# PROSPECTIVE STUDY OF EVALUATION OF THE ROLE OF VASOPRESSIN IN THE MANAGEMENT OF HYPERNATREMIA IN CLINICALLY BRAIN DEAD PATIENTS

**Dissertation submitted to**
**THE TAMILNADU DR. M.G.R.MEDICAL UNIVERSITY**

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**CHENNAI TAMILNADU**

# CERTIFICATE

This is to certify that the dissertation entitled, "**Prospective study of evaluation of the role of vasopressin in the management of hypernatremia in clinically braindead patients"** Submitted by Dr. G.BALAJI in partial fulfilment for the award of the degree of Doctor of Medicine in Anaesthesiology by the Tamilnadu Dr. M.G.R. Medical University, Chennai is bonafide record of the work done by his in the INSTITUTE OF ANAESTHESIOLOGY & CRITICAL CARE, Madras Medical College, during the academic year 2009-2012.

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# CONTENTS

# INTRODUCTION

# INTRODUCTION

In response to a traumatic brain injury or physiological “insult” to the brain (e.g., hemorrhagic or ischemic stroke), some patients suffer global and irreversible loss of brain stem function, leading to a diagnosis of brain death. Some of these patients may be candidates for organ and tissue donation, a decision mediated by the patient’s previously expressed wishes, sometimes in the form of an advance directive or organ donor card, and the preferences of the patient’s family. Patients with irreversible brainstem dysfunction are potential candidates for organ donation. As the awareness regarding organ donation and the frequency of donation are increasing with time, organ preservation strategies and protocols should be followed meticulously to improve the outcome of donation programme.

After the diagnosis of brain death the focus of patient care shifts from interventions aimed at saving the patients (donor) life to interventions aimed at maintaining viability of potentially transplantable organs.

As the brainstem dysfunction evolves the there occurs so many alterations in the normal physiology. The resultant changes in the cell

homeostasis can adversely affect the donor organ viability which in turn affect the graft function.

By understanding the pathophysiology of brain death we can manage the adverse changes reasonably, which may improve the survival of the grafted organs.

Among the major changes endocrine changes are worth mentioning. Diabetes insipidus is the most common endocrine abnormality seen in the brain-dead patients, manifests earlier or later during the process[(1)(2)].

One of the effects of diabetes insipidus is hypernatremia, defined as serum sodium level >145mEq/L[(3)].

Organs commonly harvested are kidneys, liver, heart/heart valves, cornea etc. Donor organs affected by hypernatremia are liver, kidneys, heart. Of these liver grafts are more prone to early rejection. Effects are more when the sodium levels are > 155mEq/L particularly when it is a persistent one for longer duration before procurement[(3)].

Various studies have showed the relationship between the serum sodium level and the graft survival and explained the adverse effects of hypernatremia.

So managing the hypernatremia can improve the survival of transplanted organs especially the liver. Which is the theme of this study.

There are many approaches for managing the hypernatremia. Among them I have chosen the exogenous vasopressin administration to replace the reduced serum vasopressin level as the treatment of choice because it also has potent vasopressor property which will be useful in maintaining hemodynamic stability in these patients due to the frequently accompanying autonomic failure.

Other derangements also have to be corrected with fluid replacement, dopamine, thyroxine, methyl prednisolone, insulin-KCL regimen, antibiotics etc.

In this study I have attempted to evaluate the role of vasopressin in the management of hypernatremia in clinically brain-dead patients, by comparing the serum sodium levels before and after initiating the vasopressin infusion therapy.

# BRAINDEATH
# AND
# HYPERNATREMIA

# BRAINDEATH AND HYPERNATREMIA

## BRAINDEATH

### Definition:

Irreversible cessation of all functions of the entire brain, including the brain stem.

### Causes:

- Severe head trauma
- Aneurysmal subarachnoid hemorrhage
- Cerebro vascular injury
- Hypoxic-ischemic encephalopathy
- Fulminant hepatic necrosis
- Prolonged cardiac resuscitation or asphyxia
- Tumors.

### Pathophysiology:

MECHANISM

Following any major injury there will be

(1) Ischemia and (2) Re-perfusion injury (later).

High-energy stores are depleted, Ca2+ influx overwhelms the ionic pumps, endothelial swelling develops and reactive oxygen species accumulate secondary to insufficient perfusion.

Activation of inflammatory mediators such as the complement system, thromboxanes, platelet and leukocyte factors are central to the pathophysiologic events after onset of brain death. As time progresses, there is a progressive leukocyte influx into solid organs with a continuous inflammatory deterioration that enhances the immunogenicity of the graft. There is ameasurable increase of inflammatory compounds: intercellular adhesion molecule-1 (ICAM-1), vascularcellular adhesion molecule-1 (VCAM-1), E-selectin, interleukin-6, interferon-G, macrophage inflammatory protein-1α, tumour necrosis factor-α and countless others[(4)].

Major physiologic changes:

Loss of brain stem function results in systemic physiologic instability:

- Initial catecholamine storm followed by depletion (autonomic failure) → CVS instability, arrhythmias, hypertension followed by hypotension.

- Loss of vasomotor control (Hypothalamus damage) leads to a hyperdynamic state.

- Loss of respiratory function- apnoea, impaired gas exchange

- Loss of temperature regulation (Hypothalamus damage) → Hypothermia

- Endocrine failure due to Hypothalamus & pituitary damage → DI, hypothyroid, steroid depletion, insulin resistance- intravascular volume depletion, electrolyte imbalance (hypernatremia), hyperglycemia etc[5].

**Incidence of major pathophysiological changes:**

| | | |
|---|---|---|
| - | Hypotension | 81% |
| - | Diabetes Insipidus | 72-77% |
| - | DIC | 28% |
| - | Cardiac arrhythmias | 25% |
| - | Pulmonary edema | 18% |
| - | Metabolic acidosis | 11% |

**Normal brain functions**

| Part of brain | Normal function | Brain death |
|---|---|---|
| CEREBRUM | Cognition, Voluntary movements, Sensation | Coma |
| BRAINSTEM | Cranial nerve nuclei, Respiration | Absent brainstem reflexes , Apnea |
| RAS | Wakefulness | Coma |

**Brain-Death Criteria:**

- Absent Cerebral Function(coma)
- Absent Brainstem reflexes
- Apnea- Once coma and absence of brain stem reflexes have been confirmed →Apnea test.
  - Verifies loss of most rostral brain stem function
  - Confirmed **by PaCO2 > 55 mmHg or PaCO2 >15 mmHg over baseline value during apnea period**-with no respiratory attempt
  - 2 tests at 6 hrs interval

**In paediatric age group**

- Clinical examination is same as in adults.

- Testing criteria depends on age of child.

  - Neonate < 7 days → Brain death testing is not valid.

  - 7 days – 2 months
    - Two clinical exams and two EEG 48 hrs apart.

  - 2 months – 1 year
    - Two clinical exams and two EEG 24 hrs apart.
    - or two clinical exams, EEG and blood flow study.

  - Age > 1 year to 18 years
    - Two clinical exams 12 hrs apart, confirmatory study - Optional

**Confirmatory tests**

- Cerebral Blood Flow (CBF) Studies
- Cerebral Angiography
- Nuclear Flow Study
- EEG (when brain scan is not utilized)

- Other rarely used tests
  - Transcranial doppler ultrasonogram
  - Spiral computer tomogram
  - Magnetic resonance imaging[6]

Confirmatory tests are,

- **Purely optional** when the clinical criteria are met unambiguously.
- A confirmatory test is needed for patients in whom specific components of clinical testing cannot be reliably evaluated
  - Incomplete brain stem reflex testing
  - Incomplete apnea testing
  - Toxic drug levels
  - Children younger than 1 year old.
  - Required by institutional policy

**DIABETES INSIPIDUS**

- Diabetes insipidus can be defined as urine ouptut >4 mL/kg per hr in adults and children
- Associated with rising serum sodium (≥ 145 mmol/L)
- Associated with rising serum osmolarity (≥ 300 mosM) and decreasing urine osmolarity (≤ 200 mosM)[3].

## HYPERNATREMIA

- It is defined as serum sodium level > 145meq/L

- **Causes** of hypernatremia in braindead patients

  - ADH(Vasopressin) deficiency secondary to posterior pituitary infarction(central diabetes incipidus) -which results in increased free water clearance.

  - Sodium overload (NS)

  - Rarely nephrogenic DI

Adverse effects of hypernatremia on donor organs

- Donor hypernatremia with serum sodium levels > 155meq/L has been reported to be associated poorer liver graft outcome in comparison with normonatremicdonors[3].

- Due to the formation idiogenicosmoles in donor hepatocytes to maintain IC osmolarity to avoid cellular dehydration.

- Donor hypernatremia also associated with renal and cardiac graft dysfunction.

**Hypernatremia**

- Results in early graft loss
- Affects patient survival
- Prolongs ICU stay
- Elevated liver enzymes in the post-op period

Duration of hypernatremia also influences the graft survival.

**SO, MANAGING THE SERUM SODIUM LEVEL WITHIN NORMAL LIMITS MAY IMPROVE GRAFT SURVIVAL (ESPCIALLY LIVER).**

**Management of hypernatremia in brain-dead patients:**

Hyperglycemia, cold diuresis, preceding diuretic treatment for cerebral edema, the diuretic effect of radiographic contrast material used for angiography or the diuretic reaction to an iatrogenic overhydration should be excluded before treatment with vasopressin is commenced.

Serum sodium target range is 130–150 mmol/L.

1. Vasopressin infusion - dose – 0.5 to 3U/hr (or) 0.01 to 0.04 U/min(10-40mU /kg/hr)

- max. safety dose without much CVS compromise 0.04U/min or 40mU/kg/hr
- 1U i.v bolus can be given before infusion

The pediatric dose range for vasopressin is 0.0003–0.0007 U/kg per minute (0.3–0.7 mU/kg per minute) to a maximum dose of 2.4 U/h.[3]

2. Desmopressin- adults: 1–4 μg IV then 1–2 μg IV every 6 h to achieve urine output < 4 mL/kg/h.[7]

Children : 0.25–1 μg IV every 6 h to achieve urine output <4mL/kg/h.

Intranasal10 – 40 mics in 2-3 divdeddoses.

DDAVP is an analog of AVP with a relatively pure antidiuretic effect and negligible vasopressor activity. Upper limits of DDAVP dosing are empirical. There is no clear upper limit for DDAVP dose, as it should be titrated to achieve the desired effect of reducing urine output.

Under the following circumstances, vasopressin infusion should be the first choice:

1. Hemodynamic support with vasospressin required
2. Combination hormonal therapy implemented[8]
3. Avoiding sodium cotaining fluids
4. Use fluids with high free water

**Hemodynamic Instability**

Hemodynamic instability following brain death can be attributed to three main causes. First, a sympathetic surge immediately preceding medullary level brain death leads to a massive release of catecholamines from postganglionic sympathetic nerve endings leading to elevated systemic vascular resistance, hypertension, left ventricular dysfunction, cardiac stunning, neurogenic pulmonary edema, and arrhythmias. Second, herniation following brain death leads to spinal cord infarction and loss of sympathetic tone resulting in further hypotension. Third, pituitary hormonal secretion ceases and the body enters a panhypopituitary state characterized by low cortisol, T3, T4, insulin, and ADH levels. Ensuing diabetes insipitus leads to further hypotension as the patient becomes volume depleted.

**Management of other alterations in brain-dead patients**

1. Hypotesion

- Maintain CVP at 12-15mmHg with fluids
- Inotropes (dopamine, dobutamine)
- Vasopressors(vasopressin)

2. Combined hormonal therapy is defined as administration of

- Thyroid hormone (tetraiodothyronine or T4), 20 μg IV bolus followed by 10 μg/h IV infusion
- Vasopressin, 1 U IV bolus followed by 2.4 U/h IV infusion
- Methylprednisolone, 15 mg/kg IV every 24 h.
- Insulin infusion based on hourly blood sugar.

It is recommended in donors with an ejection fraction ≤ 40%, basedon 2-dimensional echo cardiographic assessment, or hemodynamic instability. Consideration should be given to its use in all donors.

3. Tansfusion threshold:

A target hemoglobin level of 90–100 g/L is most appropriate to optimize cardiopulmonary function in the face of hemodynamic

instability. A level of 70 g/L is the lowest acceptable limit for management of stable donors in the ICU.

- There are no defined targets for platelet concentration, international normalized ratio or partial thromboplastin time. Platelet or plasma factor replacement is indicated for clinical bleeding only.

- Blood drawing for donor serology and tissue typing should occur before transfusions to minimize the risk of false results related to hemodilution.

- No special transfusion precautions are required in organ donors.

4. Antibiotics

An initial baseline blood culture should be carried out for all donors and repeated after 24 h and on an as-needed basis.

- Positive blood cultures or confirmed infections are not contraindications to organ donation.

- Antibiotic therapy should be initiated in cases of proven or presumed infection. Duration of therapy depends on the

virulence of the organism and decisions should be made in consultation with the transplant team and infectious disease services.

- No minimum duration of therapy before organ procurement can be defined at this time.

5. Oxygenation & ventilation

Mechanical ventilation with the following targets:

- fraction of inspired oxygen ($Fio_2$) titrated to keep oxygen saturation $\geq$ 95% and partial pressure of arterial oxygen ($PaO_2$) $\geq$ 80 mm Hg

- pH: 7.35–7.45, $PaCO_2$: 35–45 mm Hg

- Positive end expiratory pressure (PEEP): 5 cm $H_2O$.

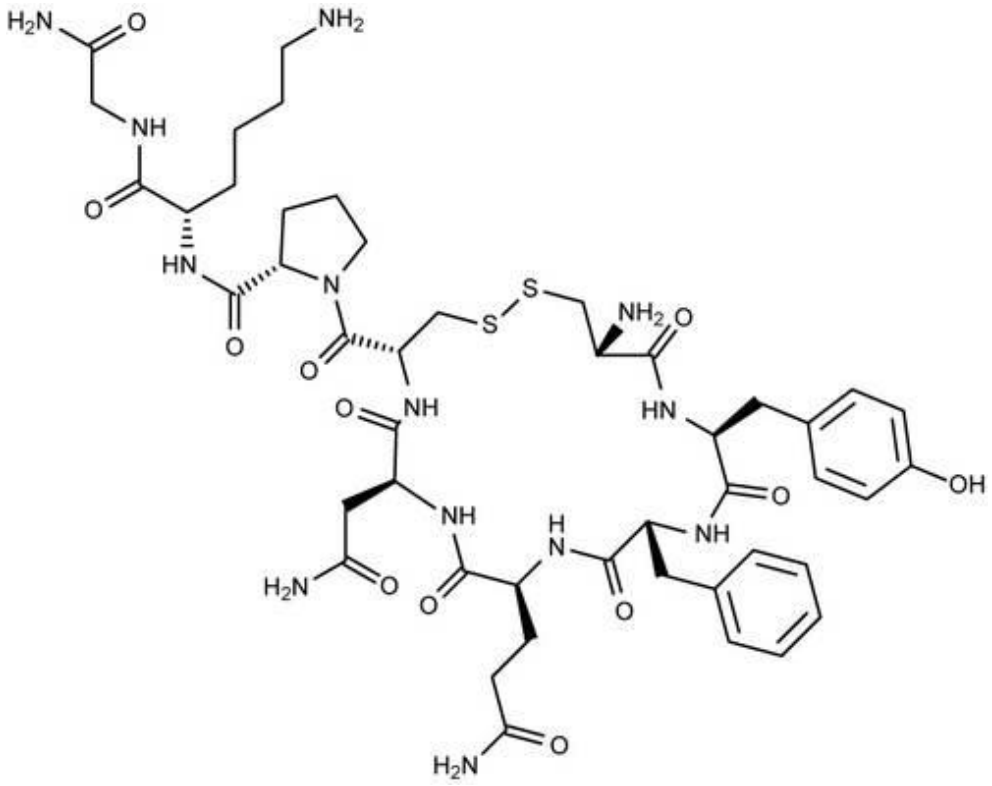
6. Glycemic control

Glucose control with insulin infusions titrated to achieve a blood glucose level of 4–8 mmol/L is recommended.

# VASOPRESSIN

# VASOPRESSIN

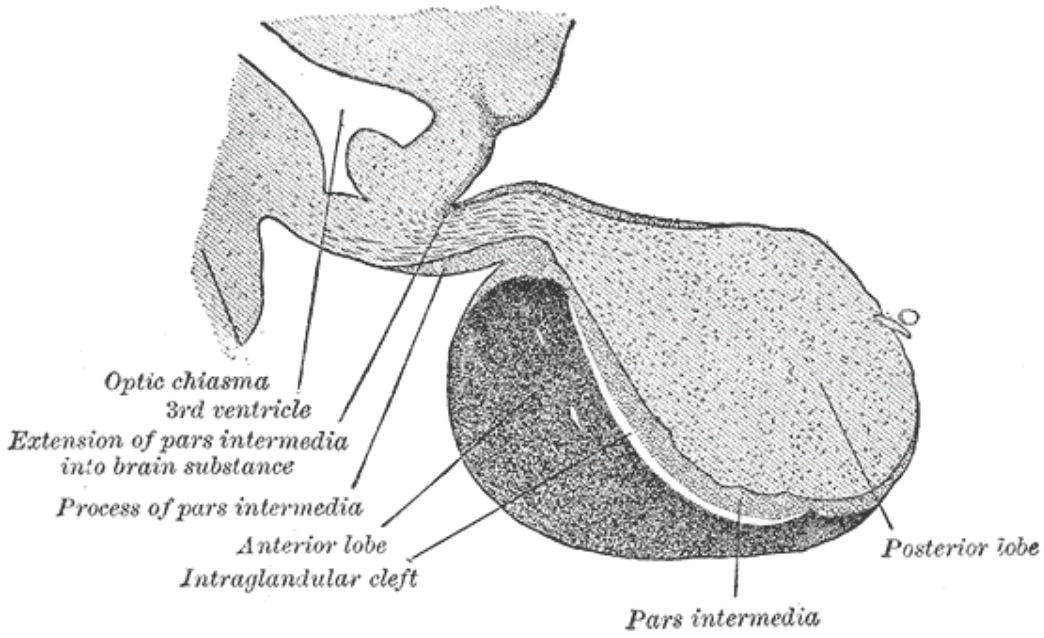
- An Amino peptide
- Vasopressin Chemical Structure



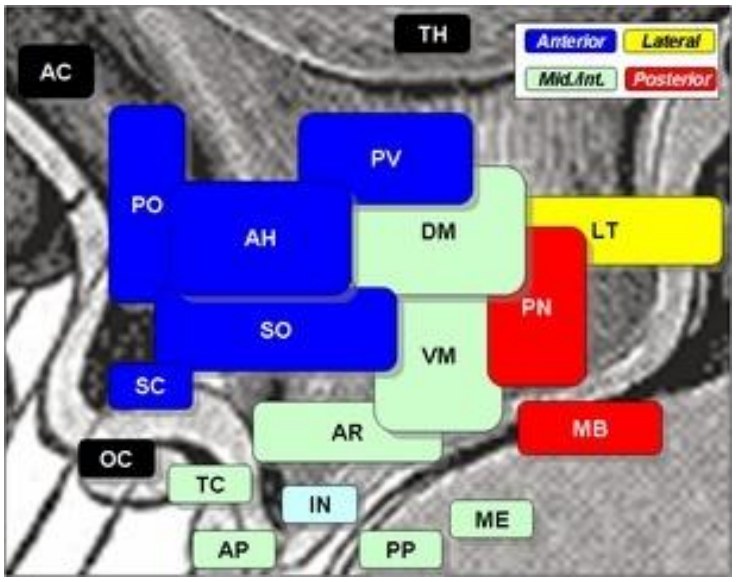

- The antidiuretic mechanism involves **two anatomical components:** a CNS component for the synthesis, transport, storage, and release of vasopressin and a renal collecting-duct system composed of epithelial cells that respond to vasopressin by increasing their permeability to water.[8]

- **Synthesis**- Hypothalamus-Supra-optic nuclei, Paraventricular nuclei (magno cellular neurons)

## PITUITARY GLAND




## HYPOTHALAMIC NUCLEI




Vasopressin synthesis appears to be regulated solely at the transcriptional level. In human beings, a 168-amino acid

preprohormoneis synthesized. During synthesis, the signal peptide is removed to form the vasopressin prohormone, which then is processed and incorporated into the Golgi compartment. The synthesis and transport of vasopressin depend on the conformation of the preprohormone. In particular, VP-neurophysin binds vasopressin and is critical to the correct processing, transport, and storage of vasopressin. Genetic mutations in either the signal peptide or VP-neurophysin give rise to central diabetes insipidus.

**Storage**- Posterior pituitary.The long axons of magnocellular neurons in the SON and PVN transverse the external zone of the median eminence to terminate in the neural lobe of the posterior pituitary (neurohypophysis), where they release vasopressin and oxytocin.-

**Stimulus**

**1. Serum Hyperosmolality**

The osmolality threshold for secretion is approximately 280 mOsm/kg. Below the threshold, vasopressin is barely detectable in plasma, and above the threshold, vasopressin levels are a steep and relatively linear function of plasma osmolality. A small increase in plasma osmolality leads to enhanced vasopressin secretion. Indeed, a

2% elevation in plasma osmolality causes a two- to threefold increase in plasma vasopressin levels, which, in turn, causes increased solute-free water reabsorption, with an increase in urine osmolality. Increases in plasma osmolality above 290 mOsm/kg lead to an intense desire for water (thirst). It is important to point out, however, that above a plasma osmolality of approximately 290 mOsm/kg, plasma levels of vasopressin exceed 5 pM. Since urinary concentration is maximal (about 1200 mOsm/kg) when vasopressin levels exceed 5 pM, further defense against hypertonicity depends entirely on water intake rather than on decreases in water loss.

Several CNS structures are involved in osmotic stimulation of vasopressin release by the posterior pituitary; these structures are collectively referred to as the osmoreceptive complex. Although magnocellular neurons in the SON and PVN are osmosensitive, afferent inputs from other components of the osmoreceptive complex are required for a normal vasopressin response.

The SON and PVN receive projections from the subfornical organ (SFO) and the organumvasculosum of the lamina terminalis (OVLT) either directly or indirectly via the median preoptic nucleus (MnPO). Subgroups of neurons in the SFO, OVLT, and MnPO are either

osmoreceptors or osmoresponders (i.e., are stimulated by osmoreceptive neurons located at other sites). Thus a web of interconnecting neurons contributes to osmotically induced vasopressin secretion. Aquaporin 4, a water-selective channel, is associated with CNS structures involved in osmoregulation and may confer osmosensitivity. In the CNS, aquaporin 4 resides on glial and ependymal cells rather than on neurons, suggesting that osmotic status may be communicated to the neuronal cell by a glial-neuron interaction.

## 2. Hypovolemia and Hypotension

Vasopressin secretion also is regulated hemodynamically by changes in effective blood volume and/or arterial blood pressure.

The neuronal pathways that mediate hemodynamic regulation of vasopressin release are different from those involved in osmoregulation. Baroreceptors in the left atrium, left ventricle, and pulmonary veins sense blood volume (filling pressures), and baroreceptors in the carotid sinus and aorta monitor arterial blood pressure. Nerve impulses reach brainstem nuclei predominantly through the vagal trunk and glossopharyngeal nerve; these signals are relayed to the solitary tract

nucleus, then to the $A_1$-noradrenergic cell group in the caudal ventrolateral medulla, and finally to the SON and PVN.

### 3. Endogenous agents

Several agents are known to stimulate vasopressin secretion, including acetylcholine (via nicotinic receptors), histamine (via $H_1$ receptors), dopamine (via both $D_1$ and $D_2$ receptors), glutamine, aspartate, cholecystokinin, neuropeptide Y, substance P, vasoactive intestinal polypeptide, prostaglandins, and angiotensin II. Inhibitors of vasopressin secretion include atrial natriuretic peptide, g-aminobutyric acid, and opioids (particularly dynorphinvia k receptors).

### 4. Drugs

Stimulators of vasopressin secretion include vincristine, cyclophosphamide, tricyclic antidepressants, nicotine, epinephrine, and high doses of morphine. Lithium, which inhibits the renal effects of vasopressin, also enhances vasopressin secretion. Inhibitors of vasopressin secretion include ethanol, phenytoin, low doses of morphine, glucocorticoids, fluphenazine, haloperidol, promethazine, oxilorphan, and butorphanol. Carbamazepine has a renal action to

produce antidiuresis in patients with central diabetes insipidus but actually inhibits vasopressin secretion via a central action.

**Receptors and mechanism**

| Type | Second Messenger | Site | Effect |
|---|---|---|---|
| V1 | G1q-PLC, IP3, DAG | Vascular smooth muscle | Vasoconstriction |
| V2 | AC-cAMP | CD of renal tubule | Anti-diuresis, viii & vwf release |
| V3 | PLC, IP3, DAG | CNS | ACTH release |

**Pharmacological effects**

$V_1$-receptor-mediated therapeutic applications are based on the rationale that $V_1$ receptors cause contraction of gastrointestinal and vascular smooth muscle.

$V_2$-receptor-mediated therapeutic applications are based on the rationale that $V_2$ receptors cause water conservation and release of blood coagulation factors. Central but not nephrogenic DI can be treated with $V_2$-receptor agonists, and polyuria and polydipsia usually are well controlled. Some patients experience transient DI (e.g., in head injury or

surgery in the area of the pituitary); however, therapy for most patients with DI is lifelong.

- CVS- Vasoconstriction-skin, skeletal muscle, fat-GIT, coronary, brain.

Despite the potency of vasopressin as a direct vasoconstrictor, **vasopressin-induced pressor responses in vivo are minimal and occur only with vasopressin concentrations significantly higher than those required for maximal antidiuresis.**

- RENAL- Aquaporin2 mediated increased water permeability in principal cells of collecting tubules. (water & electrolyte balance)
- CNS- ACTH release
- COAGULATION- Release of factor viii & Vwf from endothelium- HEMOSTASIS.
- OTHERS- smooth muscle contraction in GIT & uterus, platelet aggregation, glycogenolysis etc.

**Diseases affecting vasopressin system**

When <5pg/ml, linear decrease in body's ability to maximally concentrate urine and when it is <1pg/ml urine volume increases dramatically from <4L to >20L/day.

1. Diabetesinsipidus - central/neurogenic, nephrogenic - reduced vasopressin level or function.

2. Syndrome of Inapproprite ADH secretion-excess serum vasopressin levels

**Synthetic analogues**

- Synthetic vasopressin- nanopeptide

- Pharmacokinetics – Vasopressin
  - t 1/2- 17 to 35 mins
  - duraion – 2 to 8 hrs
  - if given orally – digested by trypsin

- Desmopressin – potent V2 receptor agonist.

It has enhanced antidiuretic potency, greatly diminished pressor activity and prolonged half-life as compared to Vasopressin.

- t 1/2, - Fast component-6.5 to 9 mins

  - Slow component-30 to 117mins

- Other Vasopressin analogues/V1 receptor agonists-e.g. terlipressin

**Therapeutic uses**

Two antidiuretic peptides are available for clinical use. Vasopressin (synthetic 8-L-arginine vasopressin; PITRESSIN) is available as a sterile aqueous solution; it may be administered subcutaneously, intramuscularly, or intranasally. (2) Desmopressin acetate (synthetic 1-deamino-8-D-arginine vasopressin; DDAVP, others) is available as a sterile aqueous solution packaged for intravenous or subcutaneous injection, in a nasal solution for intranasal administration with either a nasal spray pump or rhinal tube delivery system, and in tablets for oral administration. The therapeutic uses of vasopressin and its congeners can be divided into two main categories according to the type of vasopressin receptor involved.

- Diabetes insipidus - of acute onset and shorter duration.Vasopressin can be used as an alternative to desmopressin in the initial diagnostic evaluation of patients with

suspected DI and to control polyuria in patients with DI who recently have undergone surgery or experienced head trauma. Under these circumstances, polyuria may be transient, and long-acting agents may produce water intoxication.

Vasopressin-dose – 0.5 to 3U/hr (or)0.01 to 0.04 U/min

- max. safety dose without much CVS compromise
- 0.04U/min or 40mU/kg/hr
- 1U i.v bolus can be given before infusion.
- The pediatric dose range for vasopressin is 0.0003–0.0007 U/kg per minute (0.3–0.7 mU/kg per minute) to a maximum dose of 2.4 U/h

- Acute GI hemorrhage – $V_1$-receptor-mediated vasoconstriction of the splanchnic arterial vessels reduces blood flow to the portal system and thereby attenuates pressure and bleeding in esophagealvarices. Although endoscopic variceal banding ligation is the treatment of choice for bleeding esophagealvarices, $V_1$-receptor agonists have been used in an emergency setting until endoscopy can be performed.

Finally, $V_1$-receptor-mediated vasoconstriction has been used to reduce bleeding during acute hemorrhagic gastritis, burn wound excision, cyclophosphamide-induced hemorrhagic cystitis, liver transplant, cesarean section, and uterine myoma resection.

- Vasodilatory shock – resistant to catecholamines(1-5U/hr)
- CPR- 40U single i.v dose may replace first or second dose of epinephrine.
- Post-op- $V_1$-receptor-mediated contraction of gastrointestinal smooth muscle has been used to treat postoperative ileus and abdominal distension and to dispel intestinal gas before abdominal roentgenography to avoid interfering gas shadows.
- Hemophilia / VWD(desmopressinprefered - 0.3mics/kg)
- Nocturnal enuresis (desmopressinprefered -2.5 mics)

**Drug interaction**

- POTENTIATION-carbamazepine, chlorpropamide, TCA, opioid, NSAIDS
- ATTENUATION – demeclocycline, lithium, ethanol.

- CAUTION- angina, CHF, hypertension

- CONTRAINDICATION- ARF

**Adverse effects**

Most adverse effects are mediated through the $V_1$ receptor acting on vascular and gastrointestinal smooth muscle.

- After the injection of large doses of vasopressin, marked facial pallor owing to cutaneous vasoconstriction is observed commonly. Increased intestinal activity is likely to cause nausea, belching, cramps, and an urge to defecate. Most serious, however, is the effect on the coronary circulation. Vasopressin should be administered only at low doses and with extreme caution in individuals suffering from vascular disease, especially coronary artery disease. Peripheral vasoconstriction and gangrene have been encountered.

- Coronary vasospasm, arrhythmias, decreased cardiac output.

- The major $V_2$-receptor-mediated adverse effect is water intoxication, which can occur with desmopressin or vasopressin.

- Urticaria to anaphylaxis- allergic reaction.

# REVIEW OF LITERATURE

# REVIEW OF LITERATURE

The literature was searched and reviewed to seek the supporting evidences for role of vasopressin in the management of hypernatremiain braindead patients, effect of traumatic brainstem dysfunction on serum vasopressin level, effect of, donor hypernatremia on the grafted organs, the effect of the correction of donor hypernatremia, role of vasopressin in hemodynamic stability and catecholamine sparing effect of vasopressin.

## 1. Charles Ralston, Warwick Butt et al[9]

Study was done on five children with severe brain injury who developed diabetes insipidus. They received continuous intravenous treatment with a solution containing both aqueous vasopressin and appropriate crystalloid replacement. Major manifestations of diabetes incipidus such as polyuria, hypernatraemia, and decreased urine osmolalities were corrected in all patients within eight to 28 hours of treatment.

Diagnostic criteria for diabetes incipidus include polyuria (>30 ml/kg/day), hypernatraemia, and low urine osmolality (<250 mmol/kg).

Vasopressin infusion was started as soon as the diagnosis of diabetes insipidus was confirmed.

Vasopressin infusion was started. Crystalloid infusion aimed, to replace 80-110% of measured urine excretion. The volume replacement was according to the previous hour's urinary output. Monitoring - measurement of urine volume every hour, electrolytes every four hours, and urine osmolality every 12 hours. The serum sodium was recorded every two to four hours. Therapeutic end point was urine volume <2 ml/kg/hr, urine osmolality >300 mmol/kg, and serum sodium concentration <145 mmol/l.

Result-in all cases decrease urine output (within 8 hrs) and decrease in serum sodium were noticed. Average dose ofvasopressin administered was 9mU/kg/hour (range 5-14 mU/kg/hour).

This report describes, the effective, methods for, the treatment of diabetes insipidus and the resultant hypernatremia, which include vasopressin and crystalloid infusions.,

**2. Lee YJ, Shen EY, Huang FY, Kao HA, Shyur SD et al[10]**

In this study three comatose children with, diabetes insipidus were treated with in vasopressin infusion. As soon as the diagnosis was

confirmed Vasopressin infusion was started at a dose of 1.3 to 2.7mU /kg/hr. Responses monitored were urine flow rate and serum sodium level. Decrease in urine output was noticed in 1 to 6 hours and decrease in serum sodium, was noticed 17- 53 hours after the initiation of treatment. Sodium control was seen during a period of 2.5 to 22 days until the patients' death, Continuous infusion of vasopressin gave the advantage of faster onset and shorter duration action. Therefore it could be easily titrated. They concluded that Vasopressin infusion was a rational therapy for comatose children with neurogenic diabetes insipidus.

### 3. Pennefather et al. (Pennefather SH, Bullock RE, Mantle D, Dark JH)[11]

It was a prospective study conducted in 24 brain-dead organ donors. Patients receive either saline or a low dose arginine vasopressin, infusion after randamization. In the, 11 patients of AVP group, plasma hyperosmolality reduced ($P < 0.05$), blood pressure increased ($P < 0.01$), inotrope need decreased ($P < 0.01$), and the, cardiac output was maintained. In the 13 patients of control group, plasma hyperosmolality increased (NS); no significant change in other parameters. They, concluded that the use of a low dose AVP infusion in potential, organ

donors, reduced, the inotrope requirement, and decreased the sodium levels in the serum. Target, MAP was between 65-85 mm Hg.

**4. Kenneth Katz, Jack Lawler, Jennifer Wax, Robert O'Connor, Vinay Nadkarn[(12)]**

Vasopressin pressor effects in critically ill children during evaluation for brain death and organ recovery

They, hypothesized that low dose Vasopressin, infusion during organ recovery in critically ill children exerted a pressor effect, without major organ toxicity. Method: 34 VP-treated and 29 age-matched critically ill controls (C) ≤18 years were retrospectively reviewed during brain death evaluation and organ recovery. Vasopressin dose titrated clinically to urine output, with high variability. Pressor and inotrope management was titrated clinically to BP, cerebral perfusion and CVP in VP and C groups. Outcome measures include dose, type and number of, pressors and inotropes. Organ function was assessed at recovery and 48 h post-transplant.

Result : VP dose averaged 0.041±0.069 U/kg/h. Average baseline mean arterial pressure (MAP) before VP infusion was 79±17 mmHg VP and 76±14 mmHg C. Subsequent average, MAP were: 82±21 mmHg

after VP infusion versus 71±16 mmHg C and 80±14 mmHg VP versus 68±22 mmHg C. Ability to wean/stop pressors, and inotropes was: dopamine (14/23) 42% VP versus (10/26) 38% C, epinephrine (4/5) 80% VP versus (0/6) 0% C, norepinephrine / phenylephrine (4/4) 100% VP versus (2/5) 40% C. Alpha agonist pressor dependence was successfully weaned from 7/9 (78%) VP versus 0/9 (0%) C.

Conclusion : Vasopressin (Low dose vasopressin infusion) treated patients were 7.3 times more likely to wean from alpha agonists than comparably managed age matched controls, without adverse affect on transplant organ function.

**5. Figueras et al[13]**

They studied deleterious effect of donor hypernatremia on graft acceptance in OLT.

In the study donor risk factors associated with second OLT (Re OLT) and graft loss after OLT were evaluated. Total of 649 OLTs in 11 centres during 1992-1993 were analysed. 11 parameters were monitored including serum sodium level in donor.

Conclusion:

1. Donor plasma sodium > 155mmol/L was associated with graft loss within 1 month.

2. Patients with plasma sodium >155mmol/L should be evaluated carefully before procurement.

**6. Eishi Totsuka, Forrest Dodson, Atsushi Urakami, Natalia Moras, Tomohiro Ishii, Ming-Che Lee, Jorge Gutierrez, Mauricio Gerardo, Ernesto Molmenti, and John J. Fung[(14)]**

In this study, the effect of hypernatremia on early liver graft rejection and the effect of its management on outcome during OLT were evaluated.

181 consecutive OLTs performed between May 1997 and July 1998 were selected for, this study. They divided the patients into, three groups based on, the donor serum sodium levels.

Group A, serum sodium of 155 mEq/L or less, (n 118); group B, with peak sodium value greater than 155 mEq/L and final sodium level, 155 mEq/L or less (n, 36); and group C, final sodium level persistently greater than 155 mEq/L (n 27)., 90 days graft survival, and early

postoperative graft function after OLT were analyzed. The, observation was : The frequencies of graft loss were 12.7% in group A, 11.1% in group B, and 33.3% (P <.05 v groups A and B) in group C.

Conclusion : Elevated liver enzymes and prothrombin, time were noticed, in the post operative period in group C for 14 days. Incidence of early graft rejection was higher in hypernatremic group.

**7. Kinoshita Y, Yahata K, Yoshioka T, Onishi S, Sugimoto T et.al.[(15)]**

In this study 28 braindead patients were divided into 2 groups. 10 patients received epinephrine infusion. In 18 patients Vasopressin infusion started in addition to epinephrine. 8 out of 10 patients in epinephrine group went for cardic arrest in < 48 hrs even with higher doses. Urine output was not controlled. Renal function deteriorated progressively.

In vasopressin group blood pressure was maintained with low dose epinephrine. Survival duration was prolonged to 4 days. Urine output was controlled and RFT normalized. It was concluded that combined vasopressin and epinephrine infusion maintained normal RFT for longer time (upto 2 weeks).

**8. Jennifer A. Frontera, Thomas Kalbet al**[16].

They explained the role of hormonal therapy in braindead management. Levothyroxine, solumedrol, Vasopressin and insulin were used. Hormonal therapy was started when there were hypotension with features of diabetes insipidus, in braindead patients. In a prospective study with 19 hemodynamically unstable, braindead patients, refractory to usual treatment with fluids and inotropes, hormonal therapy was started and a significant decrease in vasopressor requirement was noticed.

In another retrospective study with 10292 patients, initiation of hormonal therapy resulted in high organ yield.

**9. Totsuka E, Fung U, Hakamada K, Tanaka M, Takahashi K, Nakai M, Morohashi S, Nishimura A, Ishizawa Y, Ono H, Toyoki Y, Narumi S, Sasaki M.**[17]

This study was done toto analyse several clinical parameters that affect 30 day graft loss after, OLT (Orthotopic Liver Transplantation). 186 liver transplantations, that have been done in the period of May 1997 to June 1998 at university of Pittsburgh medical centre, were

included. Donor variables include age, sex, dopamine dose, cold ischemia time, warm ischemia time, serum sodium level.

28 grafts were lost. Factors, that affected, the graft survival were serum sodium> 155 mmol/L, CIT >12 hrs, WIT> 45%.

It was concluded that donor hypernatremia, CIT and WIT independently affect the graft survival, after OLT. Avoiding long preservation and correcting serum sodium were suggested to, improve the graft acceptance.

**10. Yoshioka T, Sugimoto H, Uenishi M, Sakamoto T, Sadamitsu D, Sakano T, Sugimoto T.[(18)]**

This study was done in 16 braindead patients (14-head injury, 2-CVA).

10 patients were treated with epinephrine infusion alone with target systolic BP 90mmHg.Remaining, 6 patients received Vasopressin infusion at a dose of 1-2U/hr (285+/-45microunits/kg/min), along with epinephrine infusion.

10 patients treated with epinephrine alone had cardiac arrest within 48 hrs, with mean survival time 24.1+/-17.2 hrs. In patients who

received vasopressin infusion the changes noticed were, epinephrine dose requirement was not more than >0.5mg/hr and prolonged mean survival time (23.1+/-19.1 days). It was cocluded that in, braindead patients the role of Vasopressin is critical, in hemodynamic maintenance and in improving the opportunities for organ transplantation.

## 11. Luciana Mascia, Ilaria Mastromauro and Silvia Grottoli etal[19]

Chen et al demonstrated a significant decrease in catecholamine doses (dopamine/nor epinephrine), using low dose Vasopressin infusion (0.04-1.0U/min) with considerable increase in MAP and organ perfusion.They also demonstrated, a complete weaning from catecholamines in 40% brain-dead patients with the use of Vasopressin. This was supported by a study done by venkateswaran et al, and they suggested more extensive vasopressin usage as an alternative to norepinephrine in the management of brain-dead patients. Also Yoshioka et al demonstrated a prolonged hemodynamic stability with combined epinephrine and Vasopressin usage comparing the usage of epinephrine alone.

**12. Kerri M. Robertson, MD, FRCP(C), and D. Ryan Cook, MD[20]**

It is mentioned that hemodynamic effects of vasopressin are dose-dependent and include generalized systemic vasoconstriction with an increase in blood pressure and a decrease in cardiac output, coronary and renal blood flow, bradycardia, and arrhythmias. With currently available information, it appears that the benefits of early treatment of the polyuria of DI with a titratable infusion of vasopressin, thereby minimizing electrolyte abnormalities, fluid shifts, and a reduction in core temperature, outweigh the potential for ischemic end-organ injury.

**13. V. Shah, G. Bhosale et al[21]**

Organ donor problems and their management

In this study they, recommend frequent monitoring of U/O, serum electrolytes, glucose and urinary electrolytes in this study, when, U/O > 300 ml/hr or 4 ml/kg/hr, desmopress in (1-4 μg 8-12 hrly), a synthetic analogue of vasopressin was administered. It has enhanced antidiuretic potency, greatly diminished pressor activity and prolonged half-life as compared to Vasopressin. If refractory hypotension is a problem,

Desmopressinwas, changed to Vasopressin (1 U bolus + infusion 0.5-4 U/hr).

As, polyuria can cause obligatory loss of fluid and electrolytes, was aggressively managed to maintain haemodynamic and electrolyte stability. The, previous hour's U/O, was replaced with a hypotonic fluid (5% Dextrose in 0.45% NaCl), with close monitoring of electrolytes, as elevated serum sodium is a risk factor for delayed or primary nonfunction of grafted organs.

**14. Hohenegger M, Vermes M, Mauritz W, Redl G, Sporn P, Eiselsberg P[(22)]**

Serum vasopressin (AVP) levels in polyuric brain-dead organ donors.

In this study serum vasopressin level was evaluated in 11 braindead patients. There were polyuria and low urine osmolality (which was always below the serum osmolality) noticed. Serum Vasopressin levels of braindead patients were compared with that of the normal subjects.

Observation: Serum Vasopressin levels in braindead patients were between 1.32- 50 pg/ml. In normal subjects the values were between 0.7-8pg/ml.

Conclusion: Thus in this study both normal and elevated Serum Vasopressin levels were noticed in braindead patients. So the nephrogenic Diabetes Insipidus was suspected in these patients.

# AIM OF THE STUDY

# AIM OF THE STUDY

To evaluate the role of vasopressin in the management of hypernatremia in clinically brain-dead patients using intravenous vasopressin infusion at a dose of 0.01-0.04U/min in 40 clinically brain-dead patients.

# MATERIALS AND METHOD

# MATERIALS AND METHODS

It was a prospective a study of evaluation of the role of vasopressin in the management of hypernatrmia in clinically braindead patients, conducted in Government General Hospital, Chennai.

## STUDY DESIGN

Prospective, interventional.

After obtaining institutional ethical committee clearance, 40 clinically braindead patients with hypernatremia were selected using following criteria:

## INCLUSION CRITERIA

- Clinically braindead patients (ASA PS 6)
- Traumatic injury
- Serum Na+ level > 145 meq/L
- Urine output > 4ml/kg/hr

## EXCLUSION CRITERIA

- Braindead patients with serum Na+ < 146meq/L
- Urine output < 1.5-2ml/kg/hr

- Patients with known renal pathology
- Allergy to vasopressin group of drugs

## OUTCOME MEASURES

- Serum Na+ level
- Urine output
- Blood pressure
- Serum potassium
- Blood urea
- Serum creatinine
- Pulse rate
- Blood sugar

## MONITORING INTERVAL

All parameters were monitored hourly.

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

## 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 from any ward, patientswere visited and examined (History and clinical examination) thoroughly. Investigations were evaluated and if not complete instructions were given.

After confirming the existence of hypernatremia and verifying inclusion criteria, consent was obtained from patient's attenders and vasopressin infusion was started at a dose of 0.01U/min or 10mU/kg/hr. 20units vasopressin in 500ml NS (1ml =0.04U).

Above mentioned parameters were monitored at specified time intervals for 6 hours.

## RESULTS

1. Serum Na+ reaches the target value
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 vasoprssin

1. PRESENT- if there was decrease in serum Na+ level (to target level or decrease >10 to 15% from baseline)
2. NOT- if there was no change or increasing levels.

## STATISTICS

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

# OBSERVATION AND RESULTS

# OBSERVATION AND RESULTS

**Table: 1**

**Frequency Table : Demographic Profile - SEX**

| Sex | Frequency | Percent |
|---|---|---|
| MALE | 30 | 75.0 |
| FEMALE | 10 | 25.0 |
| **TOTAL** | **40** | **100.0** |

Male, Female distribution in this study was 75%, 25% respectively.

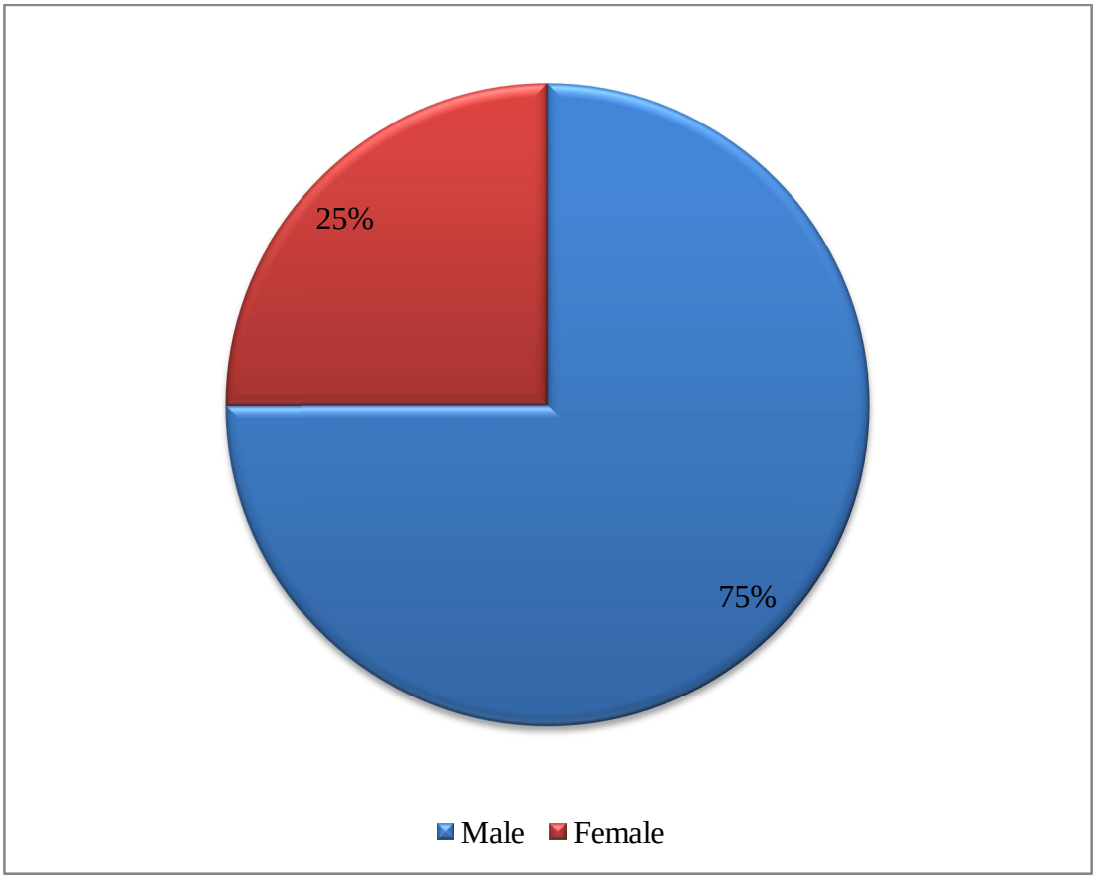


**Table: 2**

**Frequency Table : MODE OF INJURY**

| Mode of Injury | Frequency | Percent |
|---|---|---|
| RTA | 34 | 85.0 |
| Fall from Height | 6 | 15.0 |
| **Total** | **40** | **100.0** |

In this study 85% cases were road traffic accident, 15% cases were fall from height.

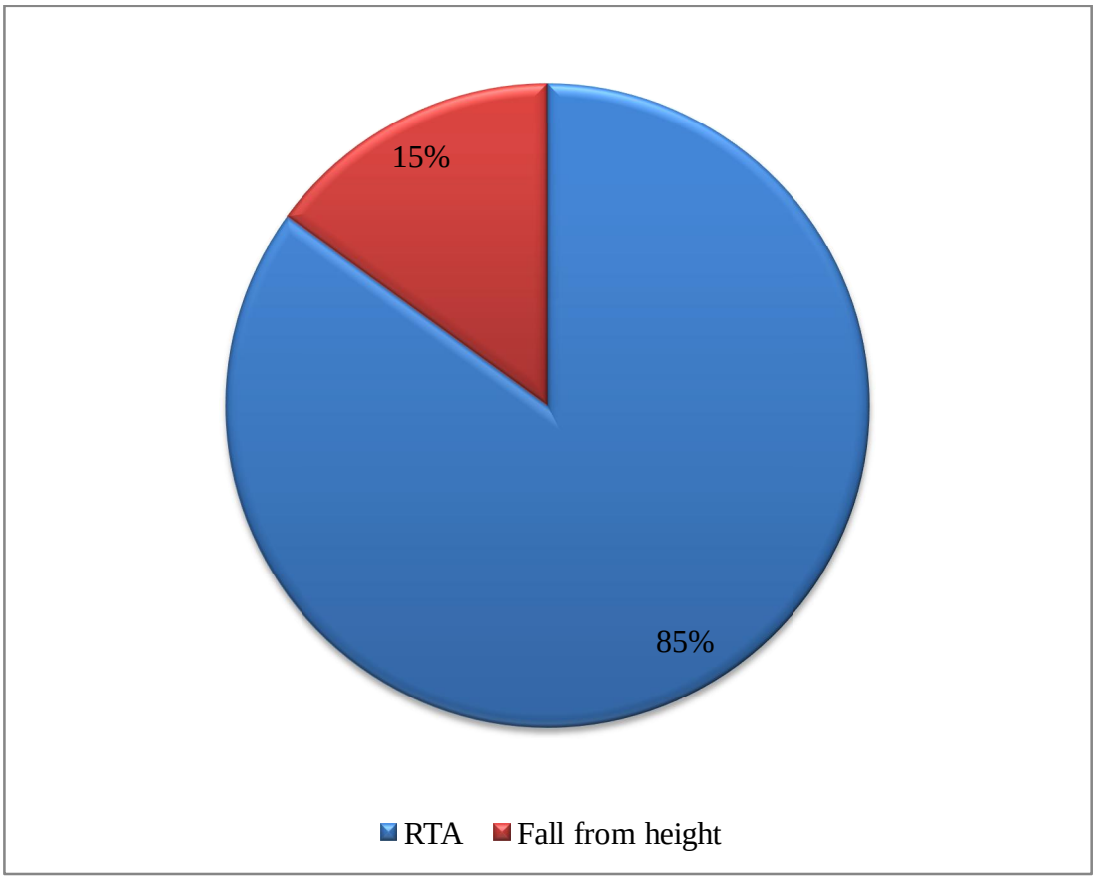


**Table: 3**

**Descriptive Statistics : AGE**

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

Mean age was -33.3.

**Table: 4**

**Frequency Table : GCS**

| GCS | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|
| 3 | 40 | 100.0 | 100.0 | 100.0 |

All the patients had GCS – 3/15

**Table:5**

**ASA**

| ASA | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|
| 6 | 40 | 100.0 | 100.0 | 100.0 |

All the patients came under ASA-6.

**Table: 6**

**RENAL DISEASE**

| Renal Disease | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|
| NIL | 40 | 100.0 | 100.0 | 100.0 |

All the patients were free of any renal pathology.

**Table: 7**

Descriptive Statistics, Friedman Test – to compare the hourly values.

**SERUM SODIUM**

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

There was a consistent decrease in serum sodium level in every hour.

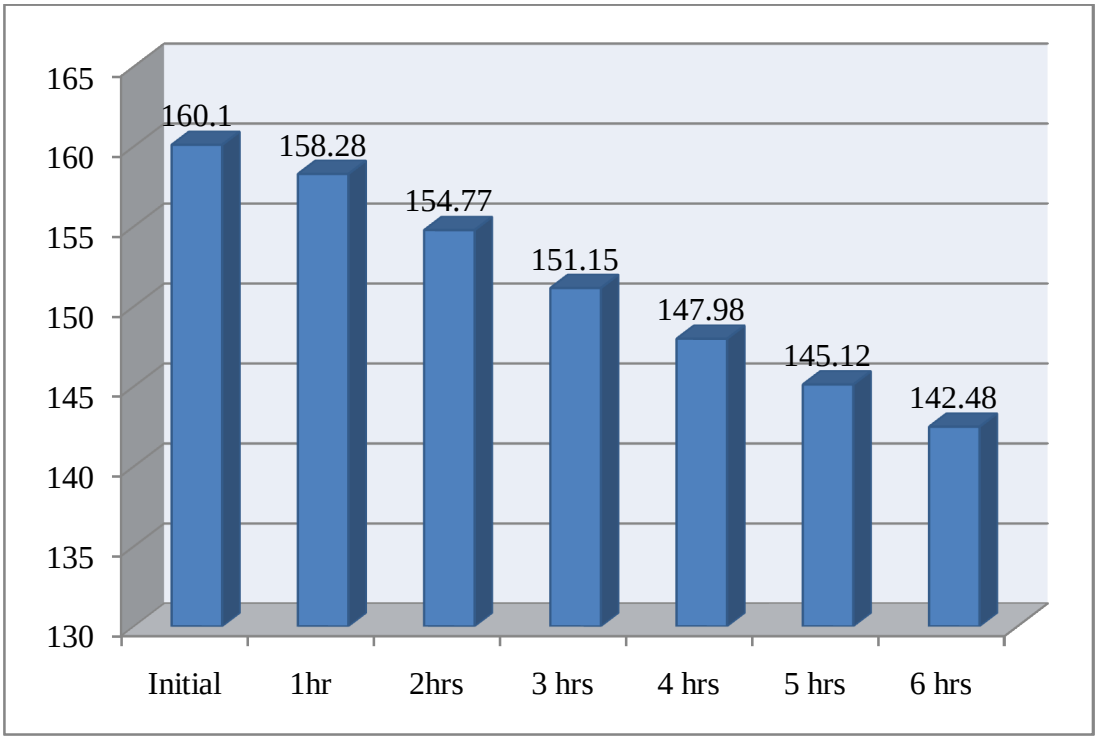


**Table: 8**

Paired Samples Statistics

Paired T-Test to compare the initial and final 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 | |

There was significant decrease in serum sodium at the end.

**Table: 9**

**Friedman Test – to compare the hourly values**

Urine output

Descriptive Statistics

| Urine output | N | Mean | Std. Deviation | Minimum | Maximum | p-value |
|---|---|---|---|---|---|---|
| Initial | 40 | 240.50 | 31.861 | 180 | 320 | |
| 1 hrs | 40 | 222.38 | 31.297 | 165 | 300 | |
| 2 hrs | 40 | 205.50 | 32.715 | 160 | 290 | |
| 3hrs | 40 | 188.25 | 33.846 | 140 | 290 | <0.001** |
| 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 | |

There was a consistent decrease in urine output.

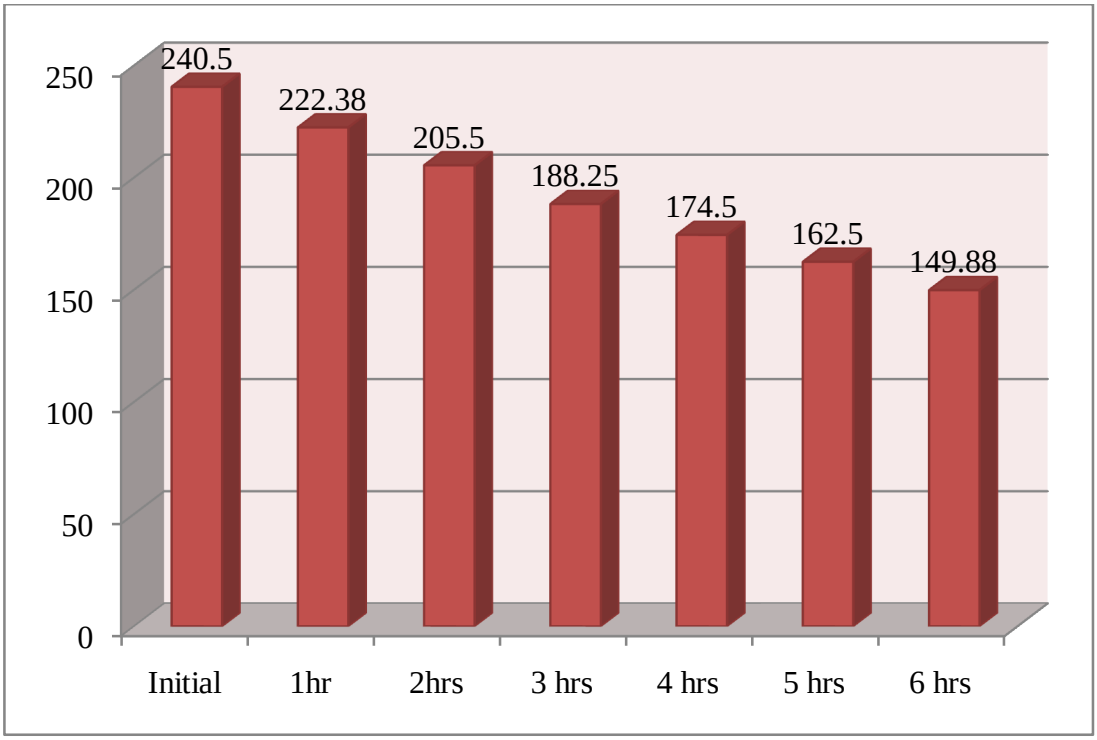


**Table: 10**

**Paired Samples Statistics**

Paired T-Test – to compare the initial and final values

| **Urine output** | **Mean** | **N** | **Std. Deviation** | **Std. Error Mean** | **p - value** |
|---|---|---|---|---|---|
| Initial | 240.50 | 40 | 31.861 | 5.038 | < 0.001** |
| 6hrs | 149.88 | 40 | 42.115 | 6.659 | |

There was significant decrease in urine output at the end.

**Table: 11**

**Systolic BP Descriptive Statistics**

Friedman Test – to compare the hourly values

| Systolic BP | N | Mean | Std. Deviation | Minimum | Maximum | p-value |
|---|---|---|---|---|---|---|
| Initial | 40 | 100.32 | 5.446 | 90 | 113 | <0.001** |
| 15mins | 40 | 102.23 | 5.323 | 92 | 114 | |
| 30mins | 40 | 103.98 | 4.886 | 94 | 114 | |
| 45mins | 40 | 105.58 | 4.877 | 96 | 117 | |
| 1 hrs | 40 | 105.98 | 4.938 | 96 | 117 | |
| 1 hrs 30mins | 40 | 108.73 | 4.883 | 98 | 121 | |
| 2 hrs | 40 | 111.05 | 4.904 | 102 | 123 | |
| 2 hrs 30mins | 40 | 113.43 | 4.766 | 105 | 125 | |
| 3 hrs | 40 | 116.07 | 4.649 | 107 | 128 | |
| 4 hrs | 40 | 121.08 | 4.376 | 113 | 130 | |
| 5 hrs | 40 | 125.63 | 4.584 | 118 | 135 | |
| 6 hrs | 40 | 130.05 | 5.223 | 122 | 142 | |

Gradual increase in systolic blood pressure was noticed.

**Table: 12**

**Paired Samples Statistics**

Paired T-Test – to compare the initial and final values

| Systolic BP | Mean | N | Std. Deviation | Std. Error Mean | p - value |
|---|---|---|---|---|---|
| Initial | 100.33 | 40 | 5.446 | .861 | < 0.001** |
| 6 hrs | 130.05 | 40 | 5.223 | .826 | |

There was definite improvement in hemodynamic status.

**Table:13**

**Diastolic BP Descriptive Statistics**

Friedman Test – to compare the hourly values

| Diastolic BP | N | Mean | Std. Deviation | Minimum | Maximum | p-value |
|---|---|---|---|---|---|---|
| Initial | 40 | 62.30 | 4.826 | 53 | 75 | <0.001** |
| 15mins | 40 | 63.38 | 4.839 | 54 | 75 | |
| 30mins | 40 | 64.68 | 4.937 | 55 | 76 | |
| 45mins | 40 | 65.50 | 4.935 | 57 | 77 | |
| 1 hrs | 40 | 66.45 | 4.878 | 57 | 78 | |
| 1.30 hrs | 40 | 68.28 | 4.904 | 60 | 78 | |
| 2 hrs | 40 | 69.50 | 5.104 | 62 | 80 | |
| 2.30 hrs | 40 | 71.70 | 4.869 | 65 | 83 | |
| 3 hrs | 40 | 73.22 | 4.605 | 66 | 84 | |
| 4 hrs | 40 | 76.58 | 4.701 | 70 | 86 | |
| 5hrs | 40 | 80.72 | 4.873 | 72 | 90 | |
| 6 hrs | 40 | 82.82 | 4.835 | 74 | 92 | |

Gradual increase in diastolic blood was also noticed.

**Table:14**

**Paired Samples Statistics**

Paired T-Test – to compare the initial and final values

| Diastolic BP | Mean | N | Std. Deviation | Std. Error Mean | p - value |
|---|---|---|---|---|---|
| Initial | 62.30 | 40 | 4.826 | .763 | < 0.001** |
| 6hrs | 82.83 | 40 | 4.835 | .765 | |

**Table:15**

**Mean arterial pressure Descriptive Statistics**

Friedman Test – to compare the hourly values

| Mean arterial pressure | N | Mean | Std. Deviation | Minimum | Maximum | p-value |
|---|---|---|---|---|---|---|
| Initial | 40 | 74.97 | 4.633 | 66 | 88 | <0.001** |
| 15mins | 40 | 77.10 | 6.515 | 67 | 105 | |
| 30mins | 40 | 77.70 | 4.603 | 68 | 88 | |
| 45mins | 40 | 78.70 | 4.575 | 70 | 90 | |
| 1 hrs | 40 | 79.63 | 4.436 | 70 | 91 | |
| 1.30 hrs | 40 | 81.68 | 4.305 | 73 | 89 | |
| 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 | |
| 5hrs | 40 | 95.60 | 4.361 | 87 | 104 | |
| 6 hrs | 40 | 98.50 | 4.546 | 92 | 108 | |

There was a definite increase in mean arterial pressure at the end of 6hrs.

## BLOOD PRESSURE VARIATION

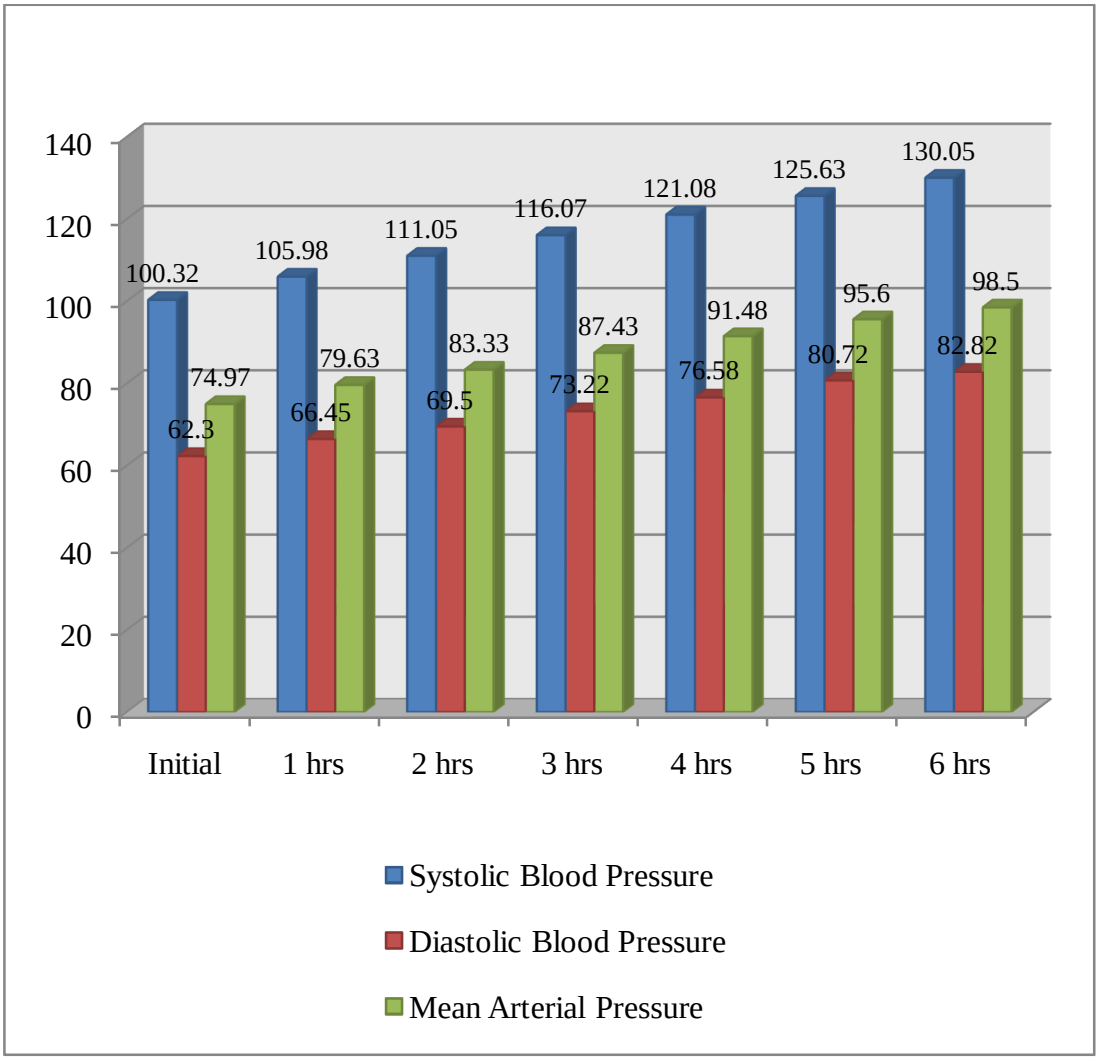


**Table: 16**

**Paired Samples Statistics**

Paired T-Test – to compare the initial and final 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 | |

There was improvement in mean arterial pressure. There was no significant difference, in serum sodium control, urine output, and blood pressure 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. But significant differences were noticed in initial and first 3hours post-vasopressin urine output values. Where higher values were noticed in the fall from height group comparing RTA group.

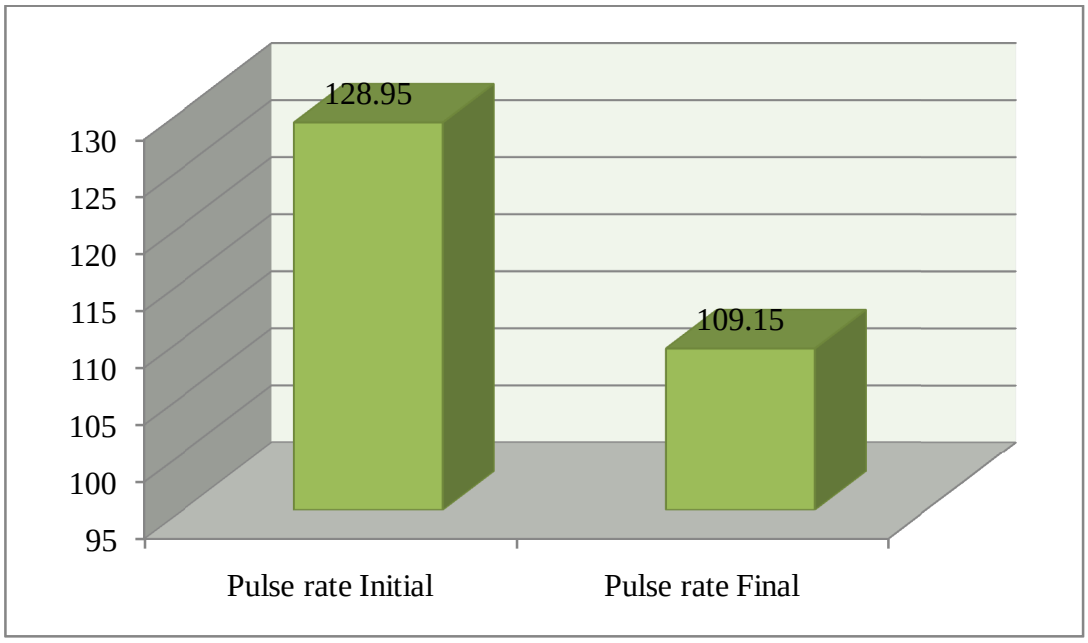
**Table : 17**

**Paired Samples Statistics**

Paired T-Test – to compare the initial and final values

| Variable | | Mean | N | Std. Deviation | p-value |
|---|---|---|---|---|---|
| Pair 1 | Sr.K+ Initial | 3.7900 | 40 | .41188 | 0.635 |
| | Sr.K+ Final | 3.8450 | 40 | .43908 | |
| Pair 2 | Sr.creatinine - Initial | 1.2075 | 40 | .24744 | 0.658 |
| | Sr.creatinine - Final | 1.2250 | 40 | .11929 | |
| Pair 3 | pulse - Inital | 128.95 | 40 | 7.56832 | < 0.001** |
| | pulse - Final | 109.15 | 40 | 16.35433 | |

There were no significant changes in serum potassium and serum creatinine seen in this study. But significant decrease in pulse rate was noticed. It may be due to the ability to reduce the catecholamine dose with time - catecholamine sparing effect of vasopressin and improved volume status.



# DISCUSSION

# DISCUSSION

Vasopressin has two major effects in braindead patients,

1. V2 receptor mediated free water retention-which helps to manage the hypernatremia in braindead patients due to the endocrine failure that follows posterior pituitary infarction ,which is otherwise harmful to the potentially transplantable organs, especially when serum sodium concentration >155mEq/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 braindead 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 $6^{th}$ hour noticed in 31 patients.

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

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

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

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

Mean final Blood pressure :

| | | |
|---|---|---|
| Systolic Blood pressure | : | 130.05mmHg |
| Diastolic Blood pressure | : | 82.82mmHg |
| Mean arterial pressure | : | 98.50mmHg |

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 decrease in serum sodium level and urine output, so the pathology in these patients may be different-could be nephrogenic diabetes insipidus.

Patients selected were cases of traumatic brain death. 2 modes of injury in these patients were Road traffic accident and fall from height. distribution was 85%RTA,15% fall from height. There was no significant difference in these groups of patients regarding drug dosage or response in serum sodium level or blood pressure or urine output.

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.

Other parameters monitored include serum potassium, blood urea, serum creatinine, pulse rate & blood sugar. There were no consistent or predictable and significant changes noticed in these parameters during the study.

So vasopressin infusion in clinically brain dead hypernatremic patients produced,

1. Significant & definite decrease in serum sodium level

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 literaturethese 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 O' 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, IlariaMastromauro and Silvia Grottoli et al[19].

Desmopressin (DDAVP) is an analog of AVP with a relatively potent antidiuretic effect and negligible vasopressor activity.

**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.

Antidiuretic peptides are the primary treatment for central DI.Vasopressin is preferred for short term uses especially when there is hypotension. Desmopressin is preferred for long term uses.

**Nephrogenic diabetes insipidus -** Nephrogenic DI may be congenital or acquired. Hypercalcemia, hypokalemia, postobstructive renal failure, lithium, foscarnet, clozapine, demeclocycline, and other drugs can induce nephrogenic DI. As many as one in three patients treated with lithium may develop nephrogenic DI. X-linked nephrogenic DI is caused by mutations in the gene encoding the V2 receptor, which maps to Xq28. These findings indicate that aquaporin 2 is essential for the antidiuretic effect of vasopressin in human beings.

The mainstay of treatment of nephrogenic DI is assurance of an adequate intake of water. Paradoxically, thiazide diuretics reduce the polyuria of patients with DI and often are used to treat non-lithium-induced nephrogenic DI.

# SUMMARY

# SUMMARY

This was a prospective study conducted in 40 clinically braindead patients with hypernatremia. Trauma patients were chosen.

After confirming hypernatremia with baseline serum sodium values and inclusion criteria vasopressin infusion was started at a dose of 0.01U/min.

Hourly serum sodium, serum potassium, urine output, blood urea, serum creatinine, blood pressure, heart rate and blood sugar were monitored for 6 hrs.

Blood pressure was monitored – every15 minutes during 1st hour, every 30 minutes during 2nd & 3rd hour, every hour for next three hours.

Observed parameters were evaluated for statistical significance.

Statistical analysis was done with appropriate tests.

It shows that the effect of vasopressin in decreasing serum sodium was statistically significant.

It's effects in decreasing urine output and maintaining hemodynamic stabily were also significant.

# CONCLUSION

# CONCLUSION

As **endocrine and autonomic failure** both are common in braindead patients, **vasopressin at a dose of 0.01-0.04U/min** will be superior to other options in managing hypernatremia in these patients as **it handles both hypernatremia and hypotension**. Other options include desmopressin (lacks vasopressor effect) and using sodium free IV fluids or IVfluids with high free water clearance.

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# BIBLIOGRAPHY


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**INSTITUTIONAL ETHICS COMMITTEE**
**MADRAS MEDICAL COLLEGE, CHENNAI -3**

Telephone No: 04425305301
Fax : 04425363970

## CERTIFICATE OF APPROVAL

To
Dr. G. Balaji
PG in MD Anaesthesia
Madras Medical College, Chennai -3.

Dear Dr. G. Balaji

The Institutional Ethics Committee of Madras Medical College reviewed and discussed your application for approval of the proposal entitled "Prospective study of evaluation of the role of vasopressin in the management of hypernatremia in clinically braindead patients " No. 32082011.

The following members of Ethics Committee were present in the meeting held on 16.08.2011 conducted at Madras Medical College, Chennai -3.

| | | |
|---|---|---|
| 1. | Prof. S.K. Rajan, MD | -- Chairperson |
| 2. | Prof. V. Kanagasabai, MD<br>Dean, Madras Medical College, Chennai-3, | -- Deputy Chairman |
| 3. | Prof. A. Sundaram, MD<br>Vice Principal , Madras Medical College, Chennai -3 | -- Member Secretary |
| 4. | Prof R. Sathianathan , MD | -- Member |
| 5. | Prof R. Nandhini, MD<br>Director, Institute of Pharmacology, MMC, Ch-3 | -- Member |
| 6. | Prof. C. Rajendiran, MD<br>Director , Institute of Internal Medicine, MMC, Ch-3 | -- Member |
| 7. | Thiru. A. Ulaganathan<br>Administrative Officer, MMC, Chennai -3 | -- Layperson |
| 8. | Thiru. S. Govindasamy . BA.BL | -- Lawyer |
| 9 . | Tmt. Arnold Soulina MA | -- Social Scientist |

We approve the proposal to be conducted in its presented form

Sd /. Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report

Member Secretary, Ethics Committee

## INFORMED CONSENT FORM

Title of the study: "PROSPECTIVE STUDY OF EVALUATION OF THE ROLE OF VASOPRESSIN IN THE MANAGEMENT OF HYPERNATREMIA IN CLINICALLY BRAINDEAD PATIENTS"

Details of the Participant : Name Age Sex IP No. Date

Name of the Principal (co-investigator):

Name of the Institution : Institute of Anaesthesiology and critical care, Madras Medical College, Chennai

**Documentation of the informed consent**

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to include my relative as a participant in ""PROSPECTIVE STUDY OF EVALUATION OF THE ROLE OF VASOPRESSIN IN THE MANAGEMENT OF HYPERNATREMIA IN CLINICALLY BRAINDEAD PATIENTS"

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the importance of vasopressin infusion in protecting donor organs (especially liver) and its adverse effects like excessive reduction of serum sodium, reduced urine output and allegic reactions.
4. I am aware of the fact that participation of my relatives in this study is voluntary and I can of my relative out of the study at any time without having to give any reason.
5. I am also aware that the investigator may terminate my relative participation in the study at any time, for any reason, without my consent.
6. I hereby give permission to the investigators to release the information obtained from me as result of my relative's participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.
7. I have understand that my relatives identity will be kept confidential if my relatives data are publicly presented

8. I have had my questions answered to my satisfaction

9. I have decided to allow my relative to participate in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

Participant's relative's

Name : Signature / thumb impression : Date :

Witness (required for illiterate patient's relative's)

Name : Signature : Date :

Investigator's

Name : Signature : Date :

# PROFORMA

## PROSPECTIVE STUDY OF EVALUATION OF THE ROLE OF VASOPRESSIN IN THE MANAGEMENT OF HYPERNATREMIA IN CLINICALLY BRAINDEAD PATIENTS

NAME : AGE : SEX : I.Po.

DIAGNOSIS:

**CASE DETAILS:**

HISTORY

MODE OF INJURY & TIME OF INJURY : CT BRAIN : TIME OF CLINICAL DECLARATION :

CO-MORBID ILLNESS & TREATMENT DETAILS (INCLUDING JAUNDICE):

EFFORT TOLERANCE _____ METS

ALCOHL INTAKE :

**GENERAL EXAMINATION :**

HEIGHT : WEIGHT : EXTERNAL INJURIES/INFECTION : GCS-

ANAEMIA- JAUNDICE – OEDEMA – CYANOSIS – PUPILS – DEM-

PULSE – BP-SPO2 CVS RS-SPONTANEOUS RESPIRATION –

**INVESTIGATIONS :**

Hb : BT : CT : BLOOD GROUPING & TYPING:

BLOOD SUGAR UREA: CREATININE ELECTROLYTES-Na+k+

ECG : CXR:

**INTERVENTION**

BASELINE ABG-Na+

TIME SINCE INJURY

VASOPRESSIN INFUSION – DOSE (01.1-0.04 U/min)

STARTING TIME

**PARAMETERS TO BE OBSERVED**

1. SERUM Na+LEVEL
2. SERUM K+
3. URINE OUTPUT
4. BLOOD UREA
5. SERUM CREATININE
6. PULSE RATE
7. BLOOD PRESSURE
8. BLOOD SUGAR

TIME TAKEN TO ATTAIN (FROM INFUSION) SERUM Na+ (146meq/L)

| TIME | Na+ | K+ | UO | UREA | CREATININE | PR | BP | SUGAR |
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LOOK FOR ADVERSE EFFECTS

| Sl.No. | Name | AGE | SEX | IPNO | MODE | GCS | ASA | RENAL DISEASE | Sr.Na+ | INITIAL | 1st hr | 2nd hr | 3rd hr | 4th hr | 5th hr | 6th hr | U.O | INITIAL | 1st hr | 2nd hr | 3rd hr | 4th hr |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Indhra | 28 | F | 74175 | RTA | 3 | 6 | NIL | | 158 | 156 | 152 | 148 | 146 | 142 | 140 | | 250 | 235 | 210 | 190 | 185 |
| 2 | Shanthakumari | 60 | F | 75615 | RTA | 3 | 6 | NIL | | 159 | 156 | 150 | 146 | 141 | 138 | 134 | | 220 | 200 | 175 | 160 | 150 |
| 3 | Ravi kumar | 31 | M | 51756 | RTA | 3 | 6 | NIL | | 174 | 173 | 170 | 166 | 166 | 168 | 166 | | 250 | 250 | 240 | 235 | 225 |
| 4 | Kasinathan | 50 | M | 57617 | RTA | 3 | 6 | NIL | | 160 | 157 | 151 | 145 | 140 | 137 | 133 | | 225 | 210 | 190 | 180 | 165 |
| 5 | Madhumitha | 18 | F | 42698 | RTA | 3 | 6 | NIL | | 146 | 150 | 156 | 162 | 166 | 171 | 174 | | 230 | 230 | 225 | 220 | 210 |
| 6 | Prabhakaran | 22 | M | 46773 | FALL | 3 | 6 | NIL | | 164 | 162 | 158 | 153 | 148 | 142 | 138 | | 300 | 275 | 260 | 220 | 185 |
| 7 | Desingh | 32 | M | 89269 | RTA | 3 | 6 | NIL | | 156 | 153 | 148 | 145 | 142 | 137 | 133 | | 200 | 185 | 165 | 150 | 140 |
| 8 | Sandiyappan | 57 | M | 87170 | RTA | 3 | 6 | NIL | | 153 | 150 | 145 | 142 | 140 | 138 | 134 | | 180 | 165 | 160 | 150 | 135 |
| 9 | Malliga | 34 | F | 22707 | RTA | 3 | 6 | NIL | | 170 | 167 | 163 | 159 | 155 | 150 | 146 | | 240 | 220 | 200 | 185 | 175 |
| 10 | Kannan | 39 | M | 23805 | RTA | 3 | 6 | NIL | | 159 | 157 | 153 | 151 | 146 | 143 | 138 | | 280 | 265 | 240 | 220 | 195 |
| 11 | Iakshmi | 45 | F | 27543 | RTA | 3 | 6 | NIL | | 150 | 147 | 145 | 142 | 140 | 137 | 135 | | 320 | 300 | 275 | 240 | 210 |
| 12 | Perumal | 30 | M | 29884 | RTA | 3 | 6 | NIL | | 155 | 154 | 150 | 146 | 142 | 139 | 136 | | 200 | 185 | 160 | 150 | 140 |
| 13 | Kali | 23 | M | 61103 | RTA | 3 | 6 | NIL | | 158 | 157 | 155 | 153 | 152 | 152 | 152 | | 220 | 210 | 200 | 190 | 200 |
| 14 | Devi | 18 | F | 61684 | RTA | 3 | 6 | NIL | | 177 | 172 | 165 | 157 | 150 | 146 | 140 | | 250 | 230 | 215 | 190 | 170 |
| 15 | Kumaran | 42 | M | 62213 | RTA | 3 | 6 | NIL | | 154 | 153 | 150 | 146 | 143 | 141 | 138 | | 275 | 250 | 220 | 180 | 170 |
| 16 | Shankar | 38 | M | 63215 | RTA | 3 | 6 | NIL | | 152 | 150 | 146 | 142 | 140 | 138 | 137 | | 230 | 210 | 195 | 185 | 170 |
| 17 | Jagan | 20 | M | 65589 | RTA | 3 | 6 | NIL | | 168 | 167 | 165 | 162 | 164 | 162 | 162 | | 240 | 230 | 230 | 220 | 230 |
| 18 | Arun | 22 | M | 10415 | FALL | 3 | 6 | NIL | | 151 | 148 | 146 | 143 | 141 | 137 | 135 | | 220 | 220 | 195 | 170 | 150 |
| 19 | Chandrayan | 42 | M | 11063 | RTA | 3 | 6 | NIL | | 157 | 157 | 155 | 153 | 152 | 152 | 150 | | 250 | 240 | 240 | 230 | 230 |
| 20 | Fathima | 55 | F | 14026 | RTA | 3 | 6 | NIL | | 161 | 159 | 156 | 152 | 148 | 145 | 143 | | 225 | 200 | 180 | 165 | 145 |
| 21 | Ashok kumar | 30 | M | 18019 | RTA | 3 | 6 | NIL | | 160 | 160 | 156 | 151 | 146 | 142 | 139 | | 240 | 215 | 200 | 175 | 160 |
| 22 | Sathish | 25 | M | 19732 | FALL | 3 | 6 | NIL | | 156 | 153 | 148 | 144 | 141 | 138 | 136 | | 225 | 210 | 180 | 155 | 150 |
| 23 | Basheer | 28 | M | 21790 | RTA | 3 | 6 | NIL | | 163 | 162 | 156 | 152 | 146 | 140 | 137 | | 240 | 220 | 195 | 175 | 150 |
| 24 | Jagadhesh | 27 | M | 24026 | FALL | 3 | 6 | NIL | | 147 | 148 | 150 | 151 | 151 | 153 | 154 | | 320 | 300 | 290 | 290 | 280 |

| Sl.No. | Name | AGE | SEX | IPNO | MODE | GCS | ASA | RENAL DISEASE | Sr.Na+ | INITIAL | 1st hr | 2nd hr | 3rd hr | 4th hr | 5th hr | 6th hr | U.O | INITIAL | 1st hr | 2nd hr | 3rd hr | 4th hr |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 25 | Kumari | 55 | F | 27140 | FALL | 3 | 6 | NIL | | 168 | 165 | 160 | 154 | 148 | 145 | 138 | | 300 | 280 | 265 | 240 | 200 |
| 26 | Rambabu | 18 | M | 35488 | RTA | 3 | 6 | NIL | | 152 | 150 | 146 | 142 | 140 | 137 | 133 | | 240 | 210 | 195 | 170 | 150 |
| 27 | Manic basha | 45 | M | 36835 | RTA | 3 | 6 | NIL | | 166 | 16 | 165 | 163 | 161 | 160 | 160 | | 230 | 220 | 230 | 240 | 220 |
| 28 | Suresh | 32 | M | 38931 | RTA | 3 | 6 | NIL | | 152 | 150 | 147 | 142 | 138 | 133 | 130 | | 190 | 175 | 160 | 140 | 130 |
| 29 | Syed ahamed | 45 | M | 40132 | RTA | 3 | 6 | NIL | | 155 | 154 | 150 | 146 | 143 | 141 | 139 | | 250 | 220 | 190 | 175 | 150 |
| 30 | Rajaul | 22 | M | 42328 | RTA | 3 | 6 | NIL | | 163 | 160 | 155 | 151 | 146 | 143 | 141 | | 230 | 210 | 185 | 160 | 145 |
| 31 | Ramya | 15 | F | 44636 | RTA | 3 | 6 | NIL | | 167 | 165 | 160 | 154 | 149 | 145 | 142 | | 220 | 190 | 170 | 150 | 140 |
| 32 | Gurulingam | 48 | M | 45938 | RTA | 3 | 6 | NIL | | 165 | 165 | 163 | 164 | 160 | 158 | 158 | | 210 | 200 | 210 | 210 | 200 |
| 33 | Manikandan | 21 | M | 47344 | FALL | 3 | 6 | NIL | | 149 | 146 | 142 | 138 | 135 | 132 | 130 | | 280 | 250 | 225 | 210 | 190 |
| 34 | Manikandan | 19 | M | 50149 | RTA | 3 | 6 | NIL | | 179 | 175 | 167 | 160 | 154 | 146 | 140 | | 240 | 220 | 200 | 175 | 155 |
| 35 | Babu | 32 | M | 54328 | RTA | 3 | 6 | NIL | | 172 | 170 | 165 | 161 | 156 | 152 | 147 | | 220 | 195 | 175 | 160 | 145 |
| 36 | Saraswathi | 35 | F | 72893 | RTA | 3 | 6 | NIL | | 154 | 154 | 156 | 154 | 155 | 153 | 153 | | 250 | 240 | 240 | 220 | 240 |
| 37 | Jaihalaudin | 31 | M | 73322 | RTA | 3 | 6 | NIL | | 159 | 156 | 152 | 148 | 145 | 142 | 140 | | 220 | 190 | 170 | 155 | 140 |
| 38 | Pari | 39 | M | 32398 | RTA | 3 | 6 | NIL | | 166 | 164 | 159 | 153 | 148 | 145 | 142 | | 220 | 200 | 175 | 160 | 155 |
| 39 | Ramesh | 29 | M | 34426 | RTA | 3 | 6 | NIL | | 165 | 162 | 157 | 151 | 146 | 140 | 137 | | 230 | 200 | 190 | 165 | 150 |
| 40 | Vatsalan | 30 | M | 29466 | RTA | 3 | 6 | NIL | | 164 | 162 | 158 | 154 | 149 | 145 | 139 | | 260 | 240 | 200 | 175 | 150 |

| 5th hr | 6th hr | BP | initial SBP | DBP | MAP | 15min SBP | DBP | MAP | 30min SBP | DBP | MAP | 45min SBP | DBP | MAP | 1hr SBP | DBP | MAP | 1hr30 min SBP | DBP | MAP | 2hrs SBP | DBP | MAP | 2hrs 30mins SBP | DBP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 180 | 170 | | 96 | 62 | 73 | 98 | 63 | 75 | 99 | 65 | 76 | 100 | 64 | 76 | 100 | 66 | 77 | 104 | 67 | 79 | 106 | 68 | 81 | 107 | 71 |
| 140 | 125 | | 102 | 64 | 77 | 105 | 64 | 78 | 106 | 65 | 79 | 106 | 66 | 79 | 108 | 66 | 80 | 110 | 69 | 83 | 111 | 69 | 83 | 115 | 73 |
| 220 | 220 | | 92 | 65 | 74 | 94 | 66 | 75 | 98 | 67 | 77 | 102 | 68 | 79 | 100 | 68 | 79 | 104 | 71 | 82 | 106 | 72 | 83 | 110 | 74 |
| 155 | 140 | | 106 | 70 | 82 | 108 | 72 | 84 | 108 | 75 | 86 | 111 | 76 | 88 | 111 | 77 | 88 | 113 | 77 | 89 | 115 | 76 | 89 | 118 | 79 |
| 200 | 210 | | 113 | 75 | 88 | 114 | 75 | 88 | 112 | 76 | 88 | 117 | 77 | 90 | 117 | 78 | 91 | 121 | 78 | 89 | 123 | 80 | 94 | 125 | 83 |
| 160 | 140 | | 104 | 67 | 79 | 104 | 68 | 80 | 108 | 70 | 83 | 108 | 71 | 83 | 110 | 73 | 85 | 111 | 76 | 88 | 114 | 78 | 90 | 117 | 81 |
| 135 | 120 | | 102 | 68 | 79 | 105 | 69 | 81 | 108 | 71 | 83 | 108 | 70 | 83 | 107 | 70 | 82 | 112 | 74 | 87 | 116 | 76 | 89 | 116 | 75 |
| 130 | 120 | | 110 | 72 | 85 | 112 | 73 | 86 | 114 | 72 | 86 | 116 | 73 | 87 | 116 | 74 | 88 | 118 | 75 | 89 | 121 | 77 | 92 | 124 | 78 |
| 160 | 140 | | 101 | 65 | 77 | 102 | 67 | 79 | 105 | 68 | 80 | 105 | 70 | 82 | 106 | 71 | 83 | 108 | 73 | 85 | 109 | 73 | 85 | 111 | 73 |
| 175 | 140 | | 94 | 65 | 75 | 97 | 66 | 76 | 99 | 67 | 78 | 101 | 68 | 79 | 100 | 68 | 79 | 103 | 70 | 81 | 105 | 72 | 83 | 108 | 74 |
| 170 | 130 | | 98 | 62 | 74 | 98 | 61 | 73 | 101 | 64 | 76 | 104 | 65 | 78 | 105 | 67 | 80 | 108 | 69 | 82 | 111 | 72 | 85 | 115 | 76 |
| 125 | 120 | | 103 | 68 | 80 | 106 | 70 | 82 | 108 | 73 | 85 | 109 | 75 | 86 | 109 | 75 | 86 | 111 | 77 | 88 | 114 | 79 | 91 | 116 | 80 |
| 200 | 200 | | 104 | 66 | 79 | 106 | 66 | 79 | 108 | 68 | 81 | 110 | 67 | 81 | 111 | 69 | 83 | 114 | 71 | 85 | 116 | 71 | 86 | 118 | 72 |
| 155 | 145 | | 94 | 58 | 70 | 95 | 58 | 70 | 97 | 59 | 72 | 100 | 59 | 73 | 102 | 61 | 75 | 105 | 63 | 77 | 108 | 63 | 78 | 111 | 65 |
| 160 | 150 | | 99 | 65 | 76 | 102 | 66 | 78 | 104 | 67 | 79 | 106 | 69 | 81 | 104 | 70 | 81 | 108 | 73 | 85 | 107 | 74 | 85 | 110 | 77 |
| 150 | 130 | | 90 | 55 | 67 | 92 | 55 | 67 | 96 | 57 | 70 | 96 | 58 | 71 | 97 | 59 | 72 | 100 | 60 | 73 | 102 | 63 | 76 | 106 | 65 |
| 220 | 220 | | 98 | 60 | 73 | 101 | 61 | 74 | 102 | 62 | 75 | 103 | 62 | 76 | 105 | 65 | 78 | 110 | 66 | 81 | 114 | 68 | 83 | 117 | 72 |
| 140 | 130 | | 96 | 62 | 73 | 98 | 63 | 78 | 100 | 64 | 76 | 101 | 64 | 76 | 103 | 66 | 78 | 105 | 68 | 80 | 108 | 69 | 82 | 110 | 72 |
| 235 | 230 | | 102 | 59 | 73 | 105 | 61 | 105 | 106 | 62 | 77 | 108 | 64 | 79 | 109 | 64 | 79 | 111 | 64 | 80 | 113 | 62 | 799 | 116 | 65 |
| 125 | 110 | | 100 | 58 | 72 | 102 | 59 | 73 | 104 | 61 | 75 | 105 | 62 | 76 | 105 | 63 | 77 | 109 | 65 | 80 | 112 | 67 | 82 | 115 | 68 |
| 140 | 130 | | 95 | 60 | 72 | 98 | 61 | 73 | 100 | 63 | 75 | 102 | 64 | 77 | 101 | 65 | 77 | 104 | 68 | 80 | 105 | 72 | 83 | 108 | 75 |
| 140 | 135 | | 104 | 66 | 79 | 105 | 66 | 79 | 107 | 68 | 81 | 108 | 69 | 82 | 108 | 69 | 82 | 110 | 70 | 83 | 112 | 72 | 85 | 114 | 73 |
| 145 | 125 | | 100 | 63 | 75 | 102 | 64 | 77 | 103 | 65 | 78 | 103 | 66 | 78 | 104 | 68 | 80 | 105 | 69 | 81 | 107 | 70 | 82 | 110 | 72 |
| 290 | 280 | | 96 | 57 | 70 | 99 | 59 | 72 | 100 | 60 | 73 | 102 | 61 | 75 | 103 | 61 | 75 | 106 | 63 | 77 | 108 | 64 | 79 | 111 | 66 |

| 5th hr | 6th hr | BP | initial SBP | DBP | MAP | 15min SBP | DBP | MAP | 30min SBP | DBP | MAP | 45min SBP | DBP | MAP | 1hr SBP | DBP | MAP | 1hr30 min SBP | DBP | MAP | 2hrs SBP | DBP | MAP | 2hrs 30mins SBP | DBP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 175 | 140 | | 105 | 68 | 80 | 107 | 69 | 82 | 108 | 70 | 83 | 111 | 71 | 84 | 110 | 71 | 84 | 112 | 73 | 86 | 114 | 73 | 87 | 115 | 75 |
| 140 | 120 | | 90 | 56 | 67 | 93 | 57 | 69 | 95 | 58 | 70 | 97 | 60 | 72 | 98 | 61 | 73 | 102 | 62 | 75 | 104 | 64 | 77 | 107 | 67 |
| 220 | 210 | | 96 | 60 | 72 | 98 | 60 | 73 | 100 | 61 | 74 | 102 | 62 | 75 | 102 | 63 | 76 | 105 | 65 | 78 | 109 | 66 | 80 | 110 | 68 |
| 125 | 110 | | 106 | 58 | 74 | 107 | 59 | 75 | 109 | 60 | 76 | 110 | 60 | 76 | 111 | 61 | 78 | 113 | 64 | 80 | 115 | 65 | 82 | 117 | 66 |
| 130 | 120 | | 103 | 60 | 74 | 105 | 62 | 76 | 107 | 63 | 78 | 106 | 64 | 78 | 107 | 64 | 78 | 108 | 67 | 81 | 111 | 66 | 81 | 113 | 67 |
| 140 | 125 | | 98 | 56 | 70 | 100 | 57 | 71 | 101 | 58 | 72 | 103 | 60 | 74 | 103 | 61 | 75 | 106 | 63 | 77 | 107 | 64 | 78 | 106 | 66 |
| 130 | 125 | | 104 | 58 | 73 | 104 | 59 | 74 | 106 | 61 | 76 | 107 | 62 | 74 | 108 | 64 | 79 | 110 | 63 | 79 | 113 | 62 | 79 | 115 | 67 |
| 190 | 190 | | 106 | 62 | 77 | 109 | 64 | 79 | 111 | 65 | 80 | 112 | 66 | 81 | 112 | 67 | 82 | 115 | 68 | 84 | 116 | 71 | 86 | 118 | 73 |
| 165 | 140 | | 98 | 58 | 71 | 99 | 60 | 73 | 100 | 60 | 73 | 103 | 61 | 75 | 104 | 61 | 75 | 106 | 63 | 77 | 109 | 65 | 80 | 111 | 68 |
| 140 | 130 | | 102 | 64 | 77 | 104 | 65 | 78 | 107 | 66 | 80 | 108 | 67 | 81 | 108 | 68 | 81 | 111 | 70 | 84 | 115 | 70 | 85 | 117 | 72 |
| 130 | 120 | | 92 | 53 | 66 | 92 | 54 | 67 | 94 | 55 | 68 | 97 | 57 | 70 | 96 | 57 | 70 | 98 | 60 | 73 | 102 | 62 | 75 | 105 | 65 |
| 230 | 230 | | 108 | 66 | 80 | 109 | 68 | 82 | 109 | 69 | 82 | 110 | 70 | 83 | 111 | 70 | 84 | 114 | 74 | 87 | 115 | 76 | 89 | 116 | 77 |
| 130 | 110 | | 94 | 61 | 72 | 97 | 63 | 74 | 99 | 64 | 76 | 100 | 64 | 76 | 100 | 65 | 77 | 102 | 66 | 78 | 105 | 68 | 80 | 108 | 70 |
| 140 | 125 | | 105 | 58 | 74 | 105 | 60 | 75 | 106 | 60 | 75 | 108 | 61 | 77 | 109 | 61 | 77 | 110 | 62 | 78 | 112 | 62 | 79 | 114 | 66 |
| 135 | 120 | | 102 | 60 | 74 | 105 | 61 | 76 | 106 | 63 | 77 | 108 | 62 | 77 | 108 | 64 | 79 | 112 | 67 | 82 | 115 | 69 | 84 | 118 | 70 |
| 130 | 120 | | 105 | 62 | 76 | 107 | 64 | 78 | 108 | 65 | 79 | 110 | 65 | 80 | 111 | 67 | 82 | 115 | 68 | 84 | 117 | 70 | 86 | 119 | 72 |

| MAP | 3hrs SBP | DBP | MAP | 4hrs SBP | DBP | MAP | 5hrs SBP | DBP | MAP | 6hrs SBP | DBP | MAP | Sr.K+ | Initial | final | Sr. creat-inine | initial | final | pulse | initial | final |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 83 | 110 | 76 | 87 | 118 | 75 | 89 | 126 | 81 | 96 | 132 | 86 | 101 | | 4.2 | 3.4 | | 1.3 | 1.2 | | 148 | 114 |
| 87 | 117 | 75 | 89 | 121 | 74 | 90 | 124 | 75 | 91 | 126 | 78 | 94 | | 3.8 | 3.6 | | 1.8 | 1.3 | | 134 | 118 |
| 86 | 115 | 75 | 88 | 126 | 80 | 95 | 135 | 83 | 100 | 142 | 85 | 104 | | 3.5 | 4.6 | | 1.1 | 1.2 | | 138 | 112 |
| 92 | 122 | 80 | 94 | 127 | 84 | 98 | 132 | 89 | 103 | 136 | 92 | 107 | | 4 | 3.2 | | 1.4 | 1.2 | | 130 | 122 |
| 97 | 128 | 84 | 99 | 130 | 86 | 101 | 133 | 87 | 102 | 134 | 89 | 104 | | 3.2 | 3.6 | | 1.3 | 1.4 | | 124 | 108 |
| 93 | 121 | 82 | 95 | 126 | 86 | 99 | 133 | 90 | 104 | 138 | 92 | 108 | | 4.5 | 3.8 | | 1.4 | 1 | | 130 | 114 |
| 89 | 117 | 74 | 88 | 120 | 77 | 91 | 122 | 80 | 94 | 124 | 82 | 96 | | 3.1 | 4.2 | | 1.6 | 1.4 | | 125 | 118 |
| 93 | 125 | 79 | 94 | 128 | 81 | 97 | 133 | 84 | 100 | 138 | 86 | 103 | | 3.3 | 4.6 | | 1.2 | 1.3 | | 118 | 110 |
| 86 | 114 | 71 | 85 | 119 | 72 | 88 | 123 | 73 | 90 | 126 | 75 | 92 | | 4.2 | 3.8 | | 1.4 | 1.1 | | 124 | 116 |
| 85 | 111 | 75 | 87 | 117 | 77 | 90 | 120 | 84 | 96 | 122 | 82 | 95 | | 4 | 3.5 | | 1.2 | 1.1 | | 146 | 122 |
| 89 | 117 | 80 | 92 | 122 | 86 | 98 | 128 | 88 | 101 | 132 | 90 | 104 | | 3.6 | 4 | | 1.1 | 1.5 | | 136 | 118 |
| 92 | 118 | 80 | 93 | 123 | 82 | 95 | 126 | 84 | 98 | 138 | 85 | 103 | | 3.8 | 3.4 | | 1.3 | 1.1 | | 128 | 106 |
| 87 | 120 | 70 | 87 | 125 | 76 | 92 | 128 | 80 | 96 | 130 | 84 | 99 | | 4.2 | 3.8 | | 1.6 | 1.2 | | 126 | 114 |
| 80 | 113 | 67 | 82 | 119 | 72 | 88 | 123 | 78 | 93 | 128 | 76 | 93 | | 4 | 3.4 | | 1.1 | 1.2 | | 128 | 116 |
| 88 | 114 | 78 | 90 | 121 | 84 | 96 | 128 | 82 | 97 | 134 | 86 | 102 | | 3.6 | 4.8 | | 1.6 | 1.4 | | 134 | 112 |
| 79 | 110 | 68 | 82 | 118 | 75 | 89 | 123 | 78 | 93 | 128 | 76 | 93 | | 3.2 | 4 | | 1 | 1.2 | | 142 | 118 |
| 87 | 119 | 74 | 87 | 124 | 80 | 95 | 128 | 86 | 100 | 132 | 84 | 100 | | 3.6 | 3.8 | | 1.2 | 1.3 | | 130 | 116 |
| 85 | 114 | 76 | 89 | 119 | 75 | 90 | 123 | 80 | 94 | 128 | 83 | 98 | | 2.9 | 3.6 | | 1.1 | 1.2 | | 124 | 106 |
| 82 | 118 | 68 | 85 | 123 | 70 | 88 | 130 | 85 | 100 | 133 | 84 | 100 | | 3.6 | 4.4 | | 1.3 | 1 | | 130 | 108 |
| 84 | 116 | 70 | 85 | 122 | 76 | 91 | 126 | 80 | 95 | 128 | 82 | 97 | | 4.2 | 3.4 | | 1.3 | 1.1 | | 124 | 112 |
| 86 | 110 | 76 | 87 | 116 | 70 | 85 | 123 | 88 | 100 | 127 | 86 | 100 | | 3.8 | 4.2 | | 1 | 1.2 | | 120 | 104 |
| 87 | 115 | 74 | 88 | 117 | 73 | 88 | 120 | 77 | 91 | 125 | 79 | 94 | | 3.4 | 4 | | 0.9 | 1.1 | | 128 | 116 |
| 85 | 112 | 73 | 86 | 115 | 77 | 90 | 119 | 82 | 94 | 124 | 86 | 99 | | 3.6 | 3.8 | | 1.1 | 1.3 | | 122 | 108 |
| 81 | 115 | 68 | 84 | 119 | 74 | 89 | 122 | 76 | 91 | 130 | 78 | 95 | | 4 | 3.4 | | 1 | 1.2 | | 142 | 118 |

| MAP | 3hrs SBP | DBP | MAP | 4hrs SBP | DBP | MAP | 5hrs SBP | DBP | MAP | 6hrs SBP | DBP | MAP | Sr.K+ | Initial | final | Sr. creat-inine | initial | final | pulse | initial | final |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 88 | 117 | 74 | 88 | 121 | 78 | 92 | 124 | 82 | 96 | 126 | 80 | 95 | | 4.8 | 3.6 | | 1.7 | 1.3 | | 132 | 14 |
| 80 | 110 | 68 | 82 | 115 | 70 | 85 | 119 | 73 | 88 | 122 | 78 | 93 | | 3.9 | 4.6 | | 1.2 | 1.4 | | 127 | 106 |
| 82 | 114 | 70 | 85 | 121 | 74 | 90 | 126 | 77 | 93 | 131 | 79 | 96 | | 4 | 3.4 | | 0.9 | 1.1 | | 118 | 104 |
| 83 | 121 | 68 | 86 | 128 | 75 | 96 | 130 | 78 | 95 | 132 | 81 | 98 | | 4.2 | 3.2 | | 1 | 1.2 | | 134 | 112 |
| 82 | 115 | 69 | 84 | 118 | 71 | 87 | 122 | 74 | 90 | 126 | 78 | 94 | | 3 | 4.4 | | 1.2 | 1.3 | | 124 | 106 |
| 79 | 110 | 68 | 82 | 115 | 72 | 86 | 119 | 78 | 92 | 124 | 81 | 99 | | 4 | 3.8 | | 1.5 | 1.3 | | 126 | 108 |
| 83 | 119 | 68 | 85 | 122 | 75 | 91 | 126 | 73 | 91 | 128 | 74 | 92 | | 4.2 | 3.6 | | 1.2 | 1.4 | | 118 | 104 |
| 88 | 121 | 75 | 90 | 127 | 80 | 96 | 130 | 86 | 101 | 138 | 92 | 107 | | 3.4 | 4.1 | | 1.2 | 1.1 | | 120 | 106 |
| 82 | 113 | 70 | 84 | 117 | 74 | 88 | 123 | 79 | 94 | 127 | 82 | 97 | | 3.8 | 4 | | 1.2 | 1.3 | | 136 | 114 |
| 87 | 120 | 74 | 89 | 126 | 79 | 95 | 133 | 83 | 100 | 140 | 86 | 101 | | 3.6 | 4.4 | | 1.4 | 1.2 | | 128 | 116 |
| 78 | 107 | 66 | 80 | 113 | 70 | 84 | 118 | 72 | 87 | 123 | 77 | 92 | | 3.8 | 4.4 | | 0.9 | 1.2 | | 122 | 104 |
| 90 | 118 | 78 | 91 | 123 | 81 | 95 | 127 | 84 | 98 | 132 | 86 | 101 | | 4.2 | 3.5 | | 1.1 | 1.3 | | 126 | 108 |
| 83 | 109 | 72 | 84 | 114 | 75 | 88 | 121 | 80 | 94 | 127 | 84 | 98 | | 4.2 | 3.8 | | 1.1 | 1.2 | | 132 | 114 |
| 82 | 116 | 68 | 84 | 118 | 70 | 86 | 122 | 73 | 89 | 125 | 76 | 92 | | 3.8 | 3.2 | | 0.8 | 1 | | 126 | 106 |
| 86 | 120 | 73 | 89 | 124 | 78 | 93 | 129 | 83 | 98 | 134 | 88 | 103 | | 3.6 | 4.1 | | 0.7 | 1.2 | | 120 | 102 |
| 88 | 122 | 75 | 91 | 126 | 79 | 95 | 128 | 84 | 99 | 132 | 85 | 101 | | 3.8 | 3.4 | | 0.9 | 1.3 | | 138 | 116 |

# Prospective study of evaluation of the role of vasopressin in the management of hypernatremia in clinically brain dead patients.


## KEY WORDS

Braindeath , diabetes insipidus , increased urine output , hypernatremia, graft rejection , vasopressin infusion, serum sodium control.


## ABSTRACT


After the diagnosis of brain death the focus of patient care shifts from interventions aimed at saving the patients life to interventions aimed at maintaining viability of potentially transplantable organs. A number of physiological changes occur in braindead patients – two important notable features are autonomic nervous system failure with hypotension and endocrine failure ,due to ischemic damage involving hypothalamus &pituitary damage . Most common endocrine abnormality is diabetes insipidus. It is characterized by – serum hyperosmolarity , hypernatremia , excessive urine output, low urine osmolarity and specific gravity .In braindead patients incidence of hypotension and hypernatremia are 81% and 75-77% respectively. Dis advantages of donor hypernatremia include increased graft loss - especially liver (when sr.Na+>155meq/L, due to formation of idiogenic osmoles ) , prolonged

prothrombin time in the post op period , prolonged ICU stay and may reduce patient survival. Duration of hypernatremia also influences the graft survival. So, maintaining serum sodium level within normal limits may improve graft outcome (especially liver ).It is supported by various studies. In this prospective interventional study vasopressin infusion was used in 40 clinically braindead patients with hypernatremia(sr.Na+> 145 meq/L) and U.O >2ml/kg/hr(diabetes incipidus) , to treat hypernatremia . Target serum sodium was < 146 meq/L or atleast <155meq/L when initial level was too high. Vasopressin infusion - dose – 0.5 to 3U/hr ( or) 0.01 to 0.04 U/min(10-40 mU/kg/hr) i.v. Decrease in serum sodium levels and decrease in urine output were seen in 31 patients. In 9 patients there was no significant change in serum sodium level. There was also considerable improvement in hemodynamic status noticed in these patients. Statistical analysis showed that the changes in serum sodium level , urine output and hemodynamic status were significant.