ROLE OF COPEPTIN IN PREDICTING SODIUM HOMEOSTASIS IMBALANCES IN PATIENTS UNDERGOING SURGERY FOR PITUITARY ADENOMA

Dr Anand Binu

MCh Neurosurgery Thesis

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A THESIS SUBMITTED BY

Dr Anand Binu

TO

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM.

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE AWARD OF

MCh NEUROSURGERY

JULY 2022

DECLARATION BY THE STUDENT

CERTIFICATE

I, Dr Anand Binu, hereby certify that I had personally carried out the work depicted in the thesis titled "***Role of Copeptin in predicting Sodium Homeostasis Imbalances in Patients undergoing Surgery for Pituitary Adenoma"*** No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.

Dr. Anand Binu,

Department of Neurosurgery,

SCTIMST, Trivandrum

Date: 27/7/2022

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

CERTIFICATE BY THE RESEARCH GUIDE

Name of the Guide: Dr Easwer HV

Department: Neurosurgery

This is to certify that Dr Anand Binu, Department of Neurosurgery of this institute has fulfilled the requirements prescribed for the MCh Neurosurgery degree of the Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum.

The thesis entitled, "***Role of Copeptin in predicting Sodium Homeostasis Imbalances in Patients undergoing Surgery for Pituitary Adenoma*** " was carried out under my direct supervision. No part of the thesis was submitted for the award of any degree or diploma prior to this date.

*Clearance was obtained from the Institutional Ethics Committee of this institute(IEC-1784/2021) for carrying out the study.

Signature

Date: 28/7/2022

Dr Easwer HV, MCh,
Professor and Head
Department of Neurosurgery,
SCTIMST, Trivandrum

Dr. EASWER H.V.
Professor & Head
Dept. of Neurosurgery
SCTIMST, Thiruvananthapuram

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
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Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

CERTIFICATE BY THE RESEARCH CO-GUIDE

Name of the Guide: Dr Prakash Nair

Department: Neurosurgery

This is to certify that Dr Anand Binu, Department of Neurosurgery of this institute has fulfilled the requirements prescribed for the MCh Neurosurgery degree of the Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum.

The work under the thesis entitled, "***Role of Copeptin in predicting Sodium Homeostasis Imbalances in Patients undergoing Surgery for Pituitary Adenoma***" was carried out under my direct supervision. No part of the thesis was submitted for the award of any degree or diploma prior to this date.

*Clearance was obtained from the Institutional Ethics Committee / Institutional Animal Ethics / Institutional Committee for Stem Cell Research / Other appropriate committees (if any, specify) for carrying out the study.

Signature

Date: 27.07.22

Dr Prakash Nair
Associate Professor,
Department of Neurosurgery,
SCTIMST, Trivandrum

Dr. PRAKASH NAIR
MS (General Surgery), MCh (Neurosurgery)
Associate Professor
Department of Neurosurgery
Sree Chitra Tirunal Institute for
Medical Sciences & Technology
Thiruvananthapuram, Kerala, India
TCMC Reg. No. 38394

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
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Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

APPROVAL OF THE THESIS

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Role of Copeptin in predicting Sodium Homeostasis Imbalances in Patients undergoing Surgery for Pituitary Adenoma

Submitted by

Dr Anand Binu

for the degree of

MCh NEUROSURGERY(AFTER MS)

of

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM

is evaluated and approved by

.....

(Name & Signature of the Guide)

Dr. EASWER H.V.
Professor & Head
Dept. of Neurosurgery
SCTIMST, Thiruvananthapuram

.....

(Name & Signature of thesis examiner)

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Dr Anand Binu

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LIST OF ABBREVIATIONS

ABBREVIATION	FULL FORM
ETS	ENDOSCOPIC TRANSSPHENOIDAL SURGERY
SIADH	SYNDROME OF INAPPROPRIATE SECRETION OF ADH
ADH	ANTIDIURETIC HORMONE
AVP	ARGININE VASOPRESSIN
CPP	COPEPTIN
CDI	CENTRAL DIABETES INSIPIDUS
TDI	TRANSIENT CENTRAL DIABETES INSIPIDUS
PDI	PERMANENT CENTRAL DIABETES INSIPIDUS
EH	EARLY HYPONATREMIA
DH	DELAYED HYPONATREMIA
C1 / COPEPTIN 1	PREOPERATIVE COPEPTIN
C2 / COPEPTIN 2	IMMEDIATE POST OPERATIVE COPEPTIN
C3 / COPEPTIN 3	DELAYED POST OPERATIVE COPEPTIN
IRC	RELATIVE PERCENTAGE CHANGE IN IMMEDIATE POST OPERATIVE COPEPTIN FROM PREOPERATIVE VALUE
DRC	RELATIVE PERCENTAGE CHANGE IN DELAYED POST OPERATIVE COPEPTIN FROM PREOPERATIVE VALUE
RPC	RELATIVE PERCENTAGE POST OPERATIVE CHANGE IN COPEPTIN
AUC	AREA UNDER THE CURVE

SYNOPSIS

Background

Arginine vasopressin(AVP) is the important hormone responsible for maintaining sodium homeostasis following pituitary surgery. The measurement of AVP levels is difficult due to its short $t_{1/2}$ and laborious method of detection. Copeptin is preprohormone of AVP and a more stable peptide, which can be used as surrogate marker for AVP. This study aimed to assess the role of Copeptin as a predictor in post operative Sodium homeostasis imbalances(SHI) in patients undergoing endoscopic pituitary adenoma surgery and to assess the role of Copeptin as a marker of pituitary reserve and its role in predicting sodium fluctuations.

Methods:

This was a prospective randomised study, including 50 patients who underwent endoscopic surgery for Pituitary Adenoma at Sree Chitra Tirunal Institute for Medical Sciences, Trivandrum, India. Serum Copeptin levels were assessed (i) Preoperatively(C1), (ii) Post extubation(C2), and (iii) Postoperative day 4(C3). Data regarding fluid and electrolyte balance was collected from patients. Statistical Analysis was done using the above data.

Results:

The Copeptin values were assessed against the sodium disturbances. 100% (20/20) of patients who developed Transient Diabetes Insipidus(TDI) had a relative decrease in C2 from C1(p - 0.0002). A 20% relative decrease in C2 from C1 offered 100% predictability for development of TDI. 88%(7/8) of patients who developed

Early Hyponatremia(EH) had a relative increase in C2 as compared to C1($p < 0.01$). 75%(6/8) of patients who developed Delayed Hyponatremia(DH) had a relative increase in C3 as compared to C1($P = 0.003$). High Pituitary reserve(C1) did not offer any additional protection from development of SHI.

Conclusion:

A relative increase or decrease in Postoperative Serum Copeptin can predict development of Early Hyponatremia or Transient DI respectively. A relative increase in Delayed Serum Copeptin can predict development of Delayed Hyponatremia.

INTRODUCTION

Pituitary adenoma is one of the most common brain tumours encountered in neurosurgical practice. The estimated prevalence of Pituitary adenoma among general population is 17%[14,15]. The treatment and outcome of Pituitary adenoma has improved dramatically over the years. This can mainly be attributed to the advent of better understanding of the skullbase anatomy, improved visualisation as well as the development of endoscopic techniques. However, the post operative electrolyte imbalances, especially the fluctuating trends of sodium post pituitary surgery remain a problem in common neurosurgical practice. Neurosurgeons are often left chasing troughs and peaks of sodium, with continous intensive monitoring of fluid balance of these patients. The presence of a predictor for the development of these Sodium homeostasis imbalances can go a long way in providing assistance in management of these imbalances.

The most important electrolyte imbalances encountered in pituitary adenoma surgery are hypernatremia and hyponatremia. Post operative hypernatremia secondary to diabetes insipidus in endoscopic transsphenoidal surgery(ETS) is common and ranges from 1.6% to 46% according to literature[1,2,3]. The main reason postulated for the development of Diabetes insipidus include surgical stress, manipulation of the neurohypophysis, or both[4,5]. Hyponatremia after Endoscopic pituitary surgery usually results from hypocortisolemia or a syndrome of inappropriate secretion of ADH (SIADH) and very rarely due to Cerebral salt wasting. These conditions are related to altered free-water homeostasis, which caused the changes in the level of serum sodium[6,7]. Serum sodium concentration as

well as plasma osmolality are maintained with the help of several homeostatic mechanisms, like free-water intake by the stimulated thirst, secretion of ADH, and renal excretion of solutes[6,7].

In this study, we try to find out the utility of Copeptin in predicting post operative Hypernatremia and Hyponatremia in patients undergoing Endoscopic pituitary adenoma surgery. We also aim to find out whether the use of Copeptin as a measure of posterior pituitary reserve offers any protection or additional vulnerability to the development of these electrolyte imbalances.

AIMS AND OBJECTIVES

- To find out the utility of Copeptin to predict the development of Sodium Homeostasis imbalances in patients undergoing endoscopic pituitary adenoma surgery, namely

    A. Transient Diabetes Insipidus

    B. Permanent Diabetes Insipidus

    C. Early Hyponatremia

    D. Delayed Hyponatremia

REVIEW OF LITERATURE

Epidemiology

Pituitary adenomas account for approximately 10 to 15% of surgically-treated primary tumors of the central nervous system (CNS)[16,17]. Pituitary adenoma is one of the most common brain tumours encountered. The estimated prevalence of Pituitary adenoma among general population is 17%[14,15]. The majority of these tumors are less than 3-5 mm in diameter and would not require medical or surgical intervention. More recently, the use magnetic resonance imaging (MRI) of healthy subjects indicate that approximately 10% of the population harbors pituitary lesions. Because disruption of the hypothalamo-pituitary-gonadal axis in women is more evident than in men, women with pituitary adenomas may present to clinical attention at a higher rate, and earlier, than men.

Symptomatology and Management options

The majority of pituitary adenomas are benign. They present either with symptoms of excess hormone secretion or secondary to mass effect by the growing tumor. The common hypersecretory syndromes include Cushing's disease, acromegaly/gigantism, and hyperprolactinemia. Whereas the local mass effects on the pituitary can cause varying degrees of hypopituitarism. When the tumor grows beyond the confines of the sella turcica, the visual pathways are commonly affected and visual field deficits ensue. Effective medical therapy is available for prolactin secreting adenomas which are managed using Dopamine agonists. With the

exception of these tumors, transsphenoidal surgery remains the first-line treatment for most other pituitary adenomas.

Transsphenoidal surgery is a minimally invasive procedure for accessing pituitary tumors or sellar masses. One of the most frequent postsurgical effects is the disturbance of salt and water homeostasis secondary to disruption of the posterior pituitary gland or nearby infundibulum. The patterns of water and electrolyte disturbances after transsphenoidal surgeries can be generally categorized as hypernatremia or hyponatremia, attributable to an abnormally low or abnormally high secretion, respectively, of antidiuretic hormone (ADH).

Electrolyte imbalances following Transsphenoidal Pituitary Surgery

Central Diabetes insipidus

Central diabetes insipidus (CDI) is a polydipsia–polyuria syndrome due to the altered synthesis and secretion of AVP. CDI often occurs after the surgical resection of pituitary tumors (16–34%), which accounts for electrolyte imbalance and more extended hospitalization[18]. Transient postoperative CDI related to the dysfunction of AVP-secreting neurons occurs 24–48 h after surgery and resolves within 10 days[19]. Permanent postoperative CDI rarely occurs until at least 80–90% of AVP secreting neurons are irreversibly damaged[20]. Several risk factors, including tumor pathology (i.e., craniopharyngioma), tumor size, the extent of surgical resection, previous surgery, visual field defect, and intraoperative cerebrospinal fluid leakage, have been identified for postoperative CDI[21,22,23]. Unrecognized

postoperative CDI often results in hypernatremia, hyperosmolarity, and progressive symptoms and signs, including lethargy, irritability, and even seizures[24]. The diagnosis of postoperative CDI is still contingent on the symptom of polydipsia and polyuria because of the lack of rapid and effective diagnostics. Although direct AVP measurement in symptomatic patients is crucial in diagnosing CDI, it is not commonly used in clinical practice owing to the technical limitations and low accuracy of the AVP commercial assay[38]. Instead, the indirect water deprivation test or hypertonic saline test is widely used in diagnosing CDI.

Hyponatremia

Hyponatremia refers to a clinical condition in which serum sodium levels are below 135 mEq/L. Management of hyponatremia is complex and requires specific knowledge of its etiology, and inadequate or inappropriate treatment may have serious consequences, including the development of central pontine myelinolysis, seizures, cardiac dysfunction, and death[39,40]. Hyponatremia after transsphenoidal surgery for pituitary adenoma is most commonly due to SIADH. Other causes like Hypocortisolism and Cerebral Salt wasting are only reported to be rare in literature. Severe hyponatremia is associated with significant morbidity and high mortality rates; a serum sodium level of less than 105 mEq/L is associated with a mortality rate greater than 50%[41]. Symptomatic hyponatremia is relatively nonspecific in its presentation. Patients may report discomforts ranging from vague

constitutional symptoms with nausea and vomiting to an altered level of consciousness. A correction of abnormal sodium levels that is too rapid can cause drastic shifts in intracerebral cell size, leading to permanent damage[42]. Thus, a methodical treatment plan is needed to determine whether the abnormality in sodium levels is due to excessive sodium excretion or SIADH; clinicians must accurately track postoperative sodium levels and treat patients quickly and appropriately.

The phenomenon of delayed postoperative hyponatremia after Transsphenoidal surgery has been described in several reports[43]. Many of these reports are limited retrospective studies based on patients readmitted with symptomatic hyponatremia. The prevalence of Delayed Hyponatremia(DH) varies among the reported case series, since symptoms of hyponatremia are often nonspecific, and patients discharged from the hospital may not contact their health care providers. In addition, the cohort size in these studies limits the ability to identify predictive demographic or perioperative factors associated with DH. Factors associated with the development of DH vary in previous reports and include age, female sex, or estrogen use, tumor size early diabetes insipidus after surgery, Cushing disease and surgical trauma to the neurohypophysis [42,,47,48,49]

Kristof et al[42] in 2009 conducted a prospective study to find out the incidence, spectrum of clinical manifestations, course, and risk factors of water and electrolyte disturbances (WEDs) following transsphenoidal pituitary adenoma surgery. They monitored 57 successive patients undergoing transsphenoidal

pituitary adenoma surgery daily for body weight, balance of fluids, serum electrolytes, plasma osmolality, plasma antidiuretic hormone (ADH) levels, urinary sodium excretion, urinary osmolality, and subjective sensation of thirst till Post Operative Day (POD)-14. They found out that Water and electrolyte disturbances occurred in the majority of patients undergoing transsphenoidal pituitary surgery, and were usually transient. Diabetes insipidus is more frequent than hyponatremia. Diabetes insipidus usually occurs during the 1st postoperative day and resolves in a majority of cases within 10 days. In few patients, DI may persist and require therapy with ADH analogues. Hyponatremia usually occurs at the end of the 1st postoperative week and resolves in most cases within 5 days. Very few patients will need treatment other than fluid-intake restriction to avoid serious complications. Thus, they concluded that careful monitoring of the WEDs in patients undergoing transsphenoidal pituitary adenoma surgery is paramount.

Although most water and electrolyte disturbances are acute, clinicians have long sought to find reliable risk factors or markers that predict prolonged water and electrolyte disturbances after these surgeries. Considerable effort has been made to establish correlations between the tumor type or specific disease and the complication rate. In addition, associations have been found with sex, age, body mass index, nadir sodium, surgeon experience, and the amount of intraoperative manipulation of the neurohypophysis[45]. Ultman et al[44] suggest that there is a single initiating factor, pituitary stalk damage, which may account for the full spectrum of homeostasis disorders after transsphenoidal surgery, with the degree of damage

determining the particular profile. However, the mechanisms behind the response variability and underlying pathophysiology remain unknown, likely in part, because assessing the degree of damage in vivo is a difficult experimental task and is usually subjective in a surgical setting.

Role of Arginine Vasopressin

Arginine Vasopressin is the prime hormone responsible for the electrolyte disturbances occurring secondary to transsphenoidal pituitary surgery. Arginine vasopressin (AVP), is a peptide hormone with osmoregulatory and hemodynamic effects, produced in the magnocellular neurons of the hypothalamus. After

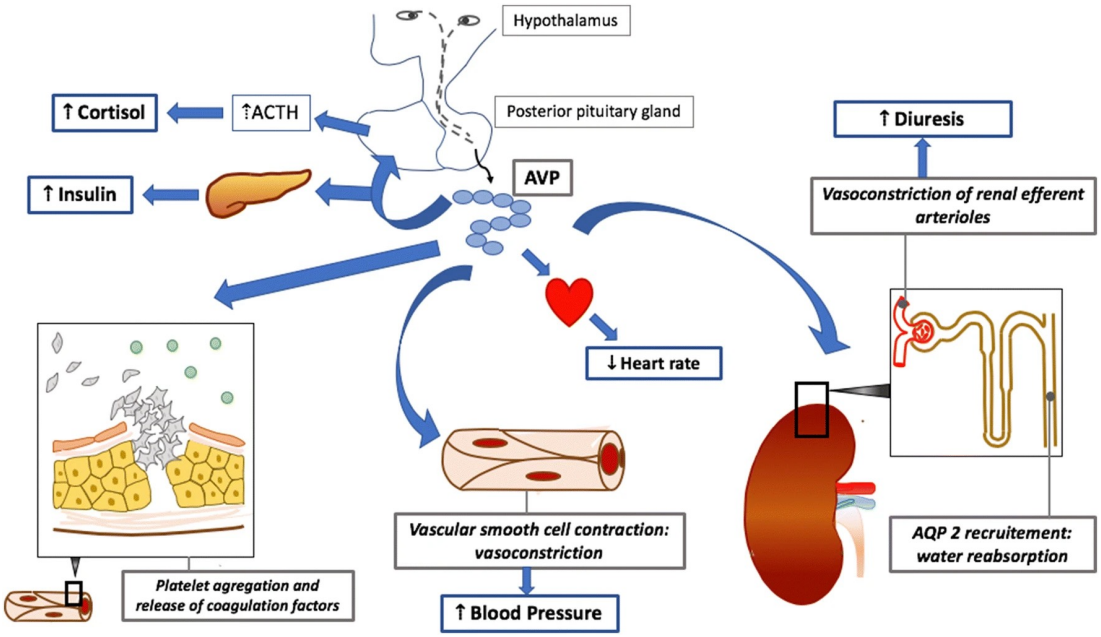

Figure 1:Physiology of Arginine Vasopressin. (AVP-Arginine Vasopressin, AQP-2-Aquaporin 2)

production, it then undergoes axonal transport to the eminentia mediana and the

posterior lobe of the pituitary gland. It is secreted in response to hemodynamic and osmotic stimuli.

AVP Receptors	Site	Function
V_{1a} receptors	vascular smooth muscle cells	Arteriolar vasoconstriction
V_{1b} receptors	adenohypophyseal and pancreatic islet cells	Induces corticotropic axis stimulation (increase in cortisol) and insulin secretion.
V_2 receptors	basolateral surface of renal tubular cells, mainly on collecting ducts	Antidiuretic effects[46]

Table 1: Type of AVP receptors, their sites and functions

After stimulation, vasopressin is released into blood circulation, to 3 receptor subtypes. Binding on V1a receptors induces vascular smooth cell contraction in the periphery and on renal efferent arteriole and platelet aggregation. Vasopressin binding on renal V2 receptors causes aquaporin 2 recruitment, leading to water re-absorption and on extra-renal V2 receptors induces the release of coagulation factors. Binding on V1b receptors induces corticotropic axis stimulation and insulin secretion. During septic shock, vasopressin plasma level is low. Administration of vasopressin or its analogues induces a strong vasoconstriction, leading to an increase in blood pressure, and higher glomerular filtration rate[46]. Certain other effects of AVP have also been reported including ones on brain functions, temperature regulation and myometrial contraction[9,10]. Though AVP

seems an ideal marker from a pathophysiological point of view, there are significant problems in assay of AVP[11].

Challenges of vasopressin (AVP) measurement

1. More than 90% of AVP in the circulation is bound to platelets, resulting in underestimation of amounts of AVP actually released[32].
2. Incomplete removal of platelets from plasma samples or prolonged storage of unprocessed blood samples can lead to falsely elevated and varying AVP levels[32,33].
3. Once secreted, AVP is rapidly cleared from the circulation, with an in vivo half-life of 24 min[34].
4. AVP is unstable in isolated plasma, even when stored at 20 degree C[35].
5. Because of its small size, AVP cannot be measured by sandwich immunoassay, but only by less sensitive competitive immunoassays.

Priebisz et al in 1983 found that, in 31 normal subjects, close to 90% of circulating arginine vasopressin (AVP), measured by radioimmunoassay, was associated with platelets[32]. Therefore, it was difficult to assay and even when assayed, it would be an underestimation too. So, another method was necessary for accurate evaluation of AVP. And hence, due to the above difficulties in estimation of Arginine Vasopressin, there was need for a more stable separate marker which

can be assayed easily and would act as a surrogate for AVP. That is where Copeptin rose to prominence.

Significance of Copeptin

Copeptin was initially described by Dirk Holwerda in 1972 as a glycopeptide obtained from the posterior pituitary in pigs. He found out that this glycopeptide was found in the same order as the posterior pituitary hormones, namely Vasopressin and Oxytocin[8]. It consists of 39 amino acids, is glycosylated, and contains a leucine-rich core segment. Together with AVP, copeptin is derived from a 164-amino acid precursor termed preprovasopressin, which consists of a signal peptide, AVP, neurophysin II and copeptin. Therefore, copeptin is the C-terminal part of pro-AVP (CT-proAVP)[11].

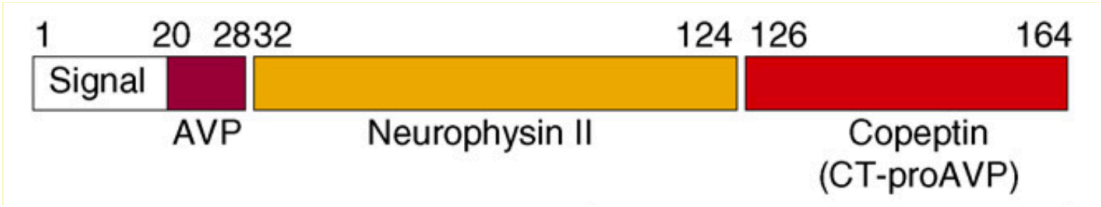

FIGURE 2: PEPTIDE PRECURSOR OF ARGININE VASOPRESSIN (PROAVP), SHOWING THE SIGNAL SEQUENCE (WHITE), AVP (DARK RED), NEUROPHYSIN II (ORANGE) AND COPEPTIN (RED). NUMBERS INDICATE AMINO ACIDS OF THE HUMAN PROTEIN. SIGNAL, SIGNAL PEPTIDE; AVP, ARGININE VASOPRESSIN; CT-PROAVP, C-TERMINAL PROAVP.

After synthesis of preprovasopressin in the magnocellular nuclei of the hypothalamus, the precursor peptide is subjected to a four-enzyme cascade to attain its bioactive conformation. After cleavage of the signal peptide, the provasopressin folds, placing AVP into a binding pocket of neurophysin II, protecting it from

proteolysis and promoting high-density packing in neurosecretory vesicles. After formation of seven disulfide bonds within neurophysin II and one within AVP, and after glycosylation of copeptin, provasopressin is packaged into neurosecretory granules and then cleaved into its product peptides during axonal transport from the hypothalamic nuclei to the neurohypophysis. This processing of the remaining three-domain precursor principally occurs in two stages: a first cleavage that splits off AVP, and a second cleavage that separates neurophysin II from copeptin. Processing is usually complete at the level of the neurohypophysis[36,37].

Advantages of Copeptin over AVP

When compared to AVP, Copeptin boasts of a number of advantages in the ease of extraction and ease of asset. The various factors that favour Copeptin over AVP arre enumerated below.

1. Copeptin assay requires only 50 µL serum or plasma, whereas AVP assays need 1 mL of plasma.
2. No extraction step or other preanalytical procedures, such as the addition of protease inhibitors, are needed.
3. Results are available in approximately 3 hours, whereas many of the competitive AVP immunoassays described require more than 12–24 h because of the extensive incubation steps involved.

4. Because the copeptin assay is a sandwich immunoassay, it is remarkably sensitive, as can be seen by the analytical detection limit of 1.7pmol/L. This is also reflected in the good total precision, with an interlaboratory coefficient of variation (CV) < 20% for all copeptin concentrations.

5. The assay can detect copeptin in the plasma or serum of 97% of the healthy population regardless of osmolality, whereas AVP is often not detectable in plasma samples with medium or low osmolality.

6. Probably the most relevant advantage of the copeptin assay is that copeptin, unlike mature AVP, is extremely stable in plasma or serum ex vivo. Ex vivo stability of copeptin (<20% loss of recovery) was shown for serum and plasma for at least 7 days at room temperature and 14 days at 48 degree Celsius[11].

In 2008, Morganthaler et al[11], deduced that Copeptin trends has a linear relationship with AVP and hence they proposed that Copeptin can be used as a surrogate marker for AVP[11]. Copeptin has been in centerstage of scientific research since and its properties and biochemistry have been described extensively. The use of Copeptin in various clinical setting have been extensively studied. They include Electrolyte imbalances like Diabetes insipidus, Myocardial infarction and Cardiac failure[12], Sepsis and Critical Illness, and Lower Respiratory Tract infections[13].

Fenske et al[25] conducted a study to evaluate the diagnostic potential of copeptin, the C-terminal part of provasopressin, as a new marker in the differential diagnosis of hyponatremia. They evaluated 106 consecutive hyponatremic patients

were classified based on their history, clinical evaluation, and laboratory tests. However they found out it that identifies patients with primary polydipsia but has limited utility in the differential diagnosis of other hyponatremic disorders[25].

Recently, reliable commercial assays of copeptin are available and several researchers have suggested that copeptin is useful for the differential diagnosis of polydipsia–polyuria syndrome and Diabetes insipidus. Fenske et al. has exhibited that the direct measurement of hypertonic saline–stimulated plasma copeptin had greater diagnostic accuracy than the water-deprivation test in patients with hypotonic polyuria[25,26]. Other studies suggested that low copeptin levels at the immediate postoperative time predicted the permanent postoperative CDI since the postsurgical stress stimulates copeptin secretion[27-29].

Refardt et al in 2019, studied the role of copeptin in the diagnosis of Diabetes insipidus and Syndrome of Inappropriate antidiuresis[30]. It was found that differentiation between central diabetes insipidus and primary polydipsia was possible with a high diagnostic accuracy. Refardt et al proved that it was possible to differentiate between central diabetes insipidus and primary polydipsia, by a stimulated copeptin level of 4.9 pmol/L upon hypertonic saline infusion differentiates these two entities with a high diagnostic accuracy and that it was clearly superior to the classical water deprivation test. On the contrary, they found copeptin measurement was of only little diagnostic value in SIAD[30].

Winzeler et al[27] in 2019, studied the role of post operative Copeptin levels in the prediction of diabetes insipidus after pituitary surgery. They found that median [25th-75th percentile] copeptin levels were significantly lower in patients developing DI vs those not showing this complication. Logistic regression analysis revealed strong association between postoperative copeptin concentrations and DI. They concluded that low copeptin levels in post operative period despite surgical stress reflect development of postoperative DI[27].

Berton et al[28], in 2020 conducted a prospective study with 66 patients. They found that a post operative copeptin value below or equal to 12.8 pmol/L had a good accuracy in identifying Central DI cases whereas a post operative copeptin peak above 4.2 pmol/L excluded permanent Central Diabetes insipidus. They concluded that a prompt increase of copeptin is expected normally at 1 hour after extubation. The absence of this peak was found to a reliable predictor of post-neurosurgical Central Diabetes Insipidus[28].

Vanasuntorn et al[29], in 2020, conducted a prospective diagnostic study in which patients who underwent neurosurgical intervention of the sellar-suprasellar regions were recruited[29]. Serum copeptin levels were measured before and after surgery, within 24 hours. Logistic regression analysis and diagnostic performance measures were calculated to determine the relationship between postoperative copeptin levels and DI. They concluded that in patients undergoing sellar-suprasellar interventions, low postoperative copeptin levels within the first postoperative day predict postoperative DI, whereas high levels exclude it and has

proposed that copeptin measurement should be applied in the clinical practice of postoperative care in patients following hypothalamic-pituitary surgery. Their results were in accordance with Winzeler et al and reaffirmed the use of Copeptin in diagnosing and predicting development of Central Diabetes Insipidus.

Hyoo Yung Kim et al[31] in 2021 studied the changes in copeptin levels before and 3 months after transsphenoidal surgery according to the presence of postoperative central diabetes insipidus CDI[31]. Consecutive patients who underwent endoscopic transsphenoidal surgery at a single tertiary hospital were recruited. Serum copeptin levels were measured preoperatively and 3 months postoperatively . They concluded that 3 months postoperative copeptin levels significantly decreased from preoperative levels in the transient CDI group as well as the permanent CDI group. However, the three-month postoperative copeptin levels ≥ 3.5 pmol/L under normal serum sodium levels may be diagnostic for excluding postoperative CDI.

Hypo Yung Kim et al in their study[31] suggested in this study that simultaneous preoperative and postoperative serum copeptin measurements provide valuable information for investigating the changes of posterior pituitary function after transsphenoidal surgery. This concept is being utilised in the present study.

MATERIALS AND METHODS

Study

This was a prospective study incorporating patients undergoing Endoscopic transnasal transsphenoidal pituitary adenoma surgery from the Department of Neurosurgery, Sree Chitra Tirunal Institute of Medical Sciences and Technology, Trivandrum, Kerala, India. Sample size of the study is 50. [Central Diabetes Insipidus were seen in 34%(upto 46%) patients[1,2,3]. This relation will be significantly high while considering both the troughs and peaks of sodium disturbances. Considering that difference as double(68%), for detecting that at 5% level of significance and 80% power, the minimum sample size in the study group is 33 patients.] They were followed up till 3 months post procedure.

Inclusion criteria

The Inclusion criteria included

1. All Patients undergoing Endoscopic Pituitary adenoma surgery (both primary and recurrent).
2. Patients above 18 years of age
3. Patient who have given Informed Consent

Exclusion criteria

The exclusion criteria included

1. Patients with prior sodium imbalance disorders, namely Central Diabetes Insipidus, (2/3 criteria-An Urine Output of more than 3ml/kg/hr for more than two hour / Urine Specific gravity of <1.002 / Serum Na > 145 mmol/L) or Hyponatremia(S. Na < 135 mmol/L)
2. Patients undergoing transcranial surgery for pituitary adenoma
3. Patients who denied consent
4. Patients with Persistent Hypocortisolism at admission. (Morning Serum Cortisol <5 mcg/dL)

Data Collection

The data regarding demographic profile, clinical presentation, pre and postoperative neurological examination was collected. A formal Visual Assessment-Acuity by Snellen's Chart and Field by Humphrey's perimetry chart was done. Hormone profile(Thyroid profile(Thyroid Stimulating Hormone, Free T3, Free T4), Adrenocorticotrophic Hormone(ACTH), Serum Cortisol, Growth Hormone(GH), Prolactin(in dilution), Follicle stimulating hormone, Lutenizing Hormone was assessed for all patients. For functioning adenomas, respective specific tests(Insulin Like Growth Factor-1, Oral Glucose Tolerance Test for GH secreting adenomas, Low dose dexamethasone suppression test, High dose dexamethesone suppression test for ACTH secreting adenoma etc) were done as per Endocrinological advise and clearance obtained prior to surgery. Thorough neurological examination was done. Surgical details, postoperative surgical and medical complications were

followed up from the 50 patients. Extent of Resection was assessed by intra operative impression and presence of residue in immediate Post operative CT scan. Post operatively, Fluid chart of the patients were maintained till discharge. Hourly Urine Output and Volume intake was monitored on Post Operative day(POD)-0 and POD 1. Daily Fluid Intake and Output was maintained till discharge. Serum Sodium was measured pre-operatively and then monitored 4th hourly on POD-0 and POD-1, 12th hourly for next 2 post operative days, then daily for 5 days, followed by alternate days till 2 weeks. Central Venous Pressure was monitored twice daily on POD-0 and POD-1. Serum osmolality was assessed twice daily on POD-0 and POD-1. Urine specific gravity was assessed on first 2 days.

Serum copeptin levels were assessed on (i) preoperatively(called Preoperative Copeptin or Copeptin 1 or C1), (ii) at extubation(called Immediate Post Operative Copeptin or Copeptin 2 or C2) and (iii) on POD 4(called Delayed Post Operative Copeptin or Copeptin 3 or C3). Preoperative Copeptin was assessed as a measure of the Posterior Pituitary Reserve of the patient. Rationale behind assessment of Copeptin 2, at extubation was to tackle the peak of Arginine Vasopressin following surgical stress, where as assessment of Copeptin 3 was made to assess the hormone levels following the initial surgical stress and immediate post operative period.

Outcome definition

Outcomes assessed include Post operative Hypernatremia as well as Hyponatremia scenarios. The outcomes assessed are Transient Diabetes Inspidus, Permanent Diabetes Insipidus, Early Hyponatremia, Late Hyponatremia.

- **Diabetes insipidus** was defined as the presence of two out of the following three criteria:

    1. An Urine Output of more than 3 ml/kg/hr for more than two hours
    2. Urine Specific gravity of <1.002
    3. Serum Na > 145 mmol/L.

- **Transient Diabetes Insipidus** was defined as that Diabetes Inspidus(meeting the above said criteria) which settles in 2-3 post operative days and required no exogenous Vasopressin supplementation at discharge.

- **Permanent Diabetes Insipidus** was defined as Diabetes Insipidus(meeting the above said criteria) which required exogenous Vasopressin analogue supplementation after discharge and follow up.

- **Early Hyponatremia** was defined as the development of Serum Na<135 mmol/L during admission period from Post op day 1-5.

- **Late Hyponatremia** was defined as development of Serum Na <135 mol/L after POD-5.

Copeptin assessment

Blood for Copeptin was drawn in an Ethylenediaminetetraacetic acid (EDTA) bottle and assayed using Genetix Biotech™ Human Copeptin CPP ELISA PG-1580H kit. Copeptin was assayed using the Competitive ELISA principle. The detecting range was 30-2000 pg/ml with a sensitivity of 18.25 pg/ml. The Genetix Biotech™ Human Copeptin CPP ELISA PG-1580H kit was procured using Learning research allowance of the Institute.

Statistical analysis

The continuous variables (copeptin values, sodium values) were expressed as mean ± standard deviation. The mean differences were tested by a two-tailed t-test. Pearson's correlation was used to analyze the association between quantitative parameters. For categorical variables, the Chi-square test was used to determine if the observed results were in line with expected results. Plots and charts included box whisker plots, bar charts, and histograms for displaying the variation in the data set. The receiver operating characteristic curve (ROC curve) was used to show the trade-off between sensitivity and specificity. The values $P < 0.05$ were considered statistically significant. Statistical analysis was done using IBM SPSS Statistics 25.

Ethics Committee Approval

This study was approved by the Institutional Ethics Committee of Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum(IEC No:1784, Year- 2021).

Funding

The Genetix Biotech™ Human Copeptin CPP ELISA PG-1580H kits used for Copeptin assay for this study were procured by the Learning Research Allowance of the Institute.

RESULTS

A. Demographics

A total of 50 patients undergoing endoscopic pituitary adenoma surgery were included in the study, of which 28 were female and 22 were male.

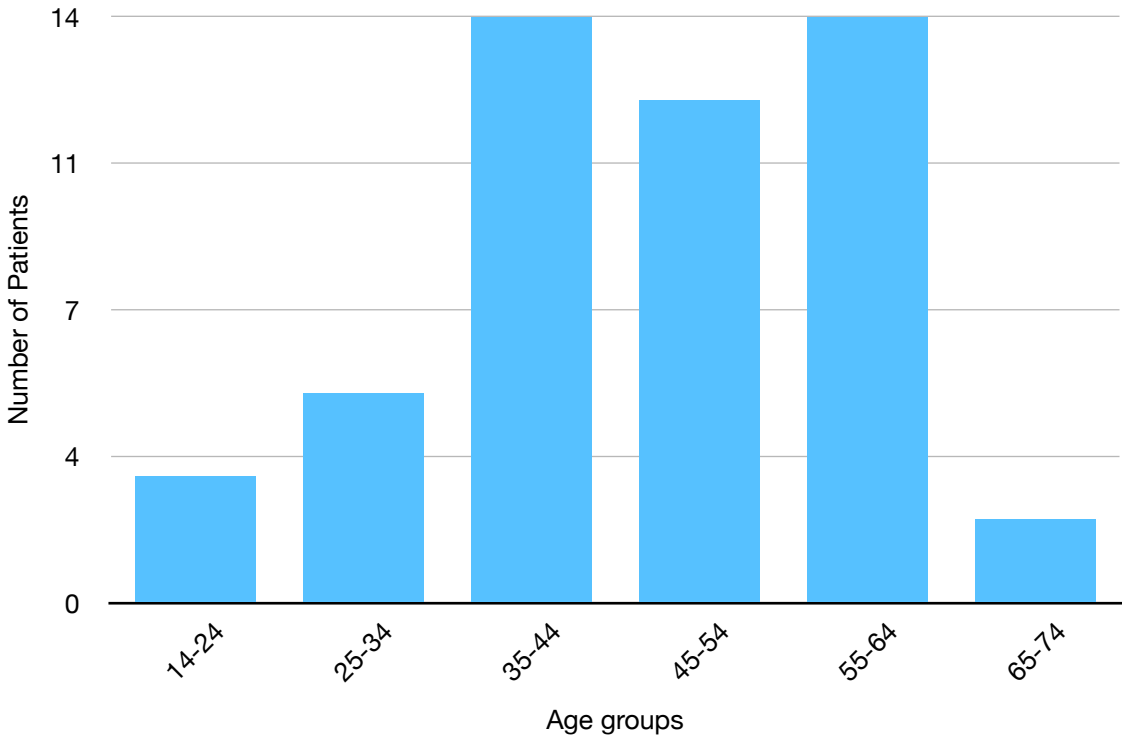

Chart 1: Bar diagram depicting the Frequency of patients in different age groups

Sex	Count
F	28
M	22
Grand Total	**50**

Table 2: Sex distribution

The age distribution of the cohort is as shown in the figure. 80% of patients (40/50) were in the age group between 35 and 64 years of age. 2 patients were above the age of 65. 3 patients were below 24 years of age.

Out of the 50 patients evaluated, 10 patients were having functioning adenoma. Out of which 5 were ACTH secreting pituitary adenoma, 3 were GH secreting pituitary adenoma and 2 were Drug resistant Prolactinoma.

Functioning status	**Count**
Non Functioning adenoma	40
Functioning adenoma	10
Grand Total	**50**

Table 3: Table showing proportion of functioning and non functioning adenoma in study sample.

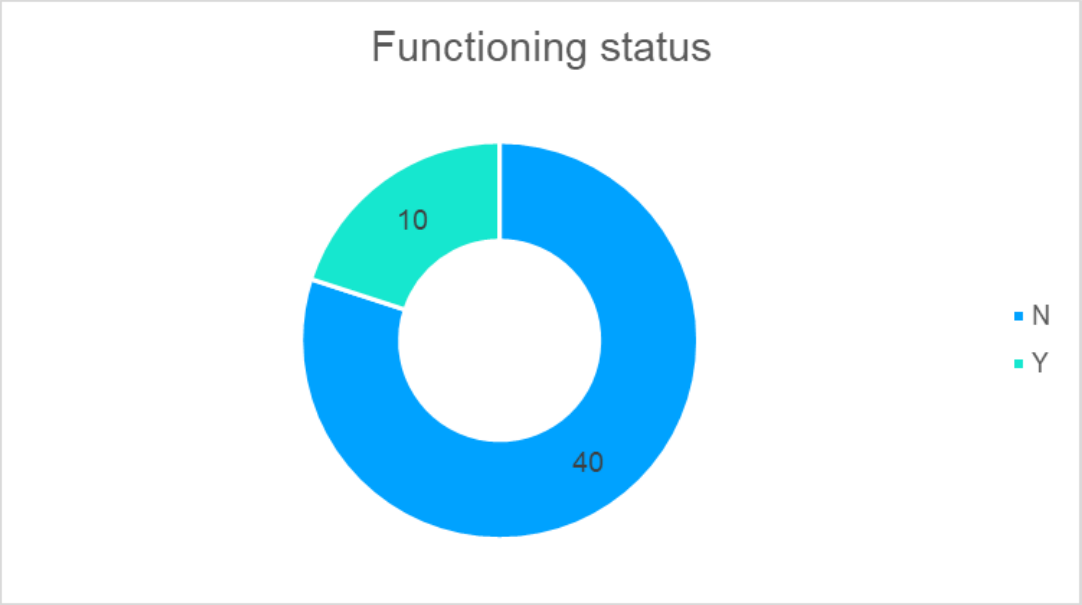

Chart 2: Proportion of functioning and non functioning adenoma in study sample.

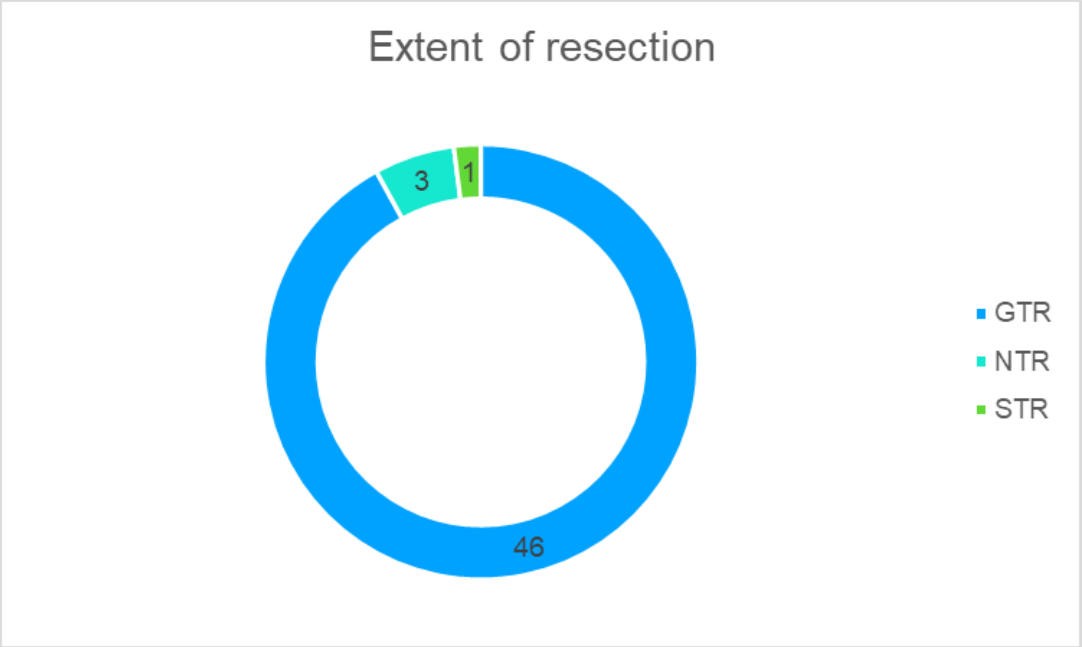

Chart 3: Proportion of Gross total resection, near total resection and subtotal resection in study sample.

Type of resection	Count
GTR	46
NTR	3
STR	1
Grand Total	**50**

Table 4: Proportion of Gross total resection, near total resection and subtotal resection in study sample.

Of the 50 patients studied, 92% of patients attained Gross total resection(46/50) and 6% (3/50) of patients attained Near Total Resection and only 2%(1/50) patients had Subtotal resection.

B. Copeptin measurements

Preoperative Copeptin

Preoperative Copeptin values assessed ranged from 98.9 pg/ml to 673.3 pg/ml with a mean of 270.6 pg/ml. The mode was 98.6 pg/ml. Standard deviation was 112.24. The values showed normal distribution, as shown in figure.

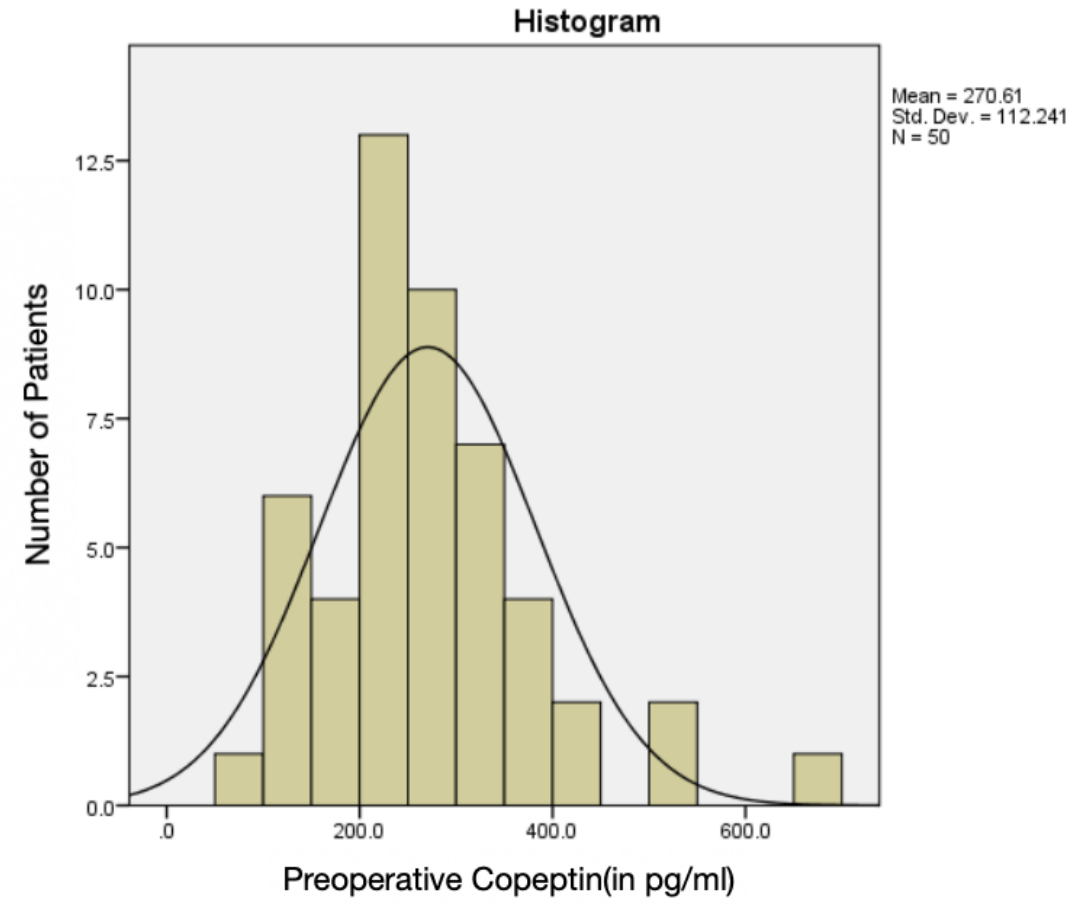

Chart 4: Distribution of Preoperative Copeptin

N	50
Mean	270.612
Median	252.950
Mode	98.6[a]
Std. Deviation	112.2414
Range	574.7
Minimum	98.6
Maximum	673.3

a. Multiple modes exist. The smallest value is shown

Table 5: Table showing distribution of Preoperative Copeptin

The Preoperative Copeptin values were analysed against preoperative trends. Pearson correlation was tested and it showed positive correlation.(R =0.107)

		Preoperative Copeptin	Preoperative Sodium
Preoperative Copeptin	Pearson Correlation	1	.107
	Sig. (2-tailed)		.458
	N	50	50
Preoperative Sodium	Pearson Correlation	.107	1
	Sig. (2-tailed)	.458	
	N	50	50

Table 6: Table showing correlation of Copeptin 1 with Preoperative Sodium(Na 1)

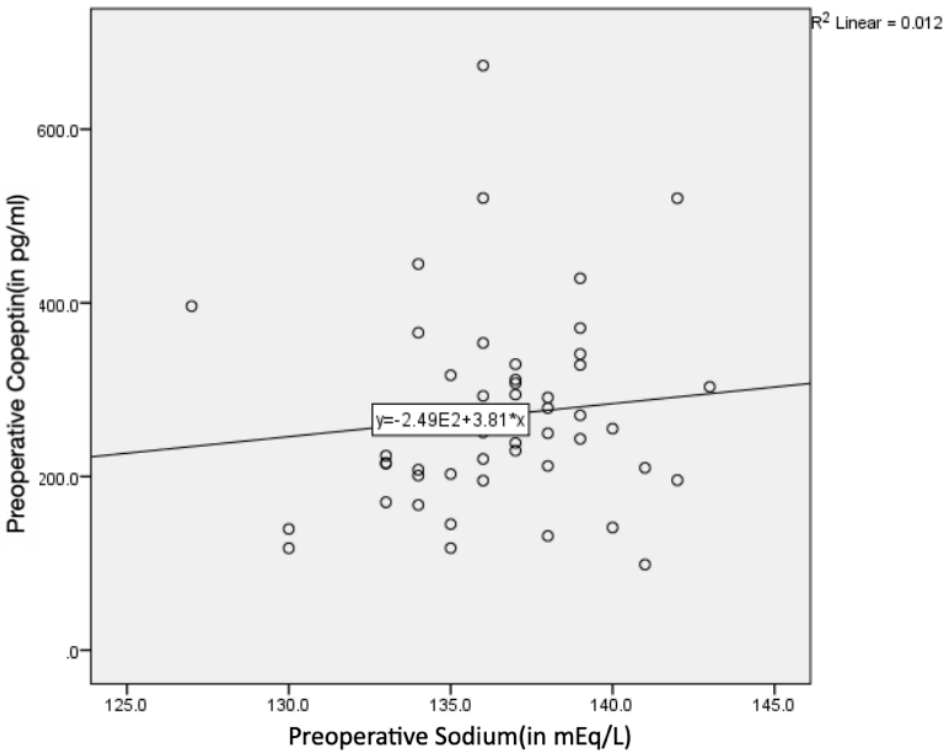

Chart 5: Scatter plot showing relationship between the Preoperative Copeptin and Preoperative Sodium

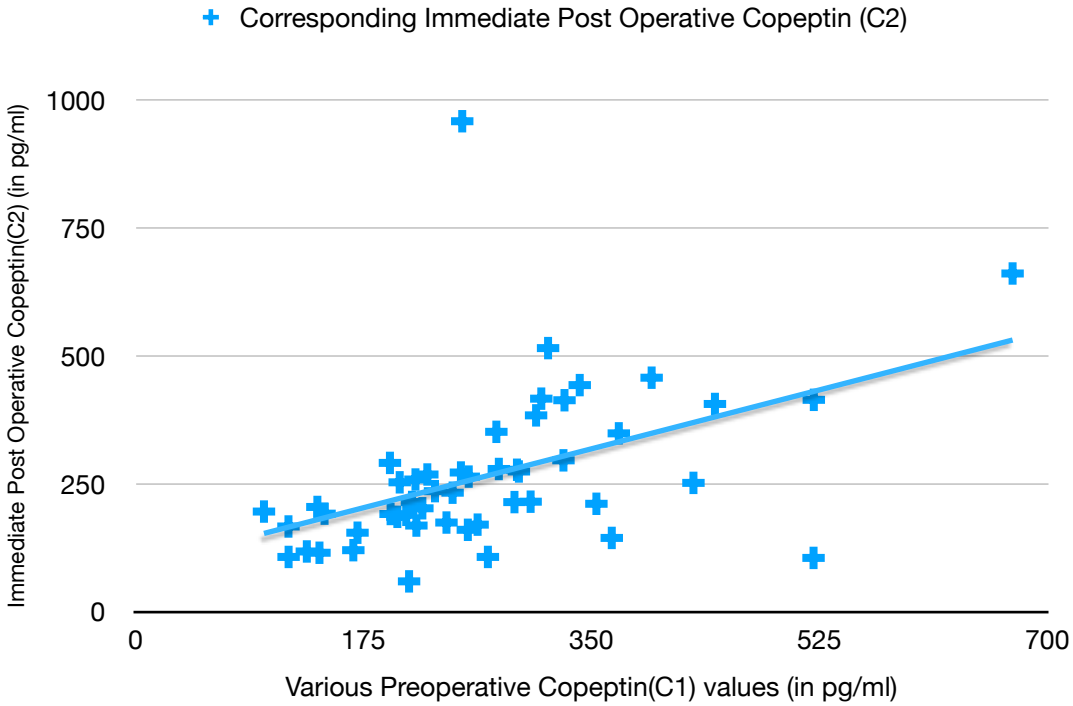

Chart 6: Scatter plot showing various Preoperative Copeptin values and their corresponding Immediate Postoperative Copeptin values

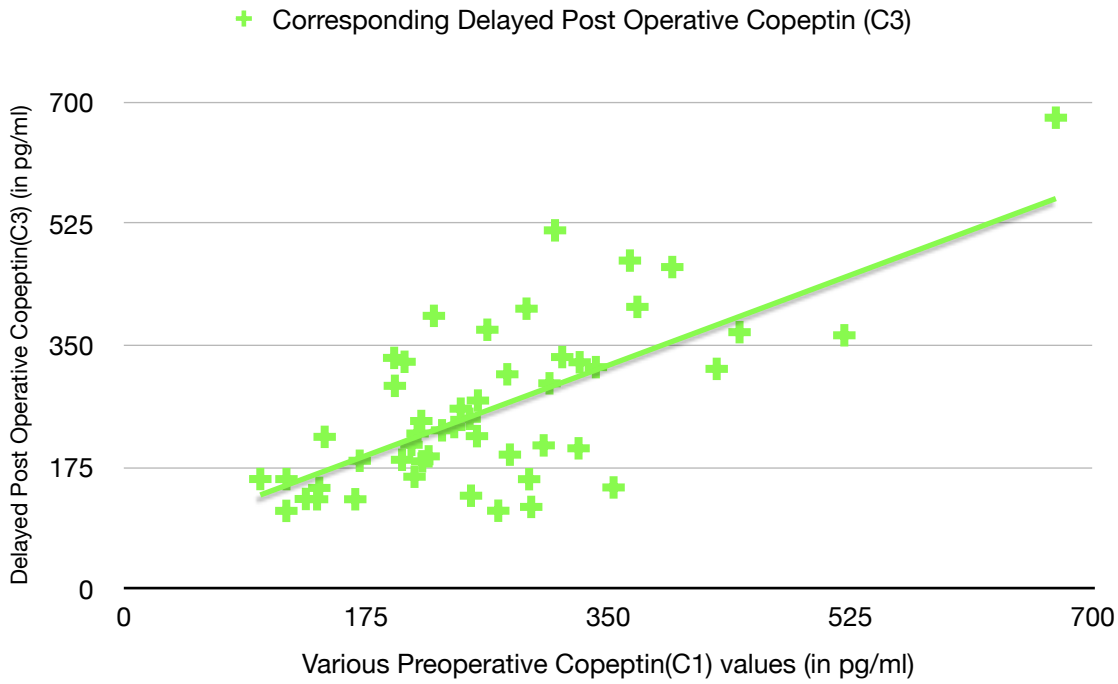

Chart 7: Scatter plot showing various Preoperative Copeptin values and their corresponding Delayed Postoperative Copeptin values

Copeptin trends

The three copeptin values assessed were the Preoperative Copeptin(C1), the Immediate postoperative Copeptin(C2) and the Delayed postoperative Copeptin(C3). The change in Copeptin levels across different timeline were studied extensively to decipher the copeptin trend through the post operative course.

1. Immediate Post Operative Relative Change in Copeptin(IRC)

Immediate Post operative Relative Change in Copeptin was the percentage increase or decrease in Copeptin 2 with respect to Copeptin 1. Of the total 50 patients, 60% (30/50) had a relative decrease in Immediate Post Operative Copeptin

with respect to preoperative value. Whereas, 40% patients(20/50) showed an relative increase in Immediate post operative Copeptin.

IRC	Number	Percentage
Increase(Positive)	20	40
Decrease(Negative)	30	60
Total	50	100

Table 7: Table showing variations in Immediate Post operative Relative Change in Copeptin(IRC)

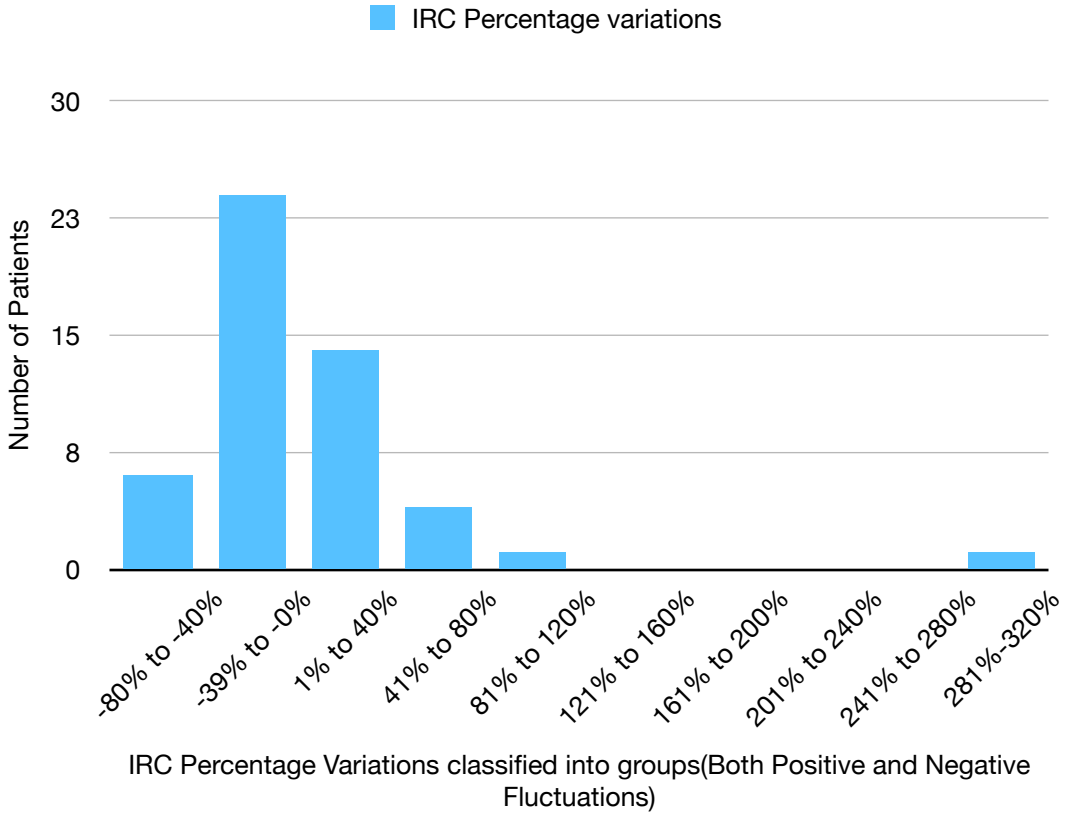

Chart 8: Number of Patients with different IRC percentages

Relationship of Percentage variations of Immediate Post Operative Relative Change in Copeptin was correlated with Immediate Post operative Sodium. Using Pearson correlation, R was found to be -0.145. There is mild negative correlation between IRC variation and Post operative sodium. For a negative shift of IRC, there's a mild increase in Post operative Sodium as is shown by the scatter diagram.

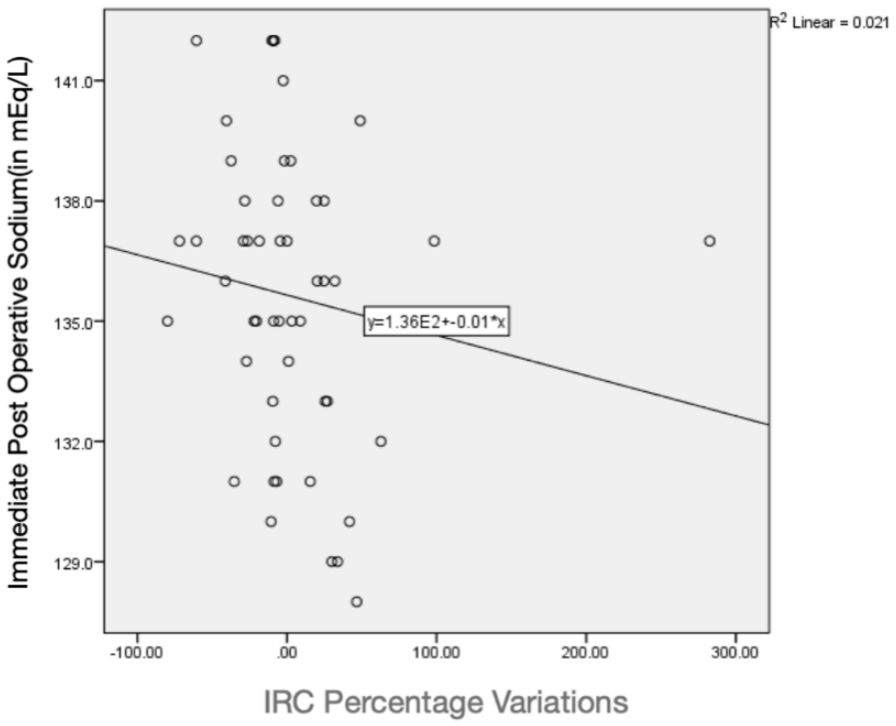

Chart 9: Scatter diagram showing relationship of Percentage variations of IRC with Immediate Post Operative Sodium

Correlations

		IRC Percentage variation	Immediate Post operative Sodium
IRC Percentage variation	Pearson Correlation	1	-.145
	Sig. (2-tailed)		.315
	N	50	50
Immediate Post Operative Sodium	Pearson Correlation	-.145	1
	Sig. (2-tailed)	.315	
	N	50	50

Table 8: Pearson correlation of IRC Percentage variation with Immediate Post Operative Sodium

2. Delayed Post Operative Relative Change in Copeptin(DRC)

Delayed Post Operative Relative Change in Copeptin(DRC) was the relative change in Delayed Post Operative Copeptin(C3) with respect to Preoperative Copeptin(C1). Of the total 50 patients assayed, 56% (28/50) had a relative decrease in Delayed Post Operative Copeptin with respect to preoperative value. Whereas, 44% patients(22/50) showed a relative increase in Delayed post operative Copeptin.

DRC	Number	Percentage
Increase(Positive)	22	44
Decrease(Negative)	28	56
Total	50	100

Table 9: Table showing variations in Delayed Postoperative Relative Change in Copeptin(DRC)

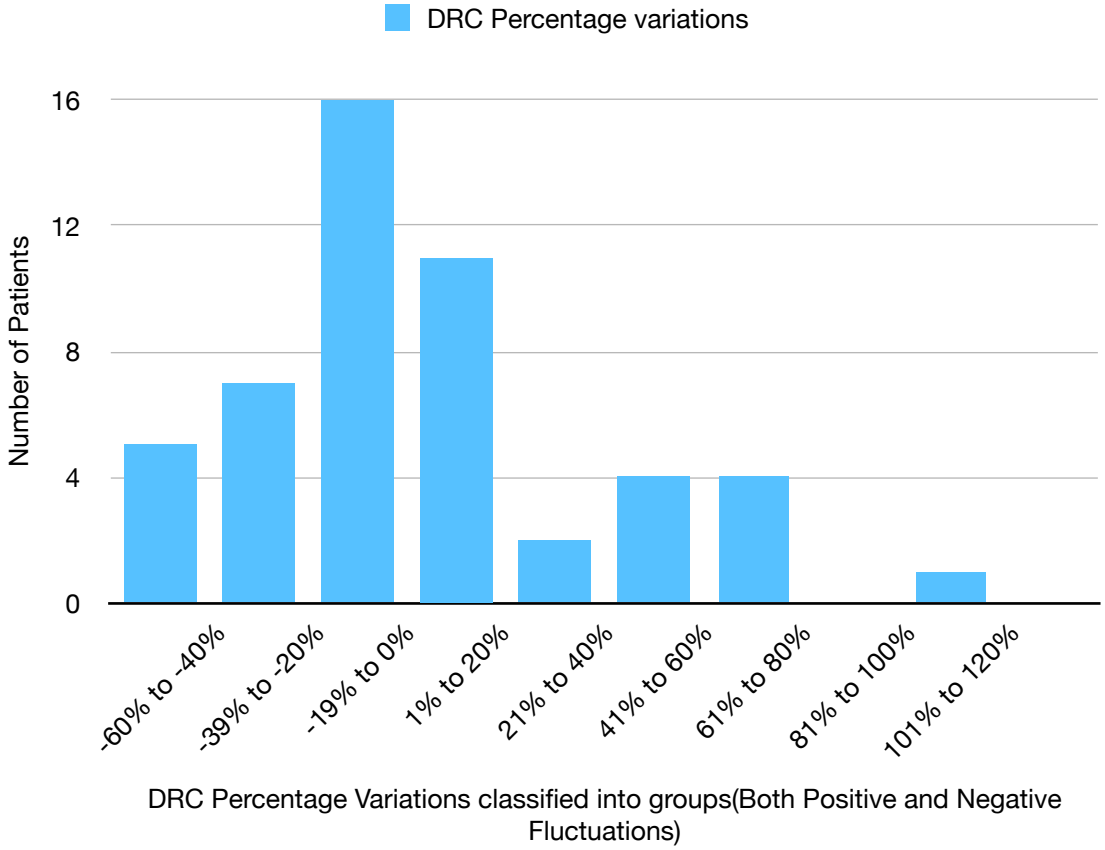

Chart 10: Bar diagram depicting the Frequency of patients having various DRC Percentage variations

3. Relative Post operative Change in Copeptin(RPC)

Relative Post Operative Change in Copeptin(C3-C2) was the relative change in Delayed Post Operative Copeptin(C3) with respect to Immediate Post operative Copeptin(C2). Of the total 50 patients assayed, 54% (27/50) had a positive fluctuation in RPC. Whereas, 46% patients(23/50) showed a negative fluctuation in DRC.

RPC	Number	Percentage
Increase(Positive)	27	54
Decrease(Negative)	23	46
Total	50	100

Table 10: Table showing variations in Relative postoperative change in Copeptin

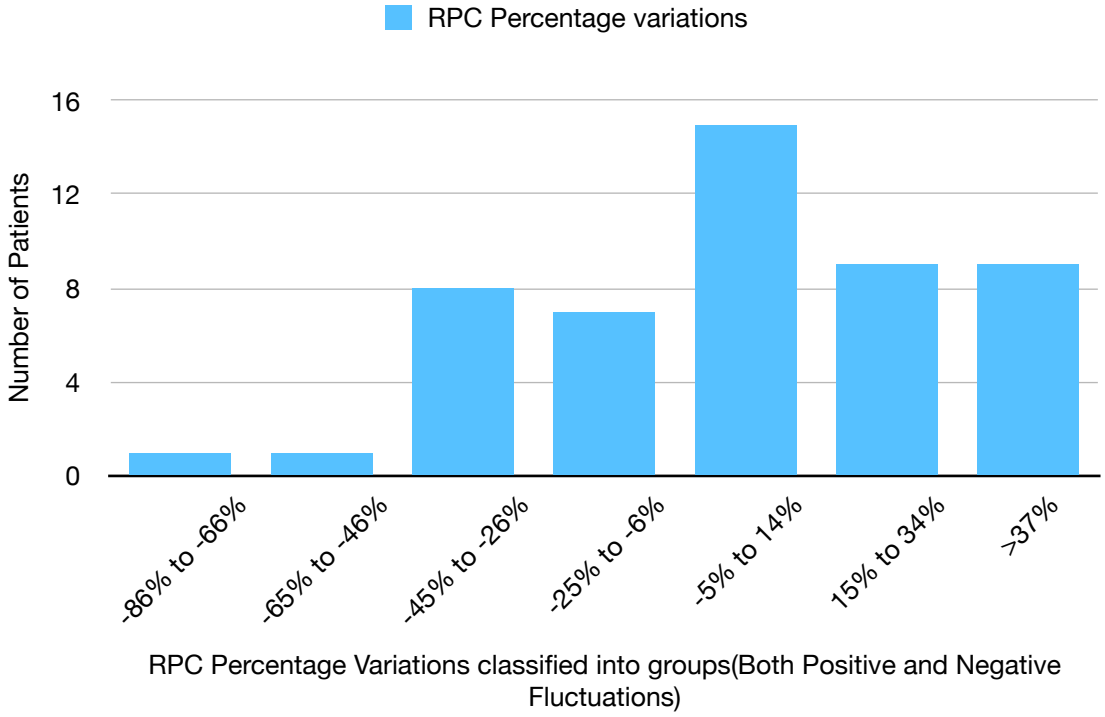

Chart 11: Bar diagram depicting the Frequency of patients having various RPC Percentage variations

C. Outcome assessment

1. Transient Diabetes Insipidus

Out of the total 50 patients that were studied, 20 patients developed Transient Diabetes Insipidus in the post operative period.

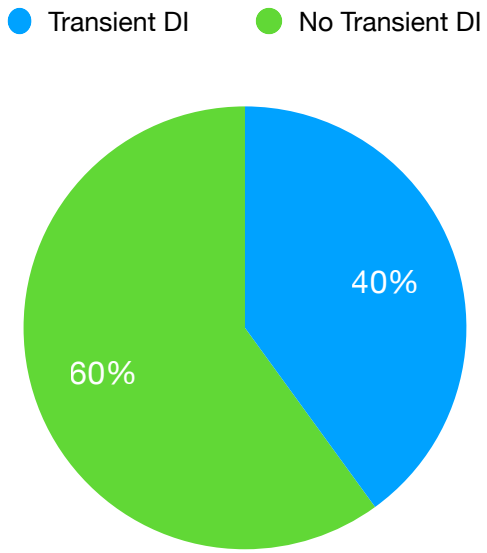

Chart 12: Incidence of Transient Diabetes Insipidus

Category	Number of patients	Percentage
Transient DI	20	40
No Transient DI	30	60
Total	50	100

Table 11: Incidence of Transient Diabetes Insipidus

The Various Copeptin trends were assessed against the Incidence of Transient diabetes insipidus and processed for any statistical significance. The relative difference in Post operative Copeptin(C2) from Pre operative Copeptin

value(C1) was assessed against the incidence of Transient Diabetes Insipidus. It was found that 100% of patients(20/20) who developed Transient Diabetes Insipidus had a decrease in Post operative Copeptin with respect to Pre operative Copeptin value.

	Category	Mean (SD)	t	P	Mean difference	95% confidence interval	
						Lower	Upper
IRC (Percentage difference)	Transient DI	-30.5913 (23.2399)	-4.2	<0.01	-55.99	-82.27	-29.7
	No Transient DI	25.4055 (55.13297)					

Table 12: Table showing relationship of Relative percentage change in Immediate postoperative copeptin to development/non development of Transient DI(Independent t test)

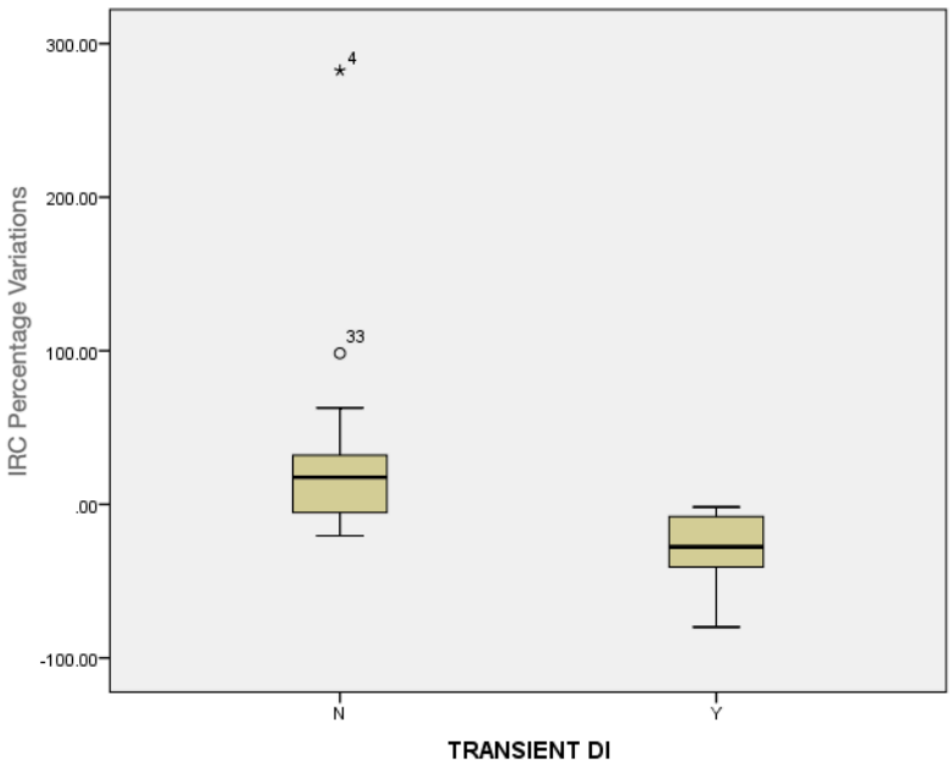

Chart 13: Box and Whisker plot showing the relationship of IRC percentage variations with Transient DI

It was found that a relative decrease in Immediate post operative Copeptin(C2-C1) is positively correlated with a development of Diabetes Insipidus. ($P<0.01$). Furthermore, all patients(100%) who had a relative decrease of Immediate Post operative Copeptin of 20% from baseline developed Transient Diabetes Insipidus.

The area under the curve for Negative IRC as a predictor for development of TDI is 0.922. The cut-off point was arrived at by the Youden Index. The point of maximum sensitivity (78%) and specificity (90%) was at -5.68 percent, beyond other clinical considerations. Therefore a negative fluctuation of IRC of more than 5.68% can predict the development of Transient Diabetes Insipidus with a sensitivity of 78% and specificity of 90%.

Area Under the Curve

Test Result Variable(s): Negative IRC fluctuation

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.922	.036	.000	.851	.993

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Table 13: Area under the curve for Negative IRC fluctuation against Transient DI

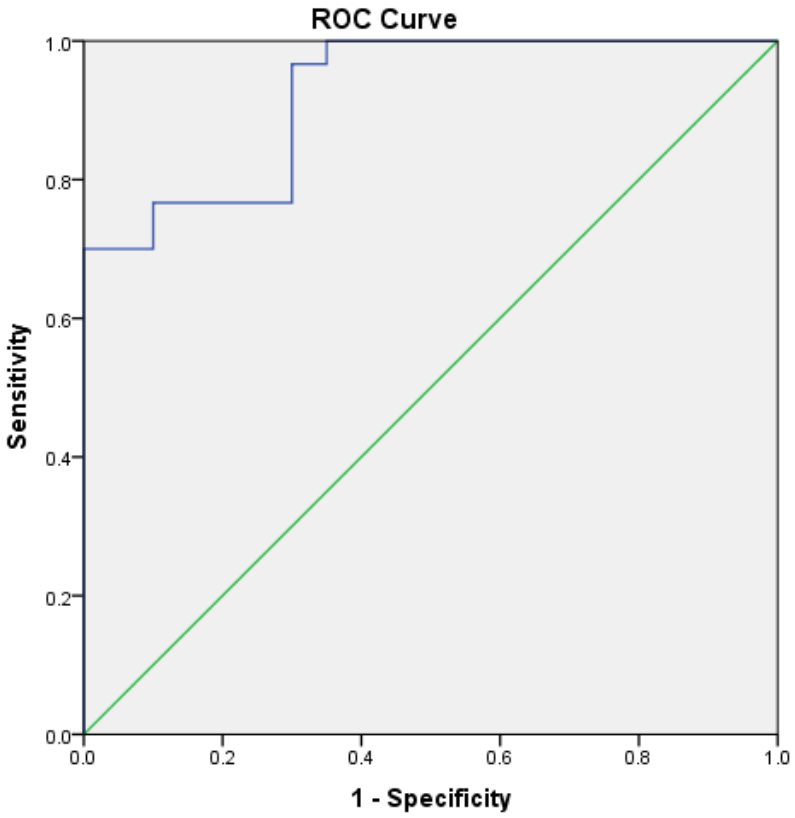

Chart 14: ROC curve for Negative IRC as a predictor for development of Transient DI

2. Permanent Diabetes Insipidus

Out of the total 50 patients that were studied, 2 patients developed Permanent Diabetes Insipidus.

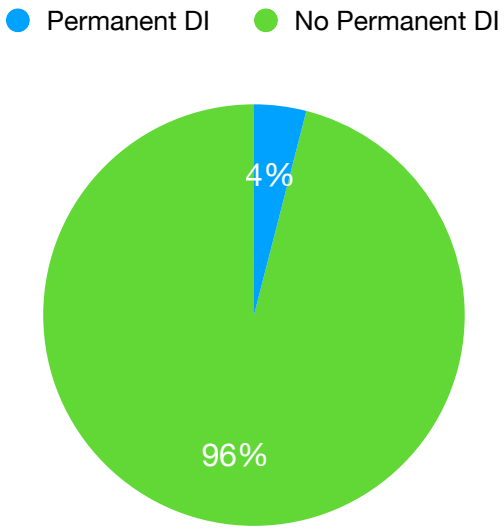

Chart 15: Incidence of Permanent DI

Category	Number of patients	Percentage
Permanent DI	2	4
No Permanent DI	48	96
Total	50	100

Table 14: Incidence of Permanent Diabetes Insipidus

The incidence of permanent Diabetes Insipidus was analysed against the Different Relative Copeptin change trends in the post operative course, including immediate and delayed relative copeptin change(C2-C1 and C3-C1) as well as relative post operative copeptin change.(C3-C2).

Statistical analysis were done to ascertain whether there are any significant results. Analysis revealed no statistically significant results.

	Category	Mean(SD)	t	P	Mean difference	95% confidence interval	
						Lower	Upper
IRC (Percentage difference)	Permanent DI	-15.12(9.7)	-0.49	0.62	-18.88	-95.94	58.16
	No Permanent DI	3.76(53.64)					
DRC (Percentage difference)	Permanent DI	-14.35(1.02)	-0.67	0.50	-18.2	-72.5	36.11
	No Permanent DI	3.85(37.8)					
RPC (Percentage difference)	Permanent DI	1.5(10.4)	-0.36	0.72	-16.72	-110.9	77.49
	No Permanent DI	18.23(65.6)					

Table 15: Table showing Relative Copeptin percentage change trends and its association with the development or non development of Permanent DI (Independent T test)

Area Under the Curve

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
IRC percentage	.333	.087	.428	.163	.504
DRC percentage	.281	.065	.299	.154	.408
RPC percentage	.448	.095	.804	.262	.634

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Table 16: Area under the curve for various Copeptin trends with development of Permanent DI

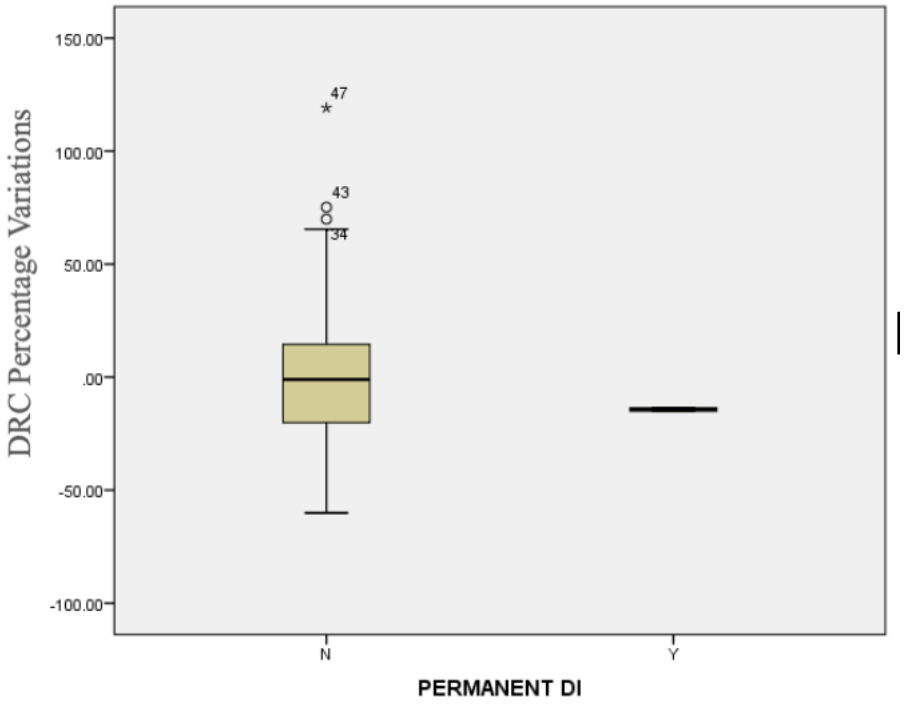

Chart 16: Box and Whisker plot for Copeptin 3-1 as a predictor for Permanent DI

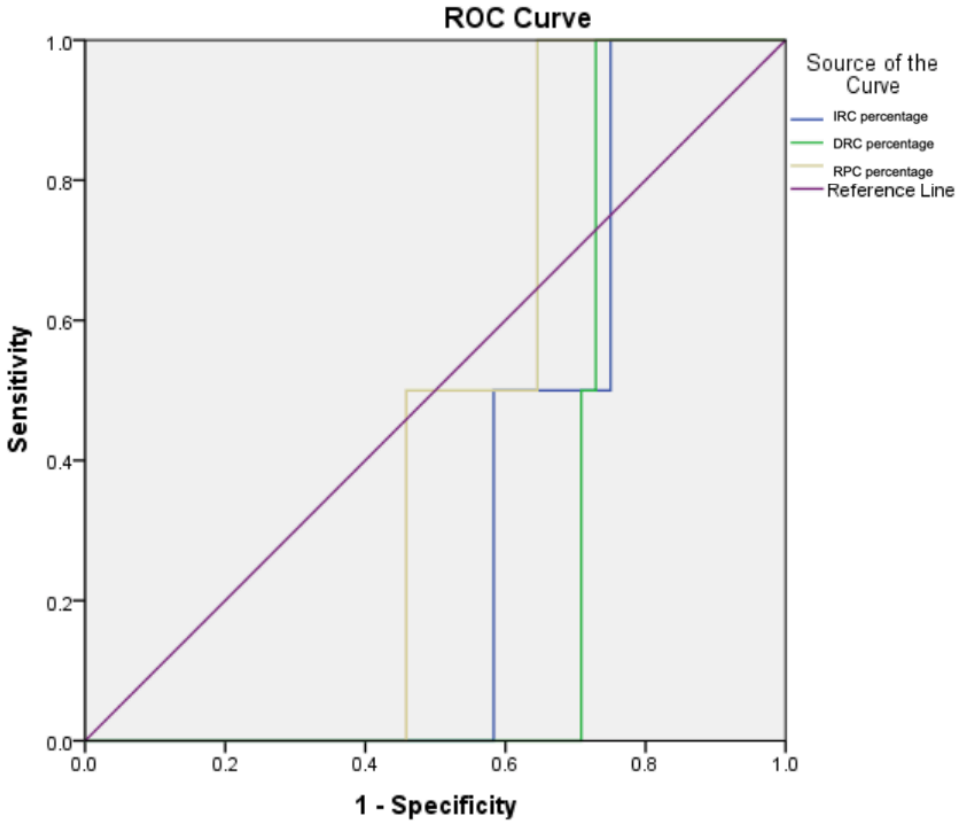

Chart 17: ROC Graph showing relationship of various Copeptin trends against development of Permanent DI

3. Early Hyponatremia

Out of the total 50 patients that were studied, 8 patients developed Early Hyponatremia in the post operative period.

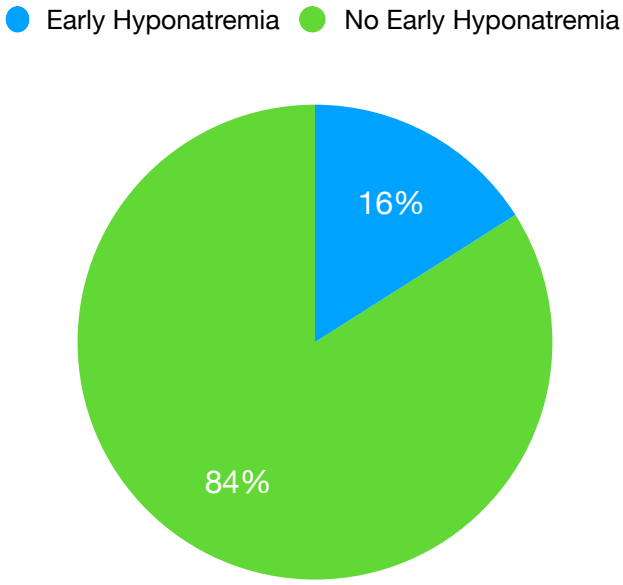

Chart 18: Incidence of Early Hyponatremia

Category	Number of patients	Percentage
Early Hyponatremia	8	16
No Early Hyponatremia	42	84
Total	50	100

Table 17: Incidence of Early Hyponatremia

The Various Copeptin trends were assessed against the Incidence of Early Hyponatremia and processed for any statistical significance. The relative difference in Post operative Copeptin(C2) from Pre operative Copeptin value(C1) was

assessed against the incidence of Early Hyponatremia. It was found that 88% of patients(7/8) who developed Early Hyponatremia had a positive fluctuation of IRC.

	Category	Mean(SD)	t	P	Mean difference	95% confidence interval	
						Lower	Upper
IRC (Percentage difference)	Early Hyponatremia	64.3(94.5)	4.14	<0.01	73.02	37.6	108.5
	No Early Hyponatremia	-8.7(30.3)					
DRC (Percentage difference)	Early Hyponatremia	12.1(32.6)	0.742	0.462	10.7	-18.3	39.7
	No Early Hyponatremia	1.4(38.4)					
RPC (Percentage difference)	Early Hyponatremia	-16.5(32.4)	-1.7	0.102	-40.6	-89.6	8.4
	No Early Hyponatremia	24.1(67.1)					

Table 18: Table showing various relative percentage change in Copeptin trends and its relationship to development and non development of Early Hyponatremia(Independent t test)

It was found that a relative increase in Immediate post operative Copeptin(C2-C1) is positively correlated with a development of Early Hyponatremia. ($P<0.01$)

The area under the curve for Positive IRC as a predictor for development of Early Hyponatremia is 0.842. The cut-off point was arrived at by the Youden Index. The point of maximum sensitivity (75%) and specificity (81%) was at 19.94 percent, beyond other clinical considerations. Therefore a positive fluctuation of

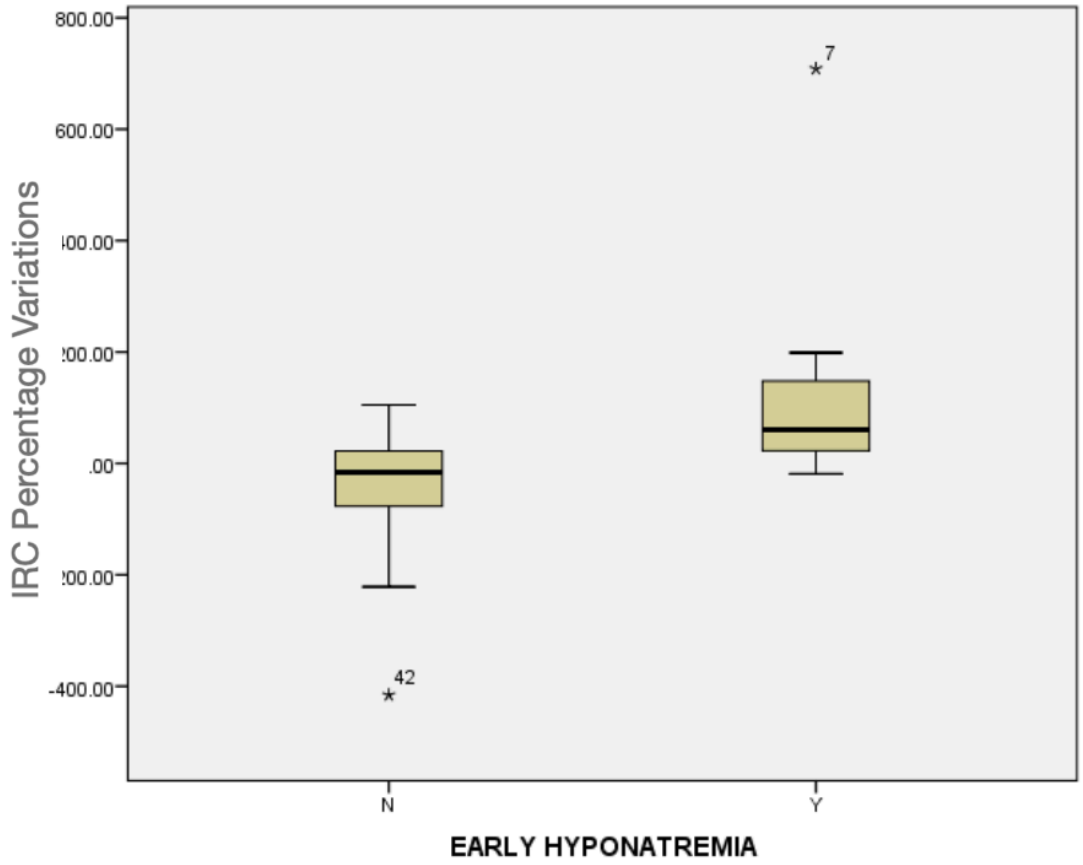

Chart 19: Box and Whisker plot showing the relationship of Relative immediate post operative Copeptin change(IRC) with development of Early Hyponatremia

more than 19.94% can predict the development of Early Hyponatremia with a sensitivity of 75% and specificity of 81%.

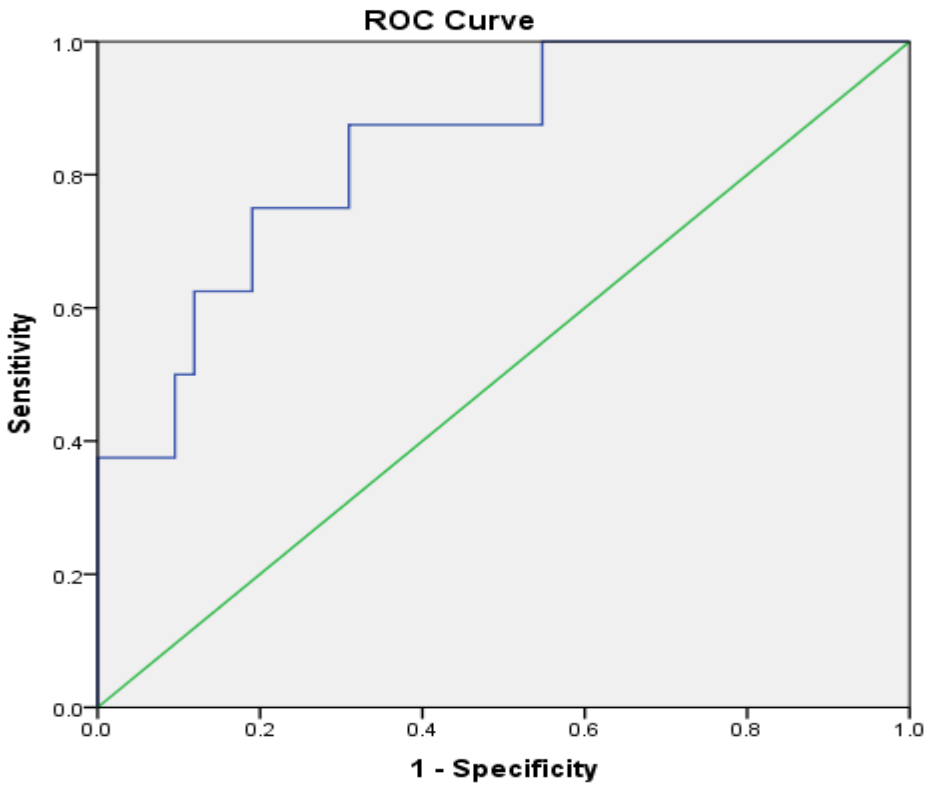

Chart 20: ROC curve for Positive IRC fluctuation with Early Hyponatremia

Area Under the Curve

Test Result Variable(s): Positive IRC fluctuation

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.842	.072	.002	.702	.983

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Table 19: Table showing Area under the curve for Positive IRC fluctuation with Early Hyponatremia

4. Delayed Hyponatremia

Out of the total 50 patients that were studied, 8 patients developed Delayed Hyponatremia in the post operative period.

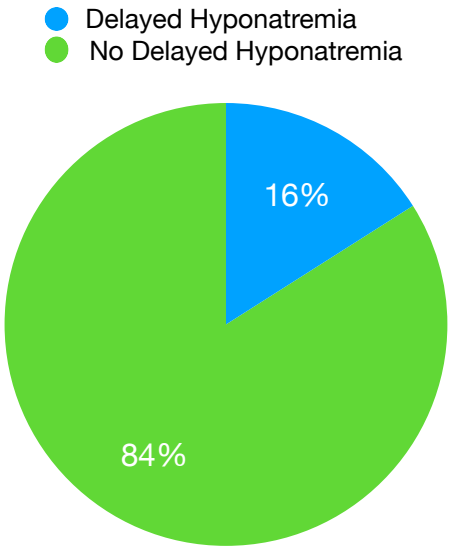

Chart 21: Incidence of Delayed Hyponatremia

Category	Number of patients	Percentage
Delayed Hyponatremia	8	16
No Delayed Hyponatremia	42	84
Total	50	100

Table 20: Incidence of Delayed Hyponatremia

The Various Copeptin trends were assessed against the Incidence of Delayed Hyponatremia and processed for any statistical significance using Independent t test as enumerated in the table. The relative difference in Post operative Copeptin(C3) from Pre operative Copeptin value(C1) was assessed against the incidence of

Delayed Hyponatremia. It was found that 75% of patients(6/8) who developed Delayed Hyponatremia had a positive fluctuation in Delayed Relative Post Operative Change in Copeptin(DRC).

	Category	Mean(SD)	t	P	Mean difference	95% confidence interval	
						Lower	Upper
RPC (Percentage difference)	Delayed Hyponatremia	45.4(62.8)	1.35	0.185	33.14	-16.35	82.65
	No Delayed Hyponatremia	12.2(63.9)					
DRC (Percentage difference)	Delayed Hyponatremia	37.7(43.1)	3.11	0.003	41.24	14.64	67.85
	No Delayed Hyponatremia	-3.5(32.5)					
IRC (Percentage difference)	Delayed Hyponatremia	3.02(30.9)	0.01	0.99	0.026	-41.26	41.31
	No Delayed Hyponatremia	3.00(56.1)					

Table 21: Table showing various relative percentage change in Copeptin trends and its relationship to development and non development of Delayed Hyponatremia(Independent t test)

It was found that a relative increase in DRC is significantly positively correlated with a development of Delayed Hyponatremia. (P=0.003).

The area under the curve for Positive DRC fluctuation as a predictor for development of Delayed Hyponatremia is 0.762. The cut-off point was arrived at by the Youden Index. The point of maximum sensitivity (75%) and specificity (72%) was at 5.46 percent, beyond other clinical considerations. Therefore a positive fluctuation of DRC of more than 5.46% can predict the development of Delayed

Hyponatremia with a sensitivity of 75% and specificity of 72%.

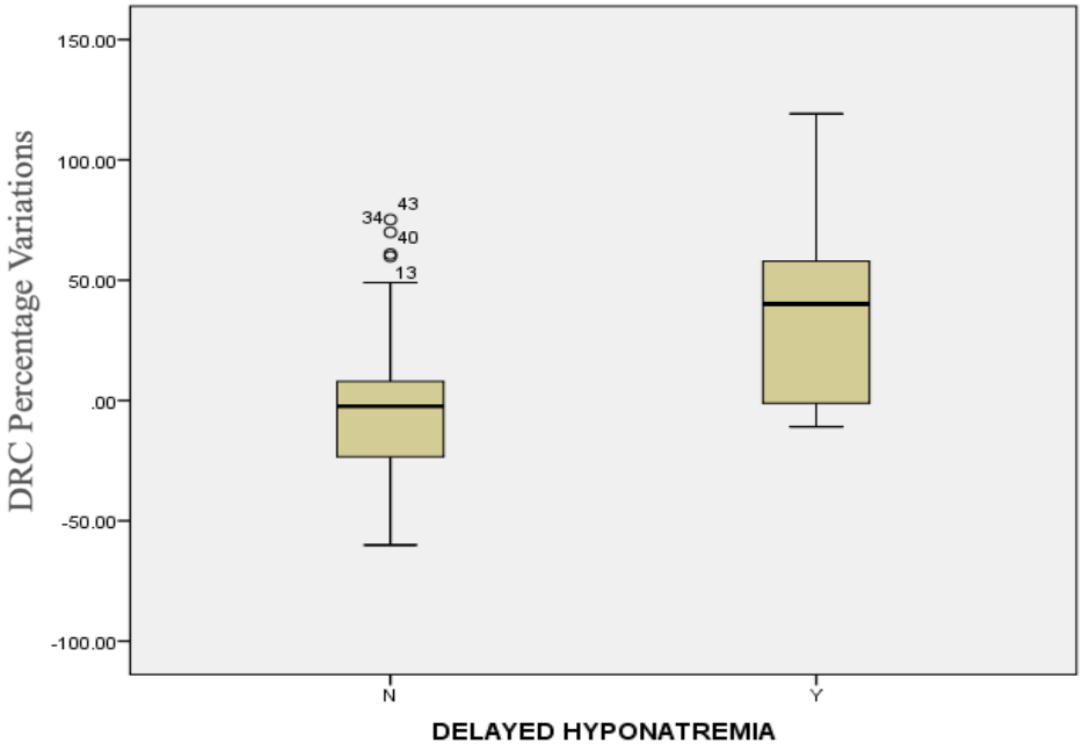

Chart 22: Box and Whisker plot showing the relationship between positive DRC fluctuation and development of Delayed Hyponatremia

Area Under the Curve

Test Result Variable(s): Positive DRC with Delayed Hyponatremia

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.762	.092	.020	.582	.942

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Table 22: Area under the curve for Positive DRC against Delayed Hyponatremia

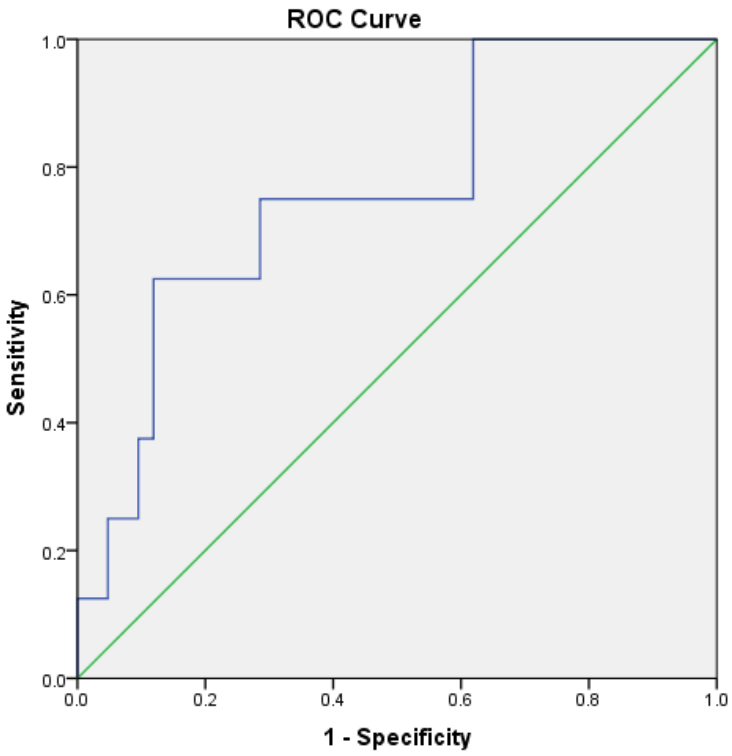

Chart 23: ROC Curve for Positive fluctuation of DRC as a predictor for Delayed Hyponatremia

D. Absolute Copeptin value

Preoperative Copeptin(C1)

Utility of Pre operative Copeptin was assessed as a tool for assessing Posterior Pituitary reserve and whether it has any protective effect from development of Sodium Homeostasis imbalances. Preoperative Copeptin showed a positive correlation with preoperative Sodium. The Statistical analysis of Preoperative Copeptin against the development of Sodium Homeostasis imbalances are enumerated in the table given below. There was no statistically significant associations noted.

	Category	Mean(SD)	t	P	Mean difference	95% confidence interval	
						Lower	Upper
Preoperative Copeptin (Copeptin1) (in pg/ml)	Transient DI	298.9(127.7)	1.47	0.147	47.2	-17.15	111.6
	No Transient DI	251.7(98.3)					
	Permanent DI	217.9(3.25)	-0.674	0.504	-54.9	-218.69	108.87
	No Permanent DI	272.8(114.1)					
	Early Hyponatremia	215.4(69.6)	-1.54	0.130	-65.74	-151.6	20.12
	No Early Hyponatremia	281.1(116.3)					
	Delayed Hyponatremia	255.5(130.6)	-0.413	0.681	-18.03	-105.8	69.76
	No Delayed Hyponatremia	273.5(109.9)					

Table 23: Table showing Preoperative Copeptin(Copeptin 1) and its relationship to development of Sodium Homeostasis Imbalances (Independent t test)

Immediate Post Operative Copeptin(C2)

The Immediate Post Operative Copeptin(C2) was assessed against the development of development of Transient Diabetes Insipidus and Early Hyponatremia. It was found that Copeptin 2(Immediate Post operative Copeptin) was lower in patients who developed Transient Diabetes Insipidus and it was found to be statistically significant with a p=0.020. It was found that Copeptin 2(Immediate Post operative Copeptin) was higher in patients who developed Early Hyponatremia, however results were not statistically significant(p=0.064).

	Category	Mean(SD)	t	P	Mean difference	95% confidence interval	
						Lower	Upper
Immediate Postoperative Copeptin (Copeptin1) (in pg/ml)	Transient DI	203.8(126.1)	-2.41	0.020	-103.7	-190.2	-17.32
	No Transient DI	307.6(162.2)					
	Early Hyponatremia	359.4(267.1)	1.89	0.064	111.13	-6.89	229.1
	No Early Hyponatremia	248.2(122.2)					

Table 24: Table showing Immediate Postoperative Copeptin(Copeptin 2) and its relationship to development to Various Sodium Homeostasis Imbalances(Independent t test)

DISCUSSION

This Prospective Randomised study aimed to find out the utility of Copeptin in predicting the development of Post operative Sodium Homeostasis imbalances. Use of Copeptin after pituitary surgery has been investigated in recent times. This study aims to find out whether Copeptin has a role as predictor in development of these Sodium homeostasis imbalances.

In the present study, we have explored the utility of Post Operative Copeptin trends against the incidence of the outcomes assessed, namely Transient Diabetes Insipidus, Permanent Diabetes Insipidus, Early Hyponatremia and Delayed Hyponatremia. Copeptin trends were assessed against the outcomes. We found significant association of a negative fluctuation in the Immediate Post Operative Relative Change in Copeptin(IRC) to the development of Transient Diabetes Insipidus($p<0.01$). This was in conjunction with the earlier studies in this regard[27,28,29,31]. It was found that a negative fluctuation of more than 5.68% of Immediate Post Operative Relative Change in Copeptin(IRC) can predict the development of Transient Diabetes Insipidus with a sensitivity of 78% and specificity of 90%. There were no statistically significant associations that could be inferred in Permanent Diabetes Insipidus outcome.

The present study also explores the horizon of relationship of various Copeptin trends against Hyponatremia outcomes. We found significant association of a positive fluctuation in Immediate Post Operative Relative Change in

Copeptin(IRC) to the development of Early Hyponatremia($p<0.01$). It was found that a positive fluctuation of more than 19.94% in Immediate Post Operative Relative Change in Copeptin(IRC) can predict the development of Early Hyponatremia with a sensitivity of 75% and specificity of 81%.

The present study found significant association of a positive fluctuation in Delayed Post Operative Relative Change in Copeptin(DRC) to the development of Delayed Hyponatremia($p=0.003$). It was found that a positive fluctuation of more than 5.46% in Delayed Post Operative Relative Change in Copeptin(DRC) can predict the development of Delayed Hyponatremia with a sensitivity of 75% and specificity of 72%.

Utility of Preoperative Copeptin(C1) as a marker for posterior pituitary reserve was assessed and it showed positive correlation with Serum Sodium. However, it had no statistically significant effects on the development or non development of Sodium Homeostasis imbalances.

Previous studies have dealt with the horizon of Copeptin with development of Diabetes Insipidus. Winzeler et al in 2019, studied the role of post operative Copeptin levels in the prediction of diabetes insipidus after pituitary surgery and found out that that a decrease in post operative Copeptin points towards Central diabetes insipidus[27]. Berton et al, in 2020 conducted a prospective study with 66 patients and they found out that a prompt increase of copeptin is expected normally at 1 hour after extubation. The absence of this peak was found to a reliable predictor of post-neurosurgical Central Diabetes Insipidus[28]. Vanasuntorn et al conducted a

prospective study and concluded that in patients undergoing sellar-suprasellar interventions, low postoperative copeptin levels within the first postoperative day predict postoperative DI, whereas high levels exclude it and has proposed that copeptin measurement should be applied in the clinical practice of postoperative care in patients following hypothalamic-pituitary surgery[29]. Hyoo Yung Kim et al in 2021 studied the changes in copeptin levels before and 3 months after transsphenoidal surgery according to the presence of postoperative central diabetes insipidus. They concluded that 3 months postoperative copeptin levels significantly decreased from preoperative levels in the transient CDI group as well as the permanent CDI group[31].

Test	Change	Outcome	P Value
Immediate Postoperative Relative Change in Copeptin (IRC)	Relative increase	Predictor for Early Hyponatremia	<0.01
	Relative decrease	Predictor for Transient Diabetes Insipidus	<0.01
Delayed Post Operative Relative Change in Copeptin (DRC)	Relative increase	Predictor for Delayed Hyponatremia	0.003

Table 25: Table briefing Post operative Copeptin trends with development of Sodium Homeostasis imbalances

The important results from the study are shown in the table above. There have been a number studies that concurs with the present study on the prediction of Central Diabetes Insipidus[27,28,29,31]. However, there is a dearth of prospective studies

Test	Percentage change	Outcome	Sensitivity	Specificity
Immediate Postoperative Relative Change in Copeptin (IRC)	19.94 % increase	Early Hyponatremia	75%	81%
	5.68 % decrease	Transient Diabetes Insipidus	78%	90%
Delayed Post Operative Relative Change in Copeptin (DRC)	5.46 % increase	Delayed Hyponatremia	75%	72%

Table 26: Table showing sensitivity and specificity of the various Copeptin trends as predictor of development of Sodium Homeostasis imbalances

that have explored the utility of Copeptin in hyponatremia following endoscopic transsphenoidal pituitary adenoma surgeries. Our study concludes that the Post Operative Copeptin trend with respect to Preoperative Copeptin levels offers predicting capacity for diagnosis of Post Operative Transient Diabetes Insipidus, Early Hyponatremia and Delayed Hyponatremia. This will go a long way in early diagnosis of post operative sodium fluctuations and the morbidities associated with it.

Limitations

The present study, however is not without its limitations. The sample size is 50. The present conclusion therefore entails a larger study before we can extrapolate our results into clinical practice. The lack of a Control group is another shortcoming of the present study. The Copeptin assay was performed using Genetix Biotech™ Human Copeptin CPP ELISA PG-1580H kit which uses the Competitive ELISA

principle. A recent study done by Sailer et al[50], in 2021, has shown that the results with Copeptin ELISA assay correlates poorly with those from Immunoflourescent and Immunoluminometric Copeptin assays and shows a poor diagnostic accuracy. However the conclusions in this study is primarily based on relative percentage change values rather than absolute values of copeptin.

CONCLUSION

Post Operative Copeptin trend with respect to Preoperative Copeptin levels offers predicting capacity for diagnosis of Post Operative Transient Diabetes Insipidus, Early Hyponatremia and Delayed Hyponatremia.

- A Relative decrease in Immediate Post Operative Copeptin predicts development of Transient Diabetes insipidus.
- A relative increase in Immediate Post Operative Copeptin predicts the development of Early Hyponatremia.
- A Relative increase in the Delayed post operative copeptin predicts the development of Delayed Hyponatremia.

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ANNEXURES

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-21)

SCT/IEC/1784/DECEMBER/ 2021 24.01.2022

Dr. Anand Binu
Senior Resident
Department of Neurosurgery
SCTIMST, Thiruvananthapuram

Dear Dr. Anand Binu,

The Institutional Ethics Committee held on 18th December, 2021, reviewed and discussed your application to conduct the study titled "**ROLE OF COPEPTIN IN PREDICTING SODIUM HOMEOSTASIS IMBALANCES IN PATIENTS UNDERGOING SURGERY FOR PITUITARY ADENOMA**" (IEC/1784).

The following members of the Ethics Committee were present at the meeting held on 18th December, 2021

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Prof. C.C. Kartha	MBBS,MD	Male	Basic Medical Scientist (Chairman)	No
2.	Dr. Kala Kesavan P	MBBS,MD	Female	Basic Medical Scientist	No
3.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
4.	Dr. Pradeep S	MBBS, MD	Male	Basic Medical Scientist	No
5.	Dr. Rejnish Kumar	MBBS,MD ,DNB	Male	Clinician	No
6.	Adv. Priya Kaimal	LLM, MBL	Female	Legal Expert	No
7.	Dr. Narayanan Namboodiri. K K	MBBS,MD,DM	Male	Clinician	Yes
8.	Dr. Manikandan.S	MBBS,MD,PDCC	Male	Clinician	Yes
9.	Dr. Biju Soman	MBBS,MD, DPH, MSc, DLSHTM	Male	Basic Medical Scientist	Yes
10.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

The following documents were reviewed:

Original submission

1. *Checklist Form*
2. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 20.07.2021*
3. *TAC Approval Letter*
4. *Covering letter addressed to the Chairperson, TAC (Clinical Studies), SCTIMST dated 23.10.2021*
5. *Covering letter addressed to the Chairperson, TAC (Clinical Studies), SCTIMST dated 23.10.2021 from Dr. Prakash Nair, Associate Professor, Department of Neurosurgey, SCTIMST*
6. *Response to TAC's comments*
7. *TAC Application Form*
8. *Dean's signature form*
9. *IEC Application Form*
10. *Patient Information Sheet in English and Malayalam*
11. *Consent Form in English and Malayalam*
12. *Project Proposal*
13. *CV of PI and Co-PIs*
14. *Declaration Form*
15. *Proforma*

Revised submission

1. *Checklist Form*
2. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 13.01.2022*
3. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 20.07.2021*
4. *TAC Approval Letter*
5. *Covering letter addressed to the Chairperson, TAC (Clinical Studies), SCTIMST dated 23.10.2021*
6. *Covering letter addressed to the Chairperson, TAC (Clinical Studies), SCTIMST dated 23.10.2021 from Dr. Prakash Nair, Associate Professor, Department of Neurosurgey, SCTIMST*
7. *Response to TAC's comments*
8. *TAC Application Form*
9. *Dean's signature form*
10. *IEC Application Form*
11. *Patient Information Sheet in English and Malayalam*
12. *Consent Form in English and Malayalam*
13. *Project Proposal*
14. *CV of PI and Co-PIs*
15. *Declaration Form*
16. *Proforma*

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:
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.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

G. Srinivas
Member Secretary, IEC

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST
THIRUVANANTHAPURAM

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST, THIRUVANANTHAPURAM

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ROLE OF COPEPTIN IN PREDICTING SODIUM HOMEOSTASIS IMBAL- ANCES IN PATIENTS UNDERGOING SURGERY FOR PITUITARY ADE- NOMA Introduction Pituitary adenoma is one of the most common brain tumours encountered in neurosurgical practice. The estimated prevalence of Pituitary adenoma among gen- eral population is 17%14,15. The treatment and outcome of Pituitary adenoma has im- proved dramatically over the years.

This can mainly be attributed to the advent of better understanding of the skullbase anatomy, improved visualisation as well as the development of endoscopic techniques. However, the post operative electrolyte im- balances, especially the fluctuating trends of sodium post pituitary surgery remain a problem in common neurosurgical practice. Neurosurgeons are often left chasing troughs and peaks of sodium, with continous intensive monitoring of fluid balance of these patients.

The presence of a predictor for the development of these Sodium ho- meostasis imbalances can go a long way in providing assistance in management of these imbalances. The most important electrolyte imbalances encountered in pituitary adenoma surgery are hypernatremia and hyponatremia. Post operative hypernatremia second- ary to diabetes insipidus in endoscopic transsphenoidal surgery(ETS) is common and ranges from 1.6% to 46% according to literature1,2,3.

The main reason postulated for the development of Diabetes insipidus include surgical stress, manipulation of the neurohypophysis, or both4,5. Hyponatremia after Endoscopic pituitary surgery usually results from hypocortisolemia or a syndrome of inappropriate secretion of ADH (SI- ADH) and very rarely due to Cerebral salt wasting. These conditions are related to altered free-water homeostasis, which caused the changes in

PROFORMA

General Instructions

Please fill in all the questions
Write Yes/No wherever applicable
if no response applies, please write NA
If the response is not known please write UK
If additional info is available please elaborate

A.GENERAL INFORMATION

1 Subject code
2 Age
3 Sex

4 Date of admission
5 Date of discharge/death

B.CLINICAL DETAILS

Mode of Presentation [Visual/apoplexy/headache/hypo-function/hyper-function / incidental/others]

For patients presenting with Positive Symptoms (Headache/Seizures/Apoplexy)

Onset of symptom:
Duration of Symptom :
LOC/Altered sensorium & duration :

Seizures :
Cranial nerve defict/Limb weakness (if yes specify): Any other symptoms :
Any specific treatment given :
Improvement in above symptom

For patients presenting with Mass effect Visual disturbances (if yes specify) Acuity Visual field

Extra ocular muscle palsies (if yes specify) Other Cranial nerve deficit (if yes, specify) Motor weakness (if yes, specify)

Speech disturbance (if yes specify) Seizures

Endocrinopathy
Clinical features of Hyper/hypopituitarism:

Thyroid/cortisol/ adrenal/gonadal /Prolactin/growth hormone:(specify details)
Secondary sexual characters:
Cardiovascular complaints:
Menstrual complaints:

Examination findings
On admission
GCS

Vitals (BP/PR)

Vision (VA/VF)

Extra ocular movements
Cranial nerve palsy (if yes, specify) Weakness (if yes, specify)

General examination:
loss of secondary sexual characters Height:
weight:
neuro-cutaneous markers:

INVESTIGATIONS
Radiology:

1.CT scan

(Size/site/Extent/Calcification/Vascular relation/bony anatomy)

2.MRI
(Mean Size/Mean height/site/Extent of calcification/Vascular relation/consistency/ morphology /contrast enhancement)

Other MRI sequences (details and findings if performed)

3.DSA (relevant finding if performed)
4.Echocardiography findings (relevant findings if performed)

Biochemical:

For Endocrine function(laboratory assessment)

1.Thyroid function test (TSH, fT3, fT4)
2.Growth hormone, Insulin like Growth factor-1 (IGF-l)
3.ACTH/Sr. Cortisol (8am)
4. S. Prolactin (in dilution)
5.Gonadal hormones (FSH, LH)
6.Testosterone

S. Copeptin assay(preoperative)

Surgery

1.Date of surgery

2.Operative time/blood loss.

3.Type of approach(endonasal-transsphenoidal/Transethmoidal/transmaxillary)

4.Extent of resection (surgeon's intraoperative impression) (gross total/subtotal/ biopsy) 5.Intra op Events:(CSF leak/carotid injury/Cranial Nerve injury)

Post operative complications:

1.CSF rhinorrhoea (if yes, specify)
2.Meningitis

3.Diplopia :

Follow up:

Clinical:

Clinical follow up:

1) Postoperative:

Serum Electrolytes

POD	Pre operative	0						1					
Na													

POD	2		3		4	5	7	9	11	13	15
Na											

CVP

POD	0		1	
CVP				

Input/Output

POD	0	1	2	3
Input				
Output				

Serum osmolality

POD	0		1	
Serum osmolality				

Copeptin level

POD	PREOP	Post Extubation	POD-4
Copeptin			

Day 1 : CT scan with contrast to assess extent of resection

2) Day 1: S Cortisol 8 am
Day 4: S Cortisol 8am

3) 3weeks post operative follow up:
3.1) Hormone estimation

S cortisol (8am), Thyroid stimulating hormone (TSH) , S Prolactin

3.2)Endocrinological
need for suppressive medication
Hormonal remission of Functioning tumors

3.2) Visual examination
Visual acuity: Using the Snellen's chart with best uncorrected and corrected vision
Perimeter: Using Humphrey's Field Analyzer to assess the visual field chart,
Fundoscopy: For assessment of fundus

3.3) any other complications noted on examination:

Patient Information Sheet

TITLE OF THE STUDY:

Role of Copeptin in predicting Sodium homeostasis imbalances in Patients undergoing surgery for Pituitary adenoma.

Brief of the Study:

You are being requested to participate in a study to evaluate if there is any benefit of measuring Copeptin level in blood to predict electrolyte abnormalities post pituitary adenoma surgery. There will be no deviation from the planned surgical resection as decided by pre-operative MRI scans due to this study. The treatment protocols for post operative care will also be followed.

We hope to include 50 patients undergoing pituitary adenoma surgery in this study. At present, there is no marker to identify electrolyte abnormalities after pituitary adenoma surgery. Hence, the need for this study was felt. Your participation in this study would contribute immensely to improving future care of patients with Pituitary adenoma.

If you take part what will you have to do?

The study will require your consent after clarifying all related queries.All treatment that you have and will be receiving shall be as per routine protocols of the institution and it will not be changed during this study. The participation in the study is purely voluntary and there will be no difference in your treatment or follow up if you decide not to cooperate for the study.

Will you have to pay for the investigations?

No. You won't have to pay extra for the investigations.

What happens if you are detected to have any fresh problems during the study?

No additional risks are anticipated due to the study. Any problems during or after surgery would be managed appropriately as per the current treatment standards.

Will your personal details be kept confidential?

The results of this study may be published in a medical journal for advancement of medical sciences and surgical standards of care.You will not be identified by name in any publication or presentation of results.

However, your medical notes may be reviewed by people associated with the study, without your additional permission.

If you have any further questions, please ask

Dr.Prakash Nair(Tel 8592833489,drprakashnair@gmail.com)

or Dr.Anand Binu (Tel: 9895007445, anandbinumangal@gmail.com)

For any clarifications regarding the study's ethics clearance you may contact the Member Secretary of the SCTIMST-IEC.

The phone number is: 234(O) 0471- 2524234 and the email id is

iec.mem.sec@sctimst.ac.in

CONSENT FORM

Title of the study:

Role of Copeptin in predicting Sodium homeostasis imbalances in Patients undergoing surgery for Pituitary adenoma.

Participant's name: Age (in years): I_____, son/ daughter/husband/wife/ ————————————————————of _____ declare that (Please tick boxes)

• I have read the above information provided to me regarding the study:**[ ]**

• I have clarified any doubts that I had. [ ]

• I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights [ ]

• I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the study. I agree to this access [ ]

• I understand that my identity will not be revealed in any information released to third parties or published [ ]

• I voluntarily agree to take part in this study [ ]

• I have been provided with the contact numbers of the principle investigator, in case I want to know more about the study and participants rights [ ].

• I received a copy of this signed consent form [ ]

Name: Name of witness:

Date: Relation to participant:

Person Obtaining Consent

Signature: Signature:

I attest that the requirements for informed consent for the medical research project described in this form have been satisfied. I have discussed the research project with the participant and explained to him or her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked were answered.

Name : Signature :

Date :

Place : SCTIMST, Thiruvananthapuram

രോഗിയുടെ വിവര ഷീറ്റ്

പഠനത്തിന്റെ ശീർഷകം:

പിറ്റ്യൂട്ടറി അഡിനോമയ്ക്ക് ശസ്ത്രക്രിയയ്ക്ക് വിധേയരാകുന്ന രോഗികളിൽ സോഡിയം ഹോമിയോസ്റ്റാസിസ് അസന്തുലിതാവസ്ഥ പ്രവചിക്കുന്നതിൽ കോപെപ്റ്റിന്റെ പങ്ക്.

പഠനത്തിന്റെ സംക്ഷിപ്തം:

പിറ്റ്യൂട്ടറി അഡിനോമ ശസ്ത്രക്രിയയ്ക്ക് ശേഷമുള്ള ഇലക്ട്രോലൈറ്റ് തകരാറുകൾ പ്രവചിക്കാൻ രക്തത്തിലെ കോപെപ്റ്റിൻ അളവ് അളക്കുന്നതിലൂടെ എന്തെങ്കിലും ഗുണം ഉണ്ടോ എന്ന് വിലയിരുത്തുന്നതിനുള്ള ഒരു പഠനത്തിൽ പങ്കെടുക്കാൻ നിങ്ങളോട് അഭ്യർത്ഥിക്കുന്നു. ഈ പഠനം കാരണം പ്രീ-ഓപ്പറേറ്റീവ് എംആർഐ സ്കാനുകൾ തീരുമാനിച്ച ആസൂത്രിത ശസ്ത്രക്രിയാ വിഭജനത്തിൽ നിന്ന് വ്യതിചലനമുണ്ടാകില്ല. പോസ്റ്റ് ഓപ്പറേറ്റീവ് കെയറിനുള്ള ചികിത്സാ പ്രോട്ടോക്കോളുകളും പിന്തുടരും. പിറ്റ്യൂട്ടറി അഡിനോമ ശസ്ത്രക്രിയയ്ക്ക് വിധേയരായ 50 രോഗികളെ ഈ പഠനത്തിൽ ഉൾപ്പെടുത്തുമെന്ന് ഞങ്ങൾ പ്രതീക്ഷിക്കുന്നു. നിലവിൽ, പിറ്റ്യൂട്ടറി അഡിനോമ ശസ്ത്രക്രിയയ്ക്ക് ശേഷം ഇലക്ട്രോലൈറ്റിന്റെ തകരാറുകൾ തിരിച്ചറിയാൻ മാർക്കർ ഇല്ല. അതിനാൽ, ഈ പഠനത്തിന്റെ ആവശ്യകത അനുഭവപ്പെട്ടു. ഈ പഠനത്തിലെ നിങ്ങളുടെ പങ്കാളിത്തം പിറ്റ്യൂട്ടറി അഡിനോമ രോഗികളുടെ ഭാവി പരിചരണം മെച്ചപ്പെടുത്തുന്നതിന് വളരെയധികം സഹായിക്കും.

നിങ്ങൾ പങ്കെടുക്കുകയാണെങ്കിൽ നിങ്ങൾ എന്തുചെയ്യും?

ബന്ധപ്പെട്ട എല്ലാ ചോദ്യങ്ങളും വ്യക്തമാക്കിയ ശേഷം പഠനത്തിന് നിങ്ങളുടെ സമ്മതം ആവശ്യമായി വരും.നിങ്ങൾക്കുള്ളതും സ്വീകരിക്കുന്നതുമായ എല്ലാ ചികിത്സകളും സ്ഥാപനത്തിന്റെ പതിവ് പ്രോട്ടോക്കോളുകൾ അനുസരിച്ചായിരിക്കും, ഈ പഠന സമയത്ത് ഇത് മാറ്റില്ല. പഠനത്തിലെ പങ്കാളിത്തം പൂർണ്ണമായും സ്വമേധയാ ഉള്ളതാണ്, പഠനത്തിന് സഹകരിക്കേണ്ടെന്ന് നിങ്ങൾ തീരുമാനിക്കുകയാണെങ്കിൽ നിങ്ങളുടെ ചികിത്സയിൽ വ്യത്യാസമില്ല അല്ലെങ്കിൽ ഫോളോ അപ്പ് ഉണ്ടാകില്ല.

പഠനസമയത്ത് എന്തെങ്കിലും പുതിയ പ്രശ്നങ്ങളുണ്ടെന്ന് കണ്ടെത്തിയാൽ എന്ത് സംഭവിക്കും?

പഠനം കാരണം അധിക അപകടസാധ്യതകളൊന്നും പ്രതീക്ഷിക്കുന്നില്ല. ശസ്ത്രക്രിയയ്ക്കിടയിലോ അതിനുശേഷമോ ഉള്ള ഏതെങ്കിലും പ്രശ്നങ്ങൾ നിലവിലെ ചികിത്സാ മാനദണ്ഡങ്ങൾക്കനുസൃതമായി ഉചിതമായി കൈകാര്യം ചെയ്യും.

നിങ്ങളുടെ സ്വകാര്യ വിശദാംശങ്ങൾ രഹസ്യമായി സൂക്ഷിക്കുമോ?

ഈ പഠനത്തിന്റെ ഫലങ്ങൾ മെഡിക്കൽ സയൻസുകളുടെ പുരോഗതിക്കും പരിചരണത്തിന്റെ ശസ്ത്രക്രിയാ മാനദണ്ഡങ്ങൾക്കുമായി ഒരു മെഡിക്കൽ ജേണലിൽ പ്രസിദ്ധീകരിക്കാം. ഏതെങ്കിലും പ്രസിദ്ധീകരണത്തിലോ ഫലങ്ങളുടെ അവതരണത്തിലോനിങ്ങളെ പേര് ഉപയോഗിച്ച് തിരിച്ചറിയാൻ കഴിയില്ല. എന്നിരുന്നാലും, നിങ്ങളുടെ അധിക അനുമതിയില്ലാതെ പഠനവുമായി ബന്ധപ്പെട്ട ആളുകൾ നിങ്ങളുടെ മെഡിക്കൽ കുറിപ്പുകൾ അവലോകനം ചെയ്തേക്കാം.

നിങ്ങൾക്ക് കൂടുതൽ എന്തെങ്കിലും ചോദ്യങ്ങളുണ്ടെങ്കിൽ, ദയവായി ചോദിക്കുക ഡോ.പ്രകാശ് നായർ (ഫോൺ 8592833489, drprakashnair @ gmail.com) അല്ലെങ്കിൽ ഡോ.അനന്ദ് ബിനു (ഫോൺ: 9895007445, anandbinumangal@gmail.com)

പഠനത്തിന്റെ എത്തിക്സ് ക്ലിയറൻസുമായി ബന്ധപ്പെട്ട ഏത് വിശദീകരണത്തിനും നിങ്ങൾക്ക് SCTIMST-IEC അംഗ സെക്രട്ടറിയുമായി ബന്ധപ്പെടാം.
ഫോൺ നമ്പർ: 234 (ഒ) 0471- 2524234, ഇമെയിൽ ഐഡി iec.mem.sec@sctimst.ac.in

സമ്മതപത്രം

പഠനത്തിന്റെ ശീർഷകം:

പിറ്റ്യൂട്ടറി അഡിനോമയ്ക്ക് ശസ്ത്രക്രിയയ്ക്ക് വിധേയരാകുന്ന രോഗികളിൽ സോഡിയം ഹോമിയോസ്റ്റാസിസ് അസന്തുലിതാവസ്ഥ പ്രവചിക്കുന്നതിൽ കോപെപ്റ്റിന്റെ പങ്ക്.

പങ്കെടുക്കുന്നയാളുടെ പേര്:

പ്രായം (വർഷങ്ങളിൽ):

ഞാൻ_____,
_____ ന്റെ മകൻ / മകൾ / ഭർത്താവ് /
ഭാര്യ / ———————————————— പ്രഖ്യാപിക്കുക (ദയവായി

ബോക്സുകളിൽ ടിക്ക് ചെയ്യുക)

ഈ പഠനത്തിൽ സംബന്ധിച്ച് എനിക്ക് നൽകിയ മുകളിൽ പറഞ്ഞ വിവരങ്ങൾ ഞാൻ വായിച്ചിട്ടുണ്ട്: []

എനിക്ക് ഉണ്ടായിരുന്ന സംശയങ്ങളെല്ലാം ഞാൻ വ്യക്തമാക്കിയിട്ടുണ്ട്. []

ഈ പഠനത്തിലെ എന്റെ പങ്കാളിത്തം പൂർണ്ണമായും സ്വമേധയാ ഉള്ളതാണെന്നുംഎന്റെ പതിവ് ചികിത്സയെയോ നിയമപരമായ അവകാശങ്ങളെയോ ബാധിക്കാതെ ഏത് സമയത്തും പങ്കെടുക്കുന്നത് തുടരാനുള്ള അനുമതി പിൻവലിക്കാൻ എനിക്ക് സ്വാതന്ത്ര്യമുണ്ടെന്നും ഞാൻ മനസ്സിലാക്കുന്നു []

ഞാൻ പിൻവലിച്ചാലും എന്റെ ആരോഗ്യ രേഖകൾ നോക്കാൻ സ്റ്റഡി സ്റ്റാഫുകൾക്കും സ്ഥാപന നൈതിക സമിതി അംഗങ്ങൾക്കും എന്റെ അനുമതി ആവശ്യമില്ലെന്ന് ഞാൻ മനസ്സിലാക്കുന്നു
പഠനത്തിൽ നിന്ന്. ഈ ആക്സസ് ഞാൻ അംഗീകരിക്കുന്നു []

മൂന്നാം കക്ഷികൾക്ക് വിട്ടുകൊടുത്തതോ പ്രസിദ്ധീകരിച്ചതോ ആയ വിവരങ്ങളിൽഎന്റെ

ഐഡന്റിറ്റി വെളിപ്പെടുത്തില്ലെന്ന് ഞാൻ മനസ്സിലാക്കുന്നു [

ഈ പഠനത്തിൽ പങ്കെടുക്കാൻ ഞാൻ സ്വമേധയാ സമ്മതിക്കുന്നു []

പഠനത്തെയും പങ്കാളികളുടെ അവകാശങ്ങളെയും കുറിച്ച് കൂടുതലറിയാൻ ഞാൻ ആഗ്രഹിക്കുന്നുവെങ്കിൽ, തത്ത്വ അന്വേഷകന്റെ കോൺടാക്റ്റ് നമ്പറുകൾ എനിക്ക് നൽകിയിട്ടുണ്ട് [].

ഒപ്പിട്ട ഈ സമ്മത ഫോമിന്റെ ഒരു പകർപ്പ് എനിക്ക് ലഭിച്ചു []

പേര്:

സാക്ഷിയുടെ പേര്:
തീയതി:
പങ്കാളിയുമായുള്ള ബന്ധം:
സമ്മതം നേടുന്ന വ്യക്തി
കയ്യൊപ്പ്:
കയ്യൊപ്പ്:

ഈ ഫോമിൽ വിവരിച്ചിരിക്കുന്ന മെഡിക്കൽ റിസർച്ച് പ്രോജക്റ്റിനായി വിവരമറിഞ്ഞുള്ള സമ്മതത്തിന്റെ ആവശ്യകതകൾ തൃപ്തികരമാണെന്ന് ഞാൻ സാക്ഷ്യപ്പെടുത്തുന്നു. ഗവേഷണ പ്രോജക്റ്റിനെക്കുറിച്ച് ഞാൻ പങ്കാളിയുമായി ചർച്ച ചെയ്യുകയും ഈ വിവരമറിഞ്ഞുള്ള സമ്മതപത്രത്തിൽ അടങ്ങിയിരിക്കുന്ന എല്ലാ വിവരങ്ങളും, അവയ്ക്ക് അല്ലെങ്കിൽ അവളോട് വിശദമായി വിശദീകരിക്കുകയും ചെയ്തിട്ടുണ്ട്, ഇതിൽ എന്തെങ്കിലും അപകടസാധ്യതകളും പ്രതികൂല പ്രതികരണങ്ങളും ഉൾപ്പെടുന്നു. ചോദ്യങ്ങൾ ചോദിക്കാൻ ഞാൻ പങ്കാളിയെ പ്രോത്സാഹിപ്പിച്ചുവെന്നും ചോദിച്ച എല്ലാ ചോദ്യങ്ങൾക്കും ഉത്തരം ലഭിച്ചുവെന്നും ഞാൻ കൂടുതൽ സാക്ഷ്യപ്പെടുത്തുന്നു.

പേര്:
കയ്യൊപ്പ് :

തീയതി:
സ്ഥലം: എസ്സിടിഎംഎസ്ടി, തിരുവനന്തപുരം