

# 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 > 145 mEq/L<sup>3</sup>.

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

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 hyponatremia 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 hypernatremia 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 hypernatremia 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 hypernatremia were selected using following criteria:

### *Inclusion Criteria*

- Clinically brain-dead patients (ASA PS 6), diagnosed by neurosurgeon or neurophysician using brainstem reflex tests, waiting for apnoea test and brain death certification.

- Traumatic injury
- Serum Na<sup>+</sup> level > 145 meq/L
- Urine output > 4 ml/kg/hr

### *Exclusion Criteria*

- Brain-dead patients with serum Na<sup>+</sup> < 146 meq/L
- Urine output < 1.5-2ml/kg/hr
- Patients with known renal pathology
- Allergy to vasopressin group of drugs

### *Outcome Measures*

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

### *Monitoring Interval*

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

All other parameters were monitored second hourly.

### *Materials*

1. 18G 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 unconsciousness like intoxication.

After verifying the inclusion criteria and confirming the diagnosis of hypernatremia, 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 500ml 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.

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).

**Results**

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

**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.

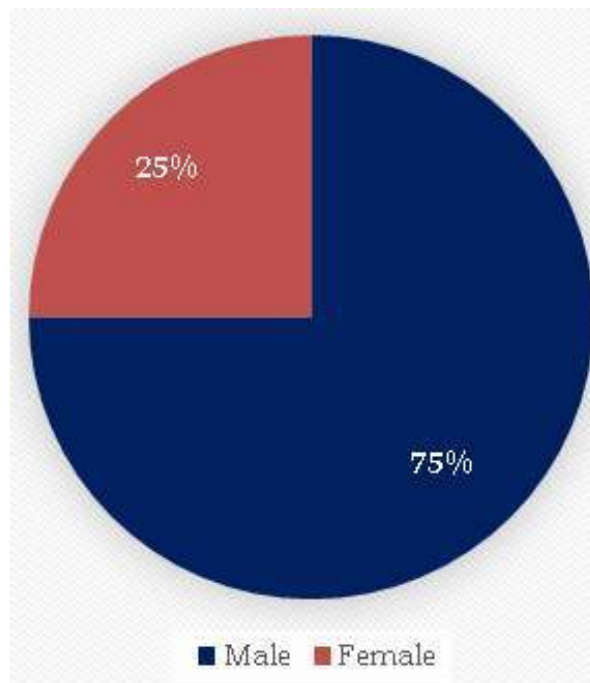
**Interpretation of results**

Response to vasopressin

1. **Present:** If there was decrease in serum Na<sup>+</sup> level (to target level <145 mEq/L or decrease >10 to 15% from baseline).

**Table 1:** Frequency Table: Demographic profile: Sex

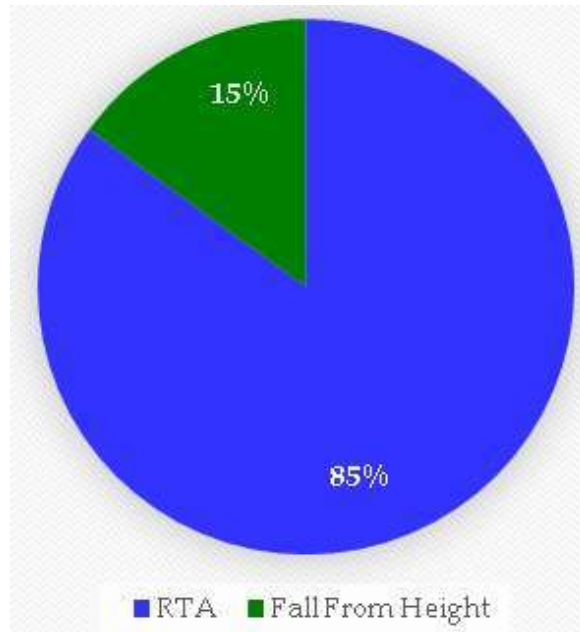
| Sex    | Frequency | Percent |
|--------|-----------|---------|
| Male   | 30        | 75.0    |
| Female | 10        | 25.0    |
| Total  | 40        | 100.00  |



**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     | <0.001** |
| 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     |          |
| 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      | <0.001** |
| 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 |          |

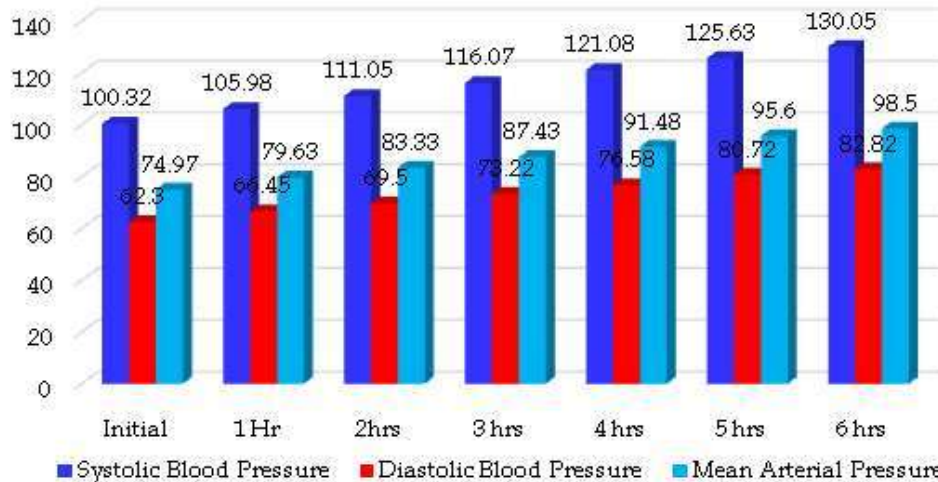


Fig. 5: Hourly MAP

Table 8: Paired Samples Statistics

**Paired 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 >155 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 6<sup>th</sup> 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 insipidus 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 hyponatremic 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.*<sup>9</sup> and Lee YJ, Shen EY, Huang -FY, Kao HA, Shyr SD *et al.*<sup>10</sup>

Catecholamine sparing effect of vasopressin is

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

**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**

Hyponatremia a frequent electrolyte disturbance from central 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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