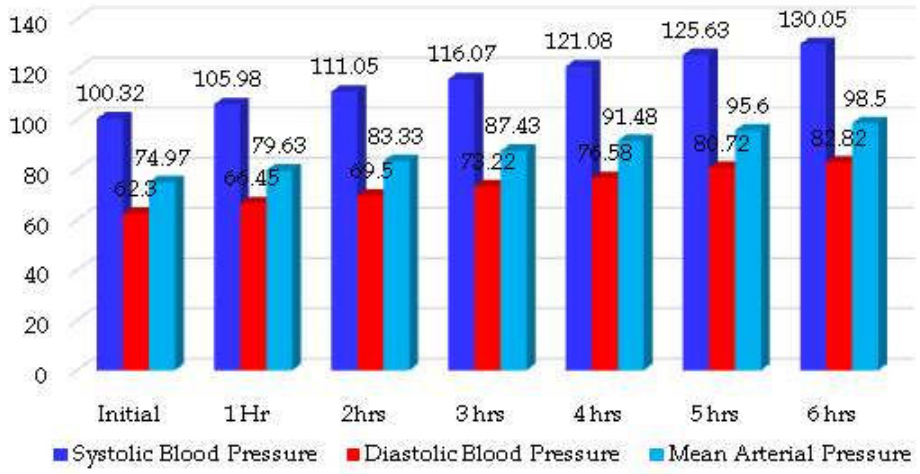

Fig. 5: Hourly MAP

Table 8: Paried Samples Statistics

Paried T- Test – to compare the initial and final MAP values

Mean arterial pressure	Mean	N	Std. Deviation	Std. Error Mean	P- Value
Initial	74.97	40	4.633	.732	<0.001**
6 hrs	98.50	40	4.546	.719	

Discussion

Vasopressin is a nano peptide with a half life 10-15 minutes and undergoes renal and hepatic metabolism. It is administered intravenously or intramuscularly. Desmopressin is a long acting (half life 1.5-2.5 hours) analog with less vasopressor property. It can be given intravenously, sub cutaneously, intranasally or orally.

Vasopressin has two major effects in braindead patients,

1. V2 receptor mediated free water retention- which helps in the management of hypermatremia in brain-dead patients due to the endocrine failure that follows posterior pituitary infarction, which is otherwise harmful to the potentially transplan table organs, especially when serum sodium concentration >l55 mEq/L. (if the diagnosis is confirmed and the patients relatives give consent for organ donation).
2. V1 receptor mediated vasoconstriction — which helps to maintain/improve hemodynamic status in brain-dead patients, who are usually prone to hemodynamic instability due to the frequently accompanying autonomic failure.

From observation and statistical analysis there was almost a steady decline in serum sodium in every hour sample with a significant decrease in sodium level at the end of 6th hour noticed in 31 patients.

Mean initial sodium was 160.10 mmol/L and final sodium concentration was 142.48 mmol/L.

There were consistent reduction in urine output in every hour and significant decrease in urine output at the end of 6th hour also noticed in those 31 patients.

Mean initial urine output was 240.50 L/hr and final urine output was 149.88 L/hr.

The pathology in these 31 patients could be the central diabetes insipid us due to posterior pituitary infarction.

In 9 patients there was no significant fall in serum sodium level and urine output, so the pathology in these patients may be different-could be nephrogenic diabetes insipidus.

Considerable improvement in blood pressure (in terms of Systolic Blood pressure, Diastolic Blood pressure, Mean Arterial Pressure) is also seen in almost all patients.

Mean initial Blood pressure:

Systolic Blood pressure	: 100.32 mmHg
Diastolic Blood pressure	: 62.30 mmHg
Mean arterial pressure	: 74.97 mmHg

Mean final Blood pressure:

Systolic Blood pressure	: 130.05 mmHg
Diastolic Blood pressure	: 82.82 mmHg
Mean arterial pressure	: 98. 50 mmHg

Sex distribution: Male-75% Female-25%.

There was no significant difference in terms of drug dosage or response in serum sodium level or blood pressure or urine output due to sex distribution.

So vasopressin infusion in clinically brain dead hypernatremic patients produced,

1. Significant & definite decrease in serum sodium level over 4-6 hours.
2. Definite decrease in urine output.
3. Considerable improvement or stability in haemodynamic status (Blood pressure), as denoted by decrease in catecholamine requirement with time.

As explained in review of literature these findings are supported by various studies.

Effect of Vasopressin on serum sodium control is supported by Charles Ralston, Warwick - Butt *et al*.[9] and Lee YJ, Shen EY, Huang -FY, Kao HA, Shyur SD *et al*.[10]

Catecholamine sparing effect of vasopressin is supported by Pennefather *et al.* (Pennefather SH, Bullock- RE, Mantle D, Dark JH)'[11], Kenneth Katz, Jack Lawler, Jennifer Wax, Robert 0' Connor, Vinay Nadkarn *et al*.[12,] Kinoshita- Y, Yahata K, Yoshioka T, Onishi S. Sugimoto T *et al*.[15] Yoshioka -T, Sugimoto H, Uenishi M, Sakamoto -T, Sadamitsu D, Sakano T, Sugimoto T[18] Luciana Mascia, Ilaria Mastromauro and Silvia Grottoli *et al*.[19]

Diabetes insipidus

Central diabetes insipidus: Head injury, either surgical or traumatic, in the region of the pituitary and or hypothalamus may cause central DI. Other causes include hypothalamic or pituitary tumors, cerebral aneurysms, CNS ischemia, and brain infiltrations and infections. Finally, central DI may be idiopathic or familial. Vasopressin is preferred for short term uses especially when there is hypotension. Desmopressin is preferred for long term uses Desmopressin (DDAVP) is an analog of AVP with a relatively potent antidiuretic effect and negligible vasopressor activity.

Nephrogenic diabetes insipidus: Nephrogenic DI may be congenital or acquired. Hypercalcemia, hypokalemia, post-obstructive renal failure, lithium, foscarnet, clozapine, demeclocycline, and other drugs can induce nephrogenic DI. The preferred treatment of nephrogenic DI is adequate intake of water. Thiazide diuretics paradoxically reduce the polyuria associated with DI and they are used to treat non-lithiuminduced nephrogenic DI.

Conclusion

Hypernatremia a frequent electrolyte disturbance from cental origin in braindead patients can be effectively treated with injection vasopressin infusion. It also mitigates the hypotension that frequently occurs in these group of patients. Other options include inj.desmopressin (lacks vasopressor effect) and IV fluids with high free water and IV fluids with less sodium content.

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