Requirement of perioperative steroid supplementation in patients undergoing transsphenoidal surgery for pituitary adenomas- A Clinical trial

Dissertation submitted to the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for the M.Ch. Neurosurgery part II Examination, August 2014

CERTIFICATE

This is to certify that the dissertation entitled ─ **Requirement of perioperative steroid supplementation in patients undergoing transsphenoidal surgery for pituitary adenomas- A Clinical trial** is the bonafide original work of Dr. Ramya L, Christian Medical College, Vellore submitted in partial fulfillment of the rules and regulations, for Branch-II M.Ch. Neurosurgery, Part-II examination of the Tamil Nadu Dr. M.G.R. Medical University to be held in August 2014 under my guidance and supervision during the academic year 2009-2014

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Sub: **FLUID Research grant project NEW PROPOSAL:**
To assess requirement of perioperative steroid supplementation in patients undergoing transsphenoidal pituitary surgery
Dr. Ramya L, PG Registrar, Neurosurgery, Dr. Ari G Chacko, Dr. Mathew Joseph, Neurological Sciences, Dr. Simon Rajaratnam, Endocrinology.

Ref: IRB Min. No. 7558 dated 09.08.2011

Dear Dr. Ramya L,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "To assess requirement of perioperative steroid supplementation in patients undergoing transsphenoidal pituitary surgery " on August 9, 2011.

The Committees reviewed the following documents:

1.   Format for application to IRB submission
2.   Patient Information Sheet and Informed Consent Form (English, Tamil and Hindi)
3.   Cvs of Drs. Ari G Chacko, Simon Rajaratnam, Mathew Joseph
4.   A CD containing document 1 – 3

The following Institutional Review Board (Ethics Committee) members were present at the meeting held on August 9, 2011 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore - 632002.

INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE
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Mr. Harikrishnan	BL	Lawyer	Non-CMC
Mrs. S. Pattabiraman	BSc, DSSA	Social Worker, Vellore	Non-CMC
Mrs. Ellen Ebenezer Benjamin (on behalf of Dr. Jayarani Premkumar)	MSc (Nursing), PhD	Nursing Superintendent, CMC.	
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M.Phil, BL.	Legal Advisor, CMC.	
Dr. Jayaprakash Muliyil	BSC, MBBS, MD, MPH, DrPH(Epid), DMHC	Academic Officer, CMC	

We approve the project to be conducted as presented.

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

A sum of ₹ 56,320/- (Rupees Fifty six thousand three hundred twenty only) is sanctioned for 2 years.

Yours sincerely,

Dr. George Mathew
Principal & Chairman (Research Committee)
Institutional Review Board

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ABSTRACT

Object:

Patients with an intact hypothalamic pituitary adrenal (HPA) axis produce an intraoperative surge of serum cortisol during transsphenoidal pituitary surgery. This surgery is considered appropriate that no further doses of steroids are required during and after surgery. In this prospective study we tested the feasibility of withholding steroids during the perioperative period for patients undergoing transsphenoidal surgery for pituitary adenomas with a normal preoperative hypothalamic pituitary axis (HPA axis).

Methods:

A total of 105 patients undergoing transsphenoidal surgery for pituitary adenomas were assessed preoperatively. Patients with an 8AM serum cortisol >16 mcg/dl were considered to have a normal HPA axis and for those with a cortisol<16 mcg/dl, a Synacthen test was done and if the cortisol levels rose to >20mcg/dl, they were considered to have a normal HPA axis. Group 1 (61) patients who had a normal HPA axis underwent surgery without perioperative steroid cover. Group 2 (44) patients received perioperative steroids because of hypocortisolism. Group 1 patients were found to have smaller tumors as compared to Group 2 ($p<0.001$). The 2 groups were similar with regard to the age, extent of excision and the incidence of intraoperative CSF leak. Group 1 patients who did not receive perioperative steroids were monitored postoperatively for hypocortisolism and results tabulated.

Results:

In Group 1 the mean 8 AM cortisol levels before surgery and on the postoperative days 1, 2 & 3 were 14.3, 21.6, 14.5 and 13.1 mcg/dl respectively (fig 1). The surge in cortisol value on Day 1 was significant (p=0.04). In Group 1, 19 out of 61 patients required steroid supplementation. Eleven of them were symptomatic and 2 patients had cortisol levels <5 mcg/dl but asymptomatic. Sixteen patients had hyponatremia out of which 10 patients were symptomatic. Eleven patients came for follow up after 3-6 months; steroids were withdrawn in 5 and 6 required long term steroids. The incidences of hyponatremia in both the groups were similar. There was a higher incidence of Diabetes Insipidus in Group 2, 9.09% vs. 3.27% in Group 1.

Conclusions

After transsphenoidal pituitary surgery 21% of patients with preoperative normal HPA axis will still require steroids replacement.

Key words   Pituitary adenomas   hyponatremia   diabetes insipidus

AIMS AND OBJECTIVES

1. To determine the postoperative cortisol levels in patients with pituitary adenomas undergoing transsphenoidal surgery without perioperative steroids.

2. To determine the incidence of hypocortisolemia and other complications in patients with pituitary adenomas undergoing transsphenoidal surgery without perioperative steroids.

INTRODUCTION

Transsphenoidal surgery for pituitary adenomas is the favoured approach for the surgical management of these tumors. Conventionally glucocorticoids are administered perioperatively to all patients undergoing transsphenoidal pituitary surgery under the presumption that there is a temporary dysfunction of the pituitary gland[1] during surgery.

Our experience is that it is possible to identify and preserve the normal adenohypophysis during transsphenoidal pituitary surgery.[2] It is debatable whether perioperative steroid supplementation is required when the preoperative cortisol levels are normal.[3, 4, 5] It has been noticed that there is an intraoperative surge of serum cortisol levels in those patients with preoperative normal HPA axis, probably an appropriate response to the stress of surgery.[6]

A prolonged postoperative course of steroids also might suppress the adrenal function that will masking a potential recovery of the HPA axis function making the postoperative assessment of the HPA axis difficult in those patients who receive supra-physiological doses of steroids.[7] Recently, trials have shown that reduction in the dose of postoperative steroid supplementation is safe and beneficial.[2]

In this study, we identified those patients with a normal pituitary adrenal axis from preoperative serum cortisol levels and a positive Synacthen test and withheld steroids for these patients perioperatively. These patients were monitored closely in the postoperative period both clinically and with daily serum cortisol estimations for 3 days and the HPA axis assessed again at 3-6 months following the surgery.

REVIEW OF LITERATURE

The pituitary gland

The pituitary gland is located within the sella turcica and weighs 0.6 g. It is composed of an anterior adenohypophysial component and a morphologically, embryologically, and functionally distinct posterior neurohypophysial component. The pituitary gland is entirely ectodermal in origin. The adenohypophysis develops from the Rathke's pouch by upward invagination and the neurohypophysis develops from the infundibulum by downward extension from the floor of the diencephalon (Fig 1 & 2).

The anterior adenohypophysis secretes the Follicle stimulating hormone (FSH), Leutinizing hormone (LH), Adrenocorticotrophic hormone (ACTH), Thyroid stimulating hormone (TSH), Prolactin and Growth hormone (GH). The neurohypophysis secretes Oxytocin which promotes uterine contractions and lactation and the anti-diuretic hormone (ADH).

Fig.1 Location of the Pituitary gland
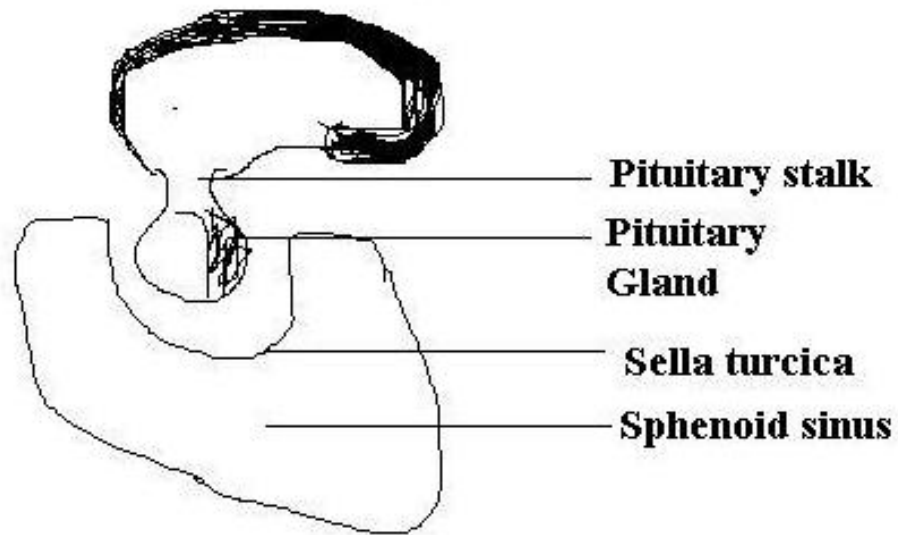
Fig.2 Anatomical relationships of the pituitary gland
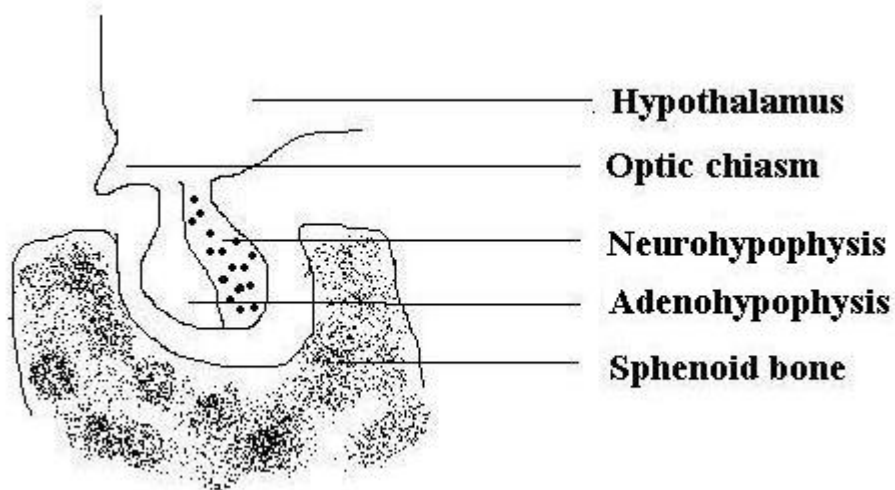
Pituitary adenomas-A brief overview

Pituitary tumors account for 10-15% of all brain tumors with the highest incidence between the 3rd-6th decades. It is found to be more common in women than men with a genetic predisposition seen only in MEN syndrome.

Prolactinoma account for nearly 30% of pituitary adenomas and are more commonly micro adenomas. They present with amenorrhea / galactorrhea. The serum prolactin levels are > 200 ng/ml. The first line treatment is pharmacologic with drugs like Bromocriptine and Cabergoline.

Growth hormone secreting tumors are most commonly macroadenomas occurring in the 4th and 5th decades. They present with coarse facial features, thickening of lips, enlargement of nose. The serum GH level is > 5 ng/ml with an elevated IGF-1 (Insulin like growth factor). Corticotroph secreting adenomas account for 8-10% of pituitary tumors. They produce a hypercortisolemic state generated in response to an ACTH-secreting pituitary tumor. They present with weight gain, truncal obesity, buffalo hump. Biochemically there is no cortisol suppression on low-dose dexamethasone testing, cortisol suppression on high-dose dexamethasone testing, and moderately elevated ACTH levels.

Thyrotroph adenomas form less than 1% of pituitary adenomas and manifest with signs of hyperthyroidism. They have a high TSH with high free T4. Clinically silent pituitary tumors account for 1/4th of pituitary tumors. They usually present due to mass effect on the optic chiasm or hypopituitarism.

Anatomical classification of pituitary adenomas

WHO classification includes a five tiered classification as

1) Clinical presentation and secretory activity

2) Size and invasiveness (e.g. Hardy)

3) Histology (typical vs. atypical)

4) Immunohistologic profile

5) Ultrastructural types

We will need to know the anatomical classification which gives information regarding the size and invasiveness of the tumor.

Hardy's classification of tumor (size and invasiveness)

Type A-Tumor with suprasellar extension not reaching the optic chiasm

Type B-Tumor reaches the floor of the 3rd ventricle, obliterating the anterior recess of the third ventricle without indenting it.

Type C-Tumor indents the floor of the third ventricle.

Type D-Tumor with intradural extension

Type E- Tumor invading the cavernous sinus

Knosp Classification of parasellar extension of tumor (Fig.3)[24]

Grade 0: The adenoma did not encroach the cavernous sinus space; not crossing the medial aspect of intra and supracavernous ICA.

Grade 1: The tumor crossed the medial tangent but does not extend beyond the intercarotid line.

Grade 2: The tumor crossed beyond the intercarotid line but does not cross beyond the lateral tangent of intra and supra cavernous ICA.

Grade 3: The tumor crossed beyond the lateral tangent of intra and supracavernous ICA

Grade 4: There was total encasement of the intracavernous carotid by the tumor.

Fig 3: Knosp classification of cavernous sinus invasion[24]
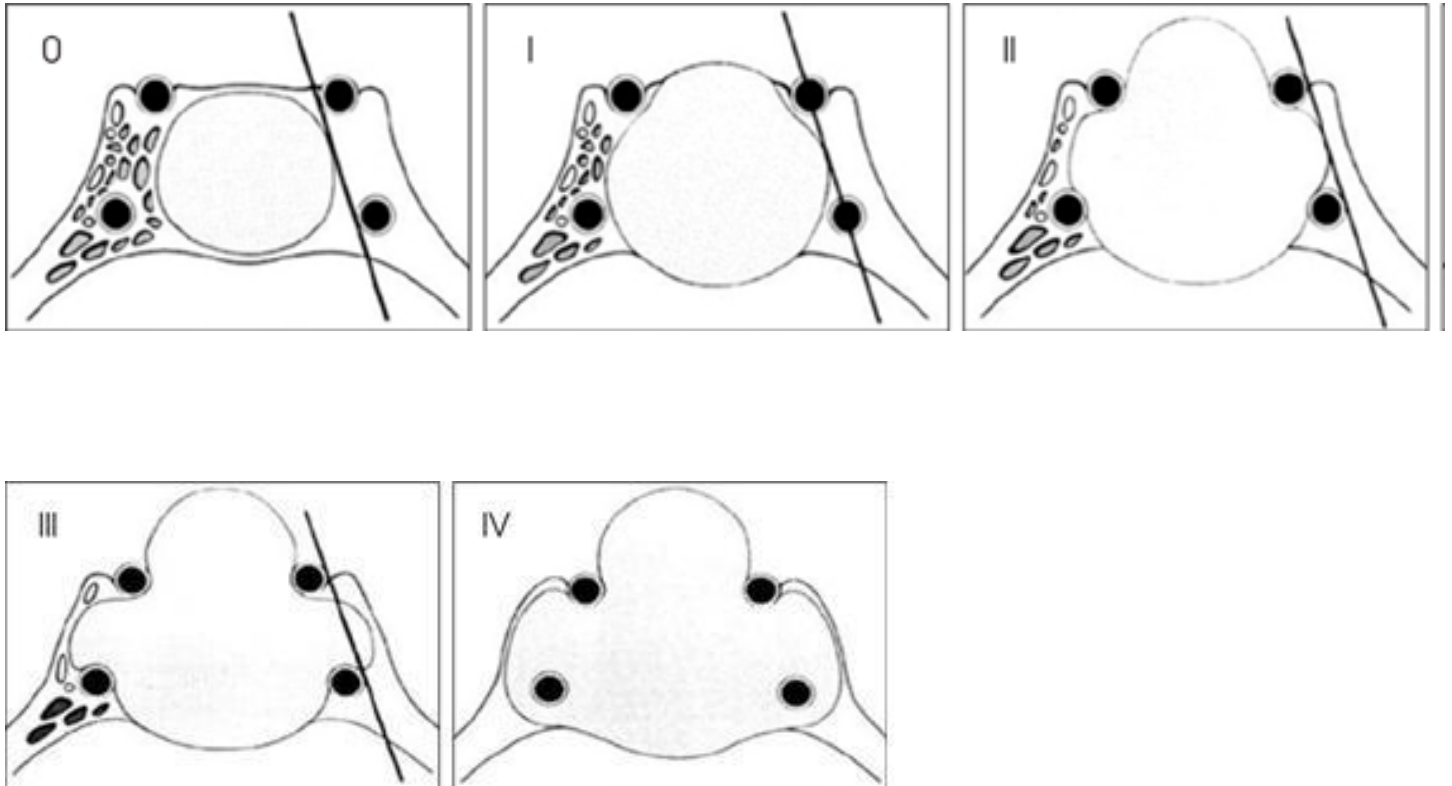
Adapted from Tumori - the Journal of Experimental and
Clinical Oncology.97(5):639-646:2011

Hypothalamo pituitary adrenal axis(HPA)

The main components of the HPA axis are the para-ventricular nucleus of the hypothalamus which contains neuro-endocrine neurons that synthesize and secrete vasopressin and corticotropin-releasing hormone (CRH)(Fig 4). The corticotrophin releasing hormone and vasopressin both stimulate the secretion of adrenocorticotropic hormone (ACTH). ACTH in turn acts on the adrenal cortices, which produce the glucocorticoid hormones. The glucocorticoids in turn act on the hypothalamus and pituitary (to suppress CRH and ACTH production) in a negative feedback cycle.[8, 9]

Hence in a patient with a pituitary adenoma, there is dysfunction at the level of the pituitary gland with a decreased secretion of the ACTH and a low serum cortisol due to a decreased release from the adrenal gland. In some patients, the adrenal reserve of cortisol is still maintained responding to exogenous ACTH. This is done in a Synacthen test which involves administration of synthetic ACTH intravenously and the serum cortisol assessed one hour later. This test can be done at anytime during the day and helps to identify patients who can still manage to produce an appropriate surge of cortisol during surgery.

Fig 4: The Hypothalamo pituitary axis (HPA)

+ *Stimulation*

- *Inhibition*

Hypothalamus
  − Corticotropin Releasing Factor
    (CRF)

+

−

−

Pituitary Gland
  − Adreno Corticotropin Hormone
    (ACTH)

+

Adrenal Gland
  - Glucocorticoids
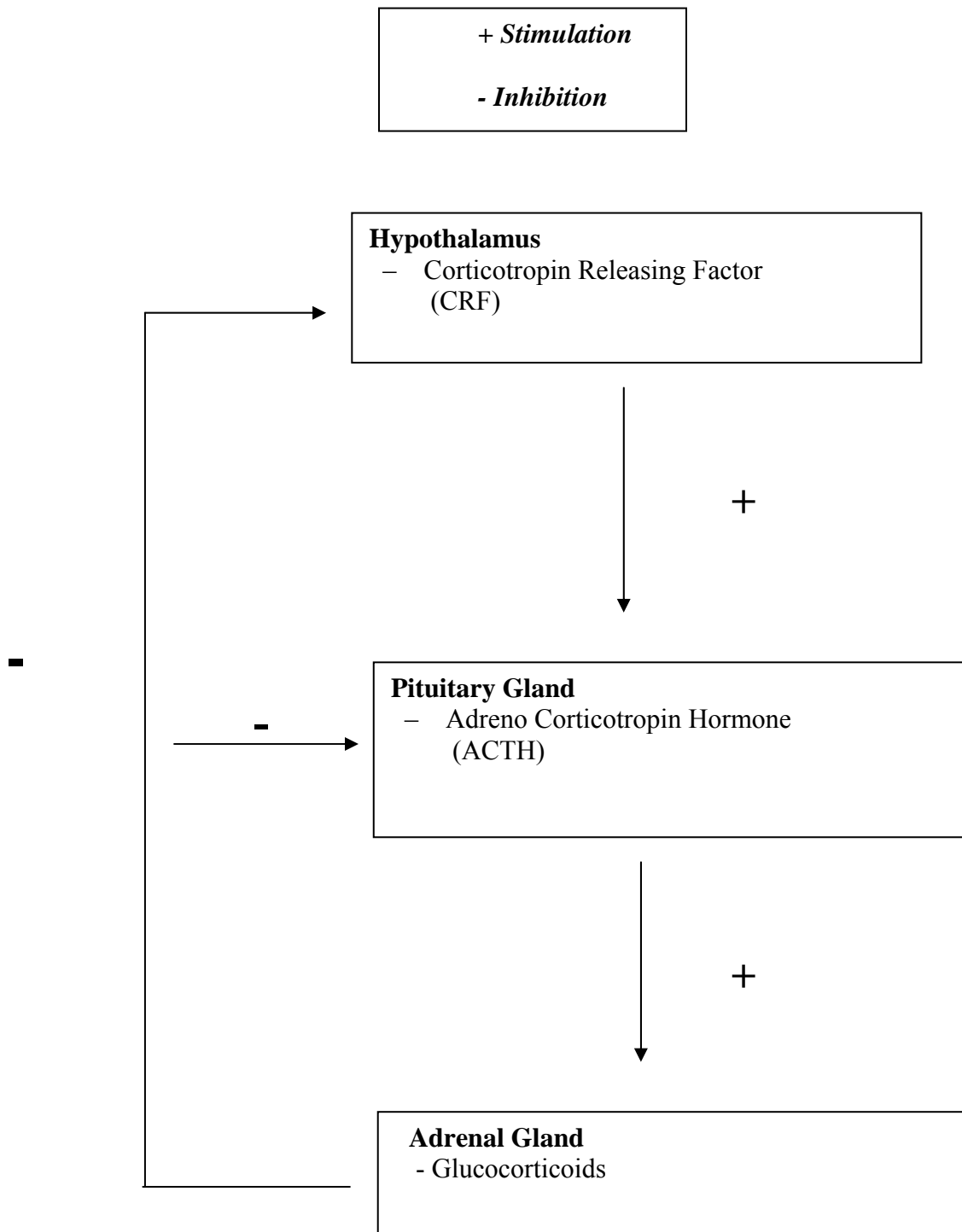
The circadian rhythm

Release of CRH from the hypothalamus is influenced by stress, blood levels of cortisol and by the sleep/wake cycle. The human sleep and wake cycles are generated by a complex interaction of the circadian and sleep processes. The main purpose of the circadian rhythm is to produce wakefulness during the day and conserve sleep for the night.

The suprachiasmatic nucleus (SCN) in the anterior hypothalamus is the central pacemaker for circadian rhythms and is synchronized with the external environment. Looking at the molecular level, the circadian clock gene proteins oscillate in an autoregulatory feedback and generate a self sustained regulated over a period of 24 hours.[10-13]

In healthy individuals, serum cortisol rises rapidly after waking up, reaching a peak within 30–45 minutes (Fig 5). It then gradually falls over the day, rises again in late afternoon. Cortisol levels then fall in late evening, reaching a trough during the middle of the night.[8, 9, 14].

This corresponds to a decrease in alertness during the midday at around 2–4 p.m and an increase in alertness peaking at the early to mid-evening hours subsequently falling by 4–6 a.m. In the early evening hours, there is an increased homeostatic drive for sleep when the circadian alternating signal is also high.[14-17]

Anatomical connections between brain areas such as the amygdala, hippocampus, and hypothalamus facilitate activation of the HPA axis. Increased production of cortisol mediates alarm reactions to stress, facilitating an adaptive phase of a general adaptation syndrome in which alarm reactions including the immune response are suppressed, allowing the body to attempt counter measures.

Fig 5: *The circadian rhythm of serum cortisol*
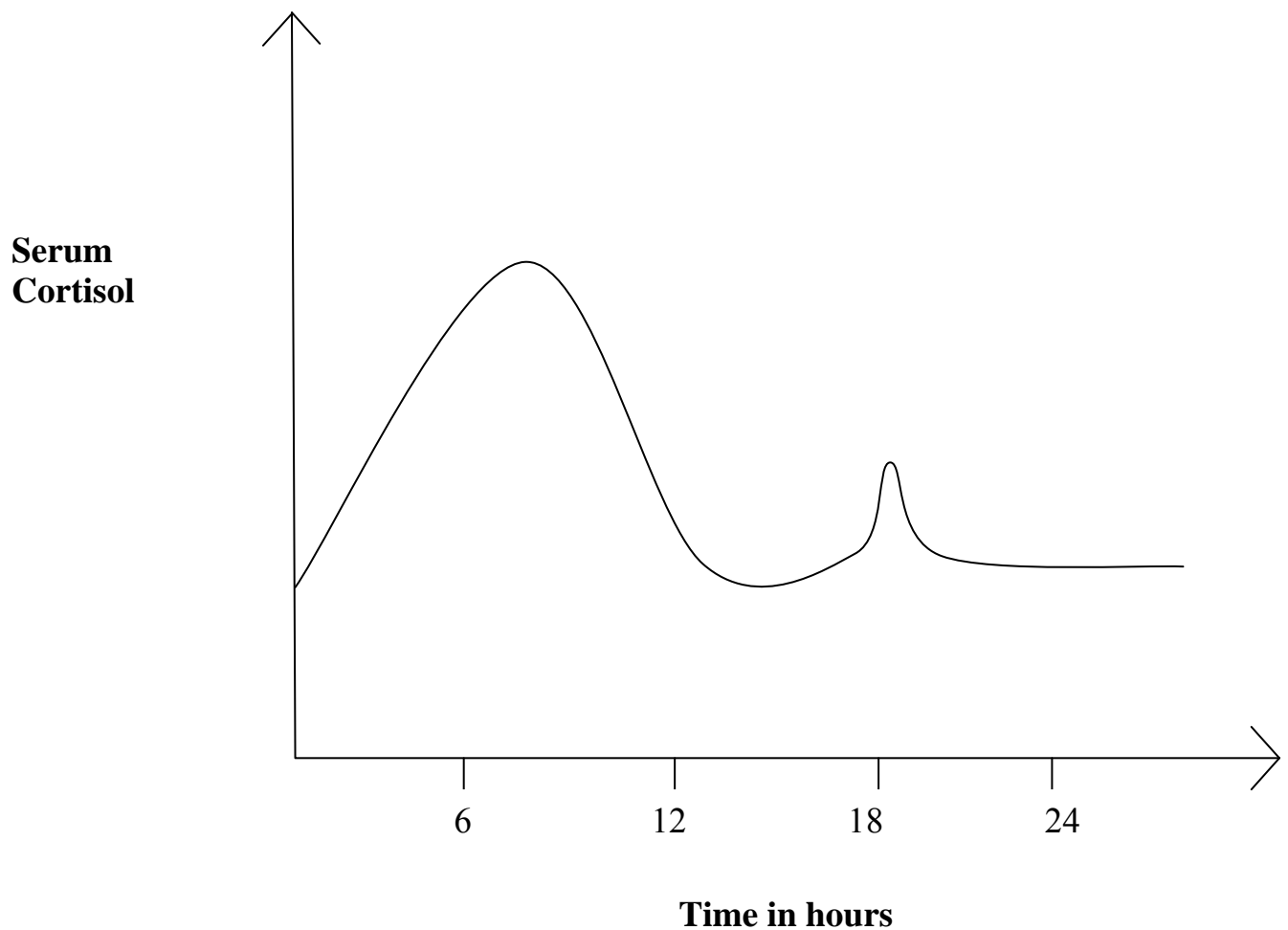
Assessment of the HPA axis

The Insulin tolerance test was considered the gold standard[15] to assess the HPA axis but the Synacthen test has become popular as it can be done easily on an outpatient basis and is equally reliable.[16, 17] The insulin tolerance test carries a risk of hypoglycemia and requires inpatient observation for the same. It also requires an assessment of the renal function. Though it remains the gold standard to assess the HPA axis, the short Synacthen test is preferred in view of convenience.[18, 19]

There are two doses of Synacthen, 250mcg and 1 mcg (low dose), each supported by literature[18-21]. However the 250 mcg dose Synacthen test is preferred because it considered close to accurate with the Insulin tolerance test.

The Synacthen test involves administration of 1ml (250 mcg) of synthetic ACTH intravenously and measuring serum cortisol level one hour following the injection. If the serum cortisol levels rise greater than 20 mcg/dl (Fig 6), these patients are considered to have normal HPA axis.[22] Earlier the authors used a cut off of 18 mcg/dl but subsequently raised it to 20 mcg/dl after a study in 1998 (unpublished observation by Inder et al) which showed that many people with cortisol levels post synacthen test between 18-20 mcg/dl still had ACTH deficiency. Hence the cut off was raised though there was a chance of falsely grouping patients with normal HPA axis as with ACTH deficiency.

In a study including 72 patients undergoing transsphenoidal resection of non-functioning pituitary adenomas by Cozzi et al, 14 patients (19.4%) had hypocortisolemia pre-operatively as defined by an 8am serum cortisol level less than 8 mcg/dl and they were given perioperative steroids.[23] Since a definitive test such as Synacthen or an Insulin tolerance test was not done preoperatively in this study the incidence of preoperative hypocortisolemia might have been underestimated. Hence the requirement of a standard test to identify patients with a normal HPA axis is required. In one of the studies by Oelkers et al[19], 13 out of 57 (22.8%) patients had an abnormal response to the short Synacthen test and 14 of 57(24.56%) patients had an abnormal response using the Insulin hypoglycaemia test.

Fig 6: Assessment of HPA axis based on Synacthen test
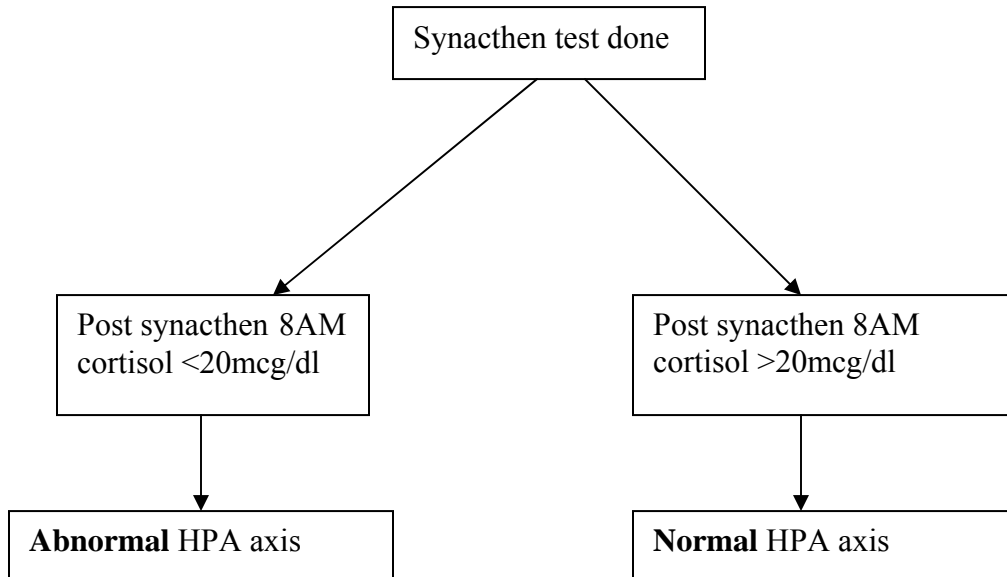
Factors causing preoperative hypocortisolemia

Tumor-related depletion of pituitary function causing steroid insufficiency occurs either due to destruction of the normal gland or due to hypothalamic disease. There is predominantly destruction of the anterior pituitary causing a deficiency in some or all pituitary hormones.[24] The size of the adenoma is found to influence the occurrence of hypocortisolemia/ hypo-pituitarism in the pre and postoperative period. Large tumors (Hardy's C, D, E tumors) are more likely to compress the normal gland and cause dysfunction of the gland. A macroadenoma (>10 mm) was found more likely to compromise normal pituitary function resulting in secondary adrenal insufficiency.[24]

Pituitary apoplexy causes sudden destruction of the normal pituitary tissue due to infarction or hemorrhage into the pituitary. Apoplexy usually spares the posterior pituitary and solely affects the anterior pituitary.[24]

The surgical approach, transsphenoidal or trans-cranial will influence the postoperative requirement of steroid administration because we administer preoperative steroids in transcranial surgeries to reduce cerebral oedema. In patients who undergo a transsphenoidal resection in our setting postoperative steroid cover is tapered rapidly over 2 to 3 days to physiologic replacement or discontinued if postoperative serum cortisol levels are normal after stopping hydrocortisone.

The safe level of serum cortisol on postoperative days 1,2 and 3 following surgery for patients in whom steroids were withheld have been analysed and a guideline has been put forward in the study by Inder et al[22] and it has been found safe to withhold steroids in patients with an 8 AM serum cortisol > 16 mcg/dl. In patients with a serum cortisol between 9-16 mcg/dl it is safe if the patient is asymptomatic and no hyponatremia. With cortisol between 3.6- 9 mcg/dl, a definitive test can be done and steroids given only during periods of stress. Definite steroid replacement needs to be given if 8 AM cortisol levels were below 3.6 mcg/dl. This cut off of 3.6 mcg/dl which defines definitive hypocortisolemia is based on the guidelines laid down by Inder et al.[22]

In a study by Zada et al[27], the cortisol index was calculated retrospectively for assessment of the cortisol stress response following transsphenoidal pituitary surgeries in 52 patients. Cortisol index was estimated from the difference between the postoperative Day 1 8am cortisol and the preoperative basal cortisol.   It was seen in that study that there was a significant difference ($p<0.005$) between the mean cortisol index in patients who required perioperative steroids (-2.8mcg/dl) and mean cortisol index in patients who did not receive steroids (+14.4mcg/dl).   From the mean cortisol index, he found that there was an 87% increase in cortisol in the immediate postoperative period. This implies an appropriate cortisol surge during surgery in all these patients.

The postoperative assessment of the HPA axis becomes crucial since the surgeon may not have preserved the adenohypophysis and it needs to be determined whether the patient requires steroids till follow up.

In patients who have received perioperative steroids the postoperative assessment performed on days 7-14 have a good predictive value of the requirement of long term glucocorticoid replacement[28, 29]. Another alternative is to do the definitive test at 4-6 weeks follow up which will offer an advantage to identify patients with a late recovery of the HPA axis postoperatively[29].

Insulin tolerance test is the preferred test and the next alternative is the Metapyrone test. But Synacthen test remains the convenient test practiced in most centres.

Factors determining requirement of perioperative steroid cover

After analyzing the preoperative factors which could cause a hypocortisolemia, the main factor that predict the normalcy of HPA axis postoperatively is the intraoperative preservation of normal gland tissue. An increased surgical experience in transsphenoidal pituitary surgeries would increase the preservation of normal gland which would influence postoperative hypocortisolemia as found by Barker et al.[25]

If the normal gland is preserved by the surgeon, it may be possible to withhold steroids in patients with a preoperative normal HPA axis. This is supported by studies[2] which show that normal gland is usually compressed to the periphery of the tumor and an intracapsular dissection might help preserve normal gland during surgery. Though extra capsular dissection offers a better surgical cure, normal gland is preserved with intracapsular dissection.

Are perioperative steroids required?

The conventional protocol has been to administer high dose steroid cover in the perioperative period for patients undergoing transsphenoidal resection of pituitary adenomas. [1]

This is under the presumption that there is a temporary dysfunction of the pituitary gland[1] during surgery. Our experience is that it is possible to identify and preserve the normal adenohypophysis during transsphenoidal pituitary surgery.[2] It is debatable whether perioperative steroid supplementation is required when the preoperative cortisol levels are normal.[3, 4, 5] It has been noticed that there is an intraoperative surge of serum cortisol levels in those patients with preoperative normal HPA axis, probably an appropriate response to the stress of surgery.[6]

A prolonged postoperative course of steroids also might suppress the adrenal function that will mask patients who can have a potential recovery of the HPA axis function. Also the postoperative assessment of the HPA axis becomes difficult in those patients who receive supra-physiological doses of steroids, as their endogenous steroid secretion is suppressed[7].

Udelsman et al[26] had earlier proved that supra-physiological doses of steroids did not offer any significant advantage during the surgical stress in adrenalectomised primates. Patients who had been taking at least 7.5 mg prednisolone daily for several months and had secondary adrenal insufficiency as defined by adrenocorticotropic hormone testing formed the study population. Patients were randomized to two groups. One group received perioperative injections of saline solution alone and included 12 patients; the other received perioperative saline solution and cortisol and included 6 patients. All patients received their usual daily prednisolone dose throughout the study. Two patients one in each group developed hypotension, which got corrected with volume replacements. None of them required additional doses of steroids than their usual doses in the perioperative period.

Rajaratnam et al[5] also supported the fact that no supraphysiological doses of steroids were required in their study wherein they studied 16 patients prospectively with Hardy's A and B tumors in whom perioperative steroids were withheld and only one patient required steroid cover because it was a second stage surgery.

Hence we can safely withhold steroids in patients identified to have a normal preoperative HPA axis using a definitive test.

Immediate postoperative HPA axis and long term glucocorticoid replacement

The immediate postoperative normal cortisol levels were found to predict the normalcy of the HPA axis in the long term. In a study by Nicholas et al[29,] 100 patients with normal preoperative HPA axis as assessed by Cortosyn stimulation test (CST) underwent 104 transsphenoidal/ trans-nasal pituitary adenoma surgical resections and steroids were withheld perioperatively. Postoperatively, HPA axis assessed as normal by CST 4-6 weeks later remained the same at 4-6 months follow up. He showed that a normal preoperative HPA axis was able to identify patients who will have normal HPA axis function after transsphenoidal pituitary surgery. The ability of immediate postoperative cortisol levels >15 mcg/dl (done 60-80 minutes after the surgery) to predict normal HPA axis function in future was assessed by standard analytical methods with a sensitivity of 98% and a positive predictive value of 99%.

Steroids and postoperative Diabetes insipidus

Diabetes insipidus has been a common side effect noticed in the postoperative period following transsphenoidal pituitary surgeries. The incidence of transient diabetes insipidus is higher about 10-66% and the permanent DI around 0.4 –15%. [30-34] Diabetes Insipidus increases the postoperative morbidity and duration of hospital stay.

A pituitary adenoma, regardless of the size, rarely causes diabetes insipidus (DI) before surgical intervention.[34] Steroids are found to suppress the release of anti diuretic hormone (ADH) produced in the pituitary gland. This is because ADH is also known to act as a corticotrophin releasing factor on the pituitary gland.[34] Hence when there is exogenous steroid administration, they suppress the release of ADH and cause diabetes insipidus. This is known to unmask the incidence of diabetes insipidus in patients undergoing trans-sphenoidal pituitary adenoma resections. Steroids also increase the threshold of serum osmolarity required for the release of vasopressin.

In the study by Rajaratnam et al[5], 114 patients were randomized into 3 groups one day before surgery, 32 patients in the conventional high dose steroid regimen, 30 in the intermediate dose regimen and 52 patients in the low dose regimen. It was noticed that there was a reduction of the incidence in DI to 46% in group 3, the low dose regimen (p=0.025). It was also

noticed that the patients in group 3 did not require change over to the high or intermediate dose regimen anytime. Steroid deficiency was associated with an increased synthesis of vasopressin. This is known to occur in high doses of steroids and the incidence is less with low doses of postoperative steroid supplementation.

MATERIALS AND METHODS

Patient population

This was a prospective study that included 105 patients who underwent transsphenoidal surgery for pituitary adenomas between June 2010-December 2012 with age <60 years. The HPA axis before surgery was assessed based on the protocol as laid down in the guidelines for perioperative steroid replacement by Inder et al[22].(Fig 7) Patients with 8 am serum cortisol greater than 16 mcg/dl were considered to have a normal HPA axis and did not receive steroid cover during surgery. All patients with preoperative cortisol levels less than 3.6 mcg/dl were covered with steroids that were continued till follow-up. Patients with a serum cortisol between 3.6-16 mcg/dl underwent a Synacthen test and were not given perioperative steroid cover if their HPA axis was normal as determined by this test.

The Synacthen test

Patients with 8 am serum cortisol between 3.6-16 mcg/dl underwent a Synacthen test to assess the adequacy of the HPA axis. The Synacthen test involved administration of 1ml (250 mcg) of synthetic ACTH intravenously and serum cortisol was measured one hour following the injection. If the serum cortisol levels increased to greater than 20 mcg/dl, these patients were considered to have a normal HPA axis [14] and did not receive steroid cover during surgery.

If the serum cortisol level was <20 mcg/dl the HPA axis was considered to be abnormal and the patient received perioperative steroids.

Fig. 7 Assessment of the preoperative HPA axis based on the 8 AM serum cortisol and Synacthen test - an algorithm
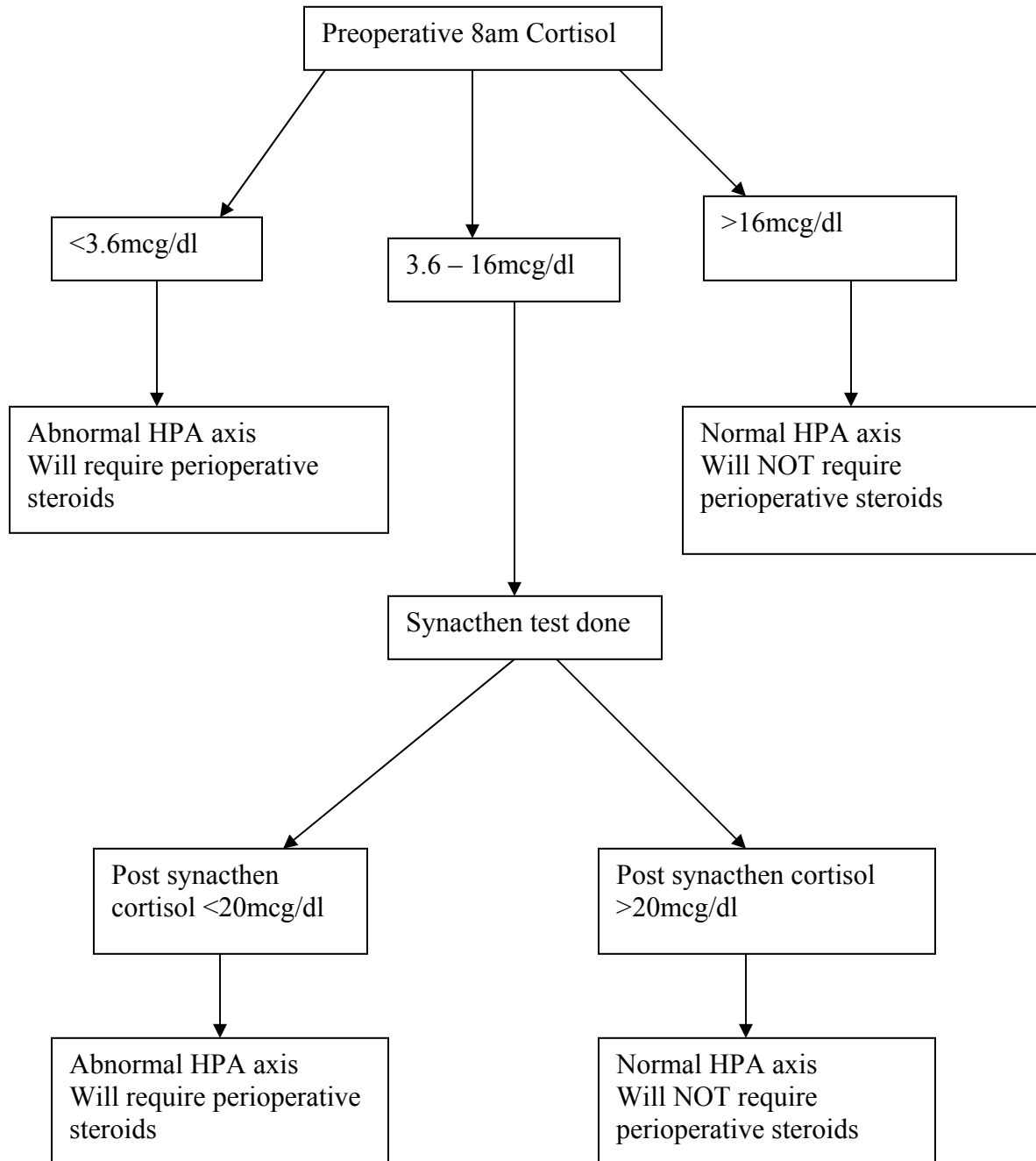
```
                    ┌──────────────────────────┐
                    │ Preoperative 8am Cortisol │
                    └──────────────────────────┘
           ┌──────────────────┼──────────────────┐
           ▼                   ▼                  ▼
    ┌────────────┐      ┌──────────────┐   ┌────────────┐
    │ <3.6mcg/dl │      │ 3.6 – 16mcg/dl│   │ >16mcg/dl  │
    └────────────┘      └──────────────┘   └────────────┘
           │                   │                  │
           ▼                   │                  ▼
 ┌─────────────────────┐       │         ┌──────────────────────┐
 │ Abnormal HPA axis   │       │         │ Normal HPA axis      │
 │ Will require        │       │         │ Will NOT require     │
 │ perioperative       │       │         │ perioperative steroids│
 │ steroids            │       │         └──────────────────────┘
 └─────────────────────┘       ▼
                        ┌──────────────────┐
                        │ Synacthen test done│
                        └──────────────────┘
                  ┌─────────────┴─────────────┐
                  ▼                           ▼
         ┌──────────────────┐       ┌──────────────────────┐
         │ Post synacthen   │       │ Post synacthen cortisol│
         │ cortisol <20mcg/dl│       │ >20mcg/dl            │
         └──────────────────┘       └──────────────────────┘
                  │                           │
                  ▼                           ▼
       ┌─────────────────────┐     ┌──────────────────────┐
       │ Abnormal HPA axis   │     │ Normal HPA axis      │
       │ Will require        │     │ Will NOT require     │
       │ perioperative       │     │ perioperative steroids│
       │ steroids            │     └──────────────────────┘
       └─────────────────────┘
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Fig. 8 *Synacthen Ampoule:*
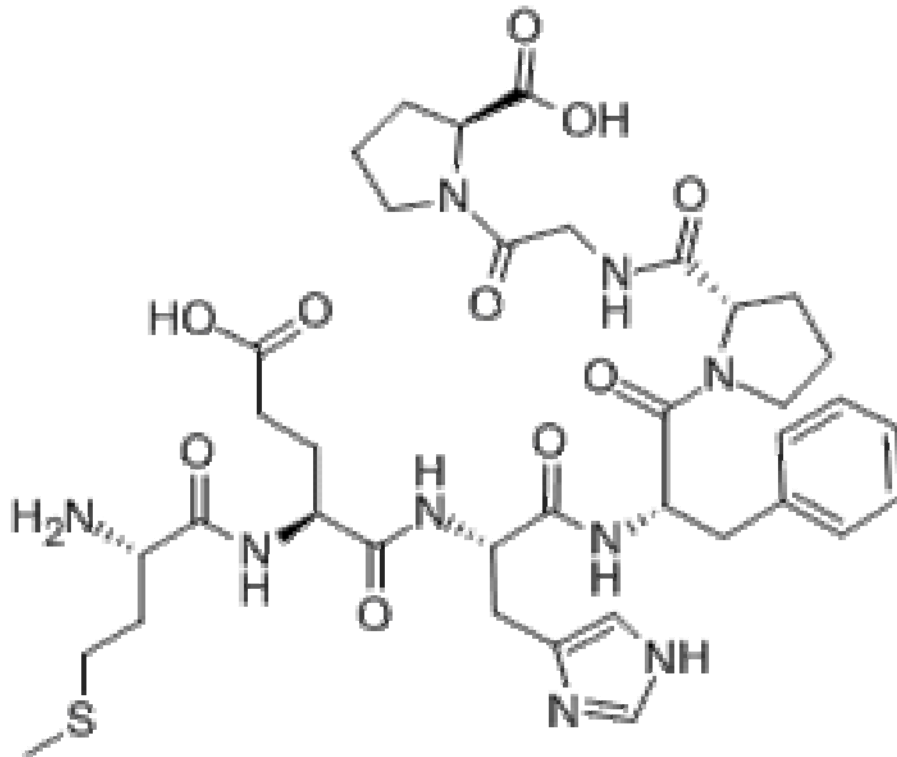
Groups 1 & 2

The 105 patients were divided into 2 groups (Table 1) based on the preoperative evaluation. Group 1 included the 61 patients with a preoperative normal HPA axis and did not receive perioperative steroid cover. Group 2 included 44 patients with abnormal HPA axis and those already on preoperative steroids. Group 2 patients received Inj.Hydrocortisone 25 mg 6thhrly on day one, followed by oral prednisolone 10 -0-5 mg on day two, 5-0-2.5 mg on day three and stopped. Steroids were continued further postoperatively only if the patients were already on steroids preoperatively or their postoperative cortisol levels were below 5 mcg/dl on any of the three days following surgery.

Table 1 Inclusion criteria for Group 1 and Group 2

Group1 (61 patients)	Group 2 (44 patients)
Normal HPA axis	Already on steroids
No perioperative steroids	Abnormal HPA axis
-	Received perioperative steroids (IV steroid for 24 hrs & oral steroids for the next 48 hours).
-	Steroids continued only if patient was on steroids prior to surgery / the post op cortisol levels were low (<5 μg/dl).

Postoperative follow up

.

If the surgeon was unable to recognize or preserve the adenohypophysis at surgery the patient was given steroid cover postoperatively irrespective of the preoperative integrity of the HPA axis.

For the first 3 days after surgery, a serum 8AM cortisol and twice daily serum sodium estimations were done. Postoperatively, the patients were monitored for symptoms of hypocortisolism in the ICU and ward such as nausea, vomiting and tiredness/lethargy. A random cortisol was done whenever hypocortisolism was clinically suspected.

Injection hydrocortisone was given if any serum cortisol value was <3.6 mcg/dl. In addition those patients who complained of nausea, vomiting or tiredness had an immediate serum sodium and a cortisol sample drawn and Injection Hydrocortisone was given immediately. Subsequently if the cortisol levels were normal but the sodium value was < 130 mEq/L, the patient was treated as for hyponatremia without continuing steroids.

RESULTS AND ANALYSIS

Multiple factors including age, gender and incidence of preoperative hypothyroidism, apoplexy and the size of tumor were compared between the 2 groups (Table 2). The postoperative factors including the extent of excision, postoperative CSF leak, incidence of diabetes insipidus and the hyponatremia were also compared (Table 2).

Analysis of perioperative data between the 2 groups

There was a significantly higher incidence of small tumors in Group 1 patients with normal HPA axis. There were 36 patients with small tumors in Group 1 as compared to 11 patients in Group 2 with a p value=0.001(Table 2).

There was almost equal incidence of apoplexy in both the groups and there was no difference in functional status of the tumor. There was also no significant difference in the incidence of preoperative hypothyroidism between the 2 Groups and hence not found to influence the steroid requirement status preoperatively. There was no significant difference in the incidence of other factors as age or gender between the 2 Groups.

Another interesting fact noticed was that there was a similar incidence of postoperative hyponatremia in Groups 1 and 2, 22.99% versus 20.45% respectively. The incidence of postoperative DI in patients in Group 1(3.27%) was less than that in Group 2 (9.09%). Although the incidence of DI was higher in Group 2 (3.27% versus 9.09%) this was not statistically significant.

Table 2: Comparison of pre and intraoperative factors in Groups 1 and 2

	Group 1 (N=61)	Group 2 (N= 44)	P Value
Age (mean / SD)	40 / 10.92	40 / 12.30	0.1
Gender Male (No:/%)	28/46	28/64	
Hypothyroidism (No:/%)	8 / 13	10 / 23	
Apoplexy (No:/%)	10/16.	7/16	

Type of adenoma
    GH (No: / %)
    Non-functional
	
	36 / 59
	25 / 41
		
		15 / 34
		29 / 66	

Size of adenoma
    Hardy A
        B
        C
        D
    Invasive
    Micro
	
	12 / 20%
	18 / 30%
	22 / 36%
	1 / 2%
	2 / 3%
	6 / 10%
		
		1 / 2%
		9 / 20%
		25 / 57%
		3 / 7%
		5 / 11%
		1 / 2%
			
			0.001 - Small tumors
			<0.001 - Large tumors

Radical excision	34 / 56 %	19 / 43%	0.23
Subtotal / Partial Excision	26 / 43%	25 / 57%	0.17
Intra-operative CSF leak	26 / 43%	17 / 39%	0.69
Gland not preserved	0	15 / 34%	0.0001

Table 3: Comparison of the postoperative complication factors in Group 1 and Group2

	Group 1	**Group 2**	**P Value**
Symptoms of hypocortisolemia	11 / 18%	-	0.0001
Hyponatremia	16 / 23%	9 / 20%	0.64
Post-operative diabetes insipidus	2 / 3%	4 / 9%	0.40

Postoperative serum cortisol levels in Group 1

The mean serum cortisol levels in Group 1 preoperatively and on the postoperative days 1,2 and 3 as well as at follow up are shown in Figure 11. The mean preoperative 8am serum cortisol value was 14.77 mcg/dl with a standard deviation (SD) of 6.72. The mean / SD values for the postoperative cortisol levels on days 1,2 and 3 for all the 61 patients were 23.00 / 13.79, 15.68 / 16.38 and 14.96 / 7.32 mcg/dl respectively. It was found there was significant difference between the mean preoperative cortisol and mean cortisol on day 1 (p=0.04) suggesting a definite cortisol surge in the immediate postoperative period by 55.7% compared to the preoperative cortisol. The maximum surge of cortisol noticed among the 61 patients was 111%.

Complications in the postoperative period

Among the 61 patients in whom steroids were withheld, 42 patients(69%) did not have any problem postoperatively and their cortisol levels also remained normal during the first 3 days and were followed up after 3-6 months without steroids. The remaining 19 patients(31%) required steroids, 16 of them developed hyponatremia and hence were given steroids. Of the remaining 3 patients, two had a low serum cortisol level, one with a cortisol value 1.88 mcg/dl on day 1 and another with a cortisol value 1.36 mcg/dl on day 2 after surgery and hence were given steroids. One patient developed generalized tiredness and vomiting on Day 3 after surgery with a cortisol level of 9.02 mcg/dl and had no hyponatremia and was given steroids. The mean serum cortisol value for the 16 patients who developed hyponatremia(Fig 14) were 19.84, 12.36 and 9.20 mcg/dl respectively on days 1,2 and 3. 10 of 16 patients had a serum cortisol less < 16 mcg/dl on the day steroids were administered for hyponatremia. Of the 19 patients who required steroids, 16 patients had hyponatremia of which 10 patients only were symptomatic. 5 patients had a serum cortisol< 3.6 mcg/dl considered as definite hypocortisolemia of which 3 patients only were symptomatic. This accounts for the overlap of the number of patients described as a bar graph in Fig 14.

Fig. 10 Algorithm showing postoperative requirement of steroids in Group 1 and the reason and day of administration of steroids.

61 patients

42 (no steroids)   19 (steroids given)

16 (hyponatremia)
   Day 3 - 1
   Day 5 - 5
   Day 7 - 6
   Days 7-11 - 4

3 pts

2 had Cortisol level
< 3.6mcg/dl /
Asymptomatic

1 had symptoms
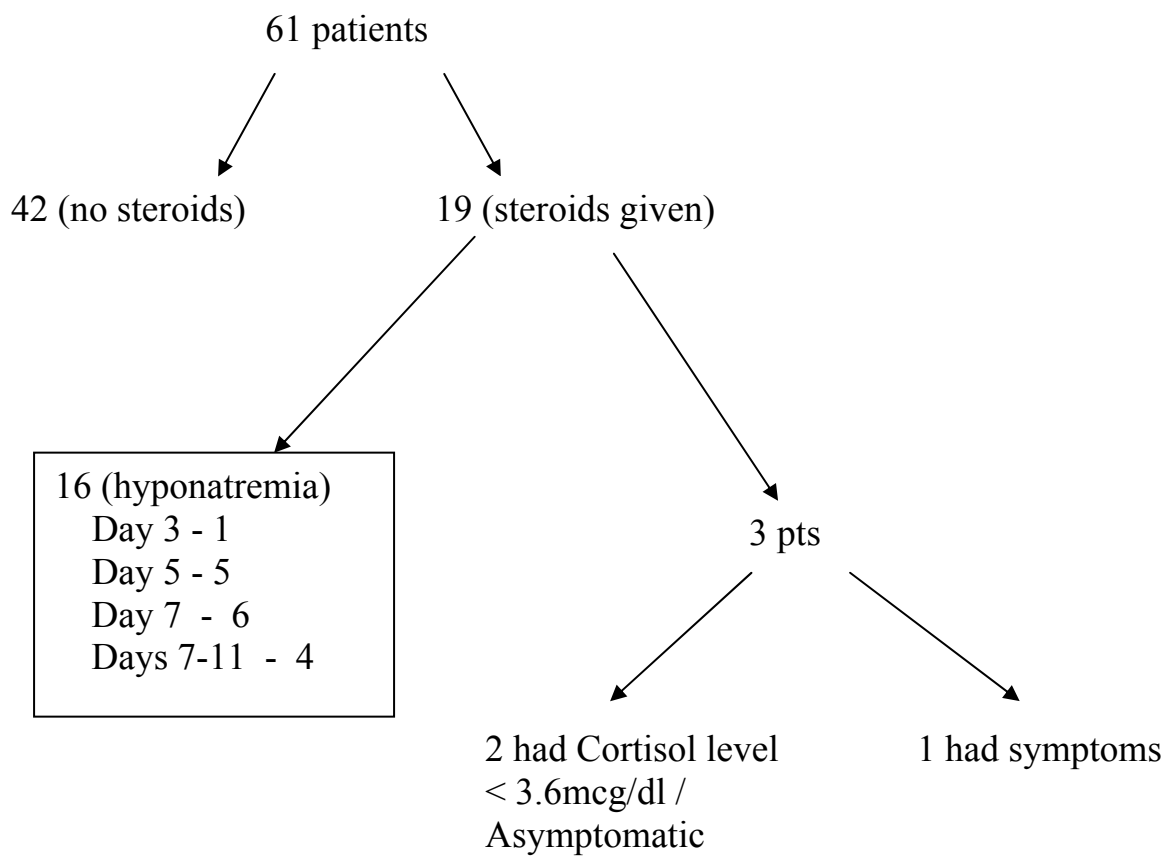
Fig.11 Shows the trends in the mean serum cortisol before surgery, on days 1,2 and 3 following surgery and at 3-6 months follow up for 61 patients in Group 1. It was seen that there was a definite surge in serum cortisol on Day 1 after surgery suggesting a normal intraoperative surge.

Preop & Days 1, 2 , 3 & follow up cortisol in all 61 patients
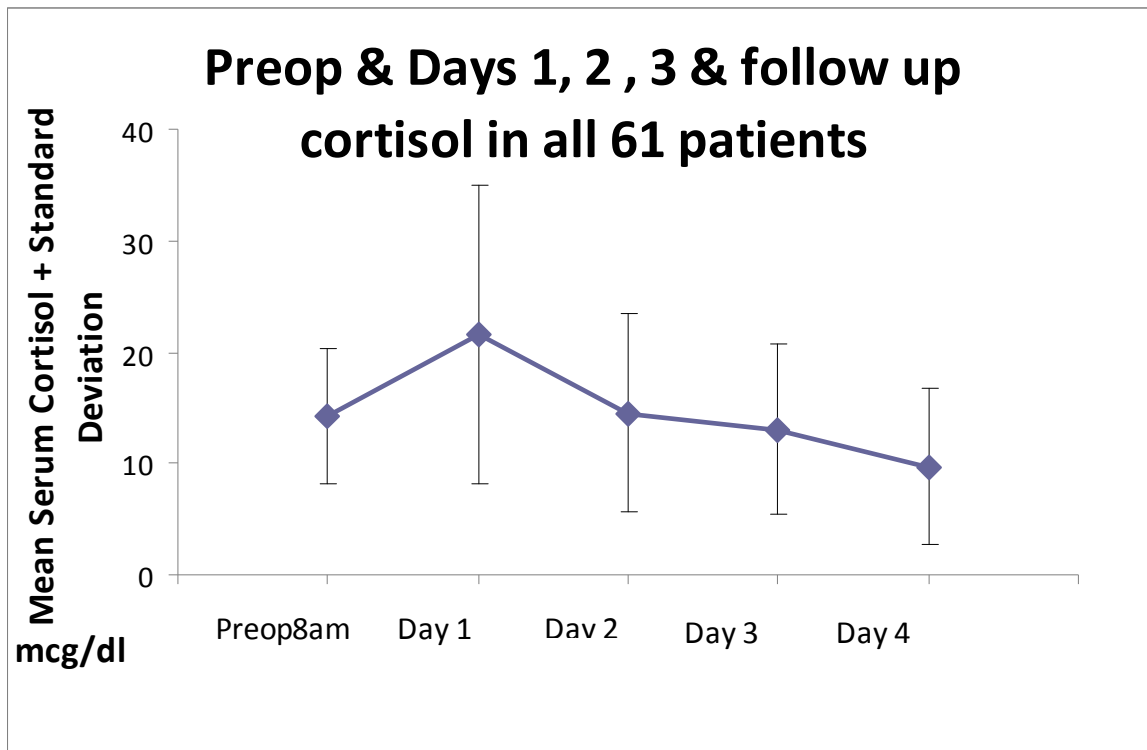
Fig 12: The mean cotisol levels on Days1,2 and 3 compare between the patients who
required and did not require steroids in Group 1

Comparison values for Preop & Days 1, 2 , 3 & follow
up cortisol in all 42 and 19 patients

42 Patients
19 Patients

Mean Serum Cortisol + Standard Deviation

mcg/dl

Preop8am   Day1   Day2   Day3   Day4
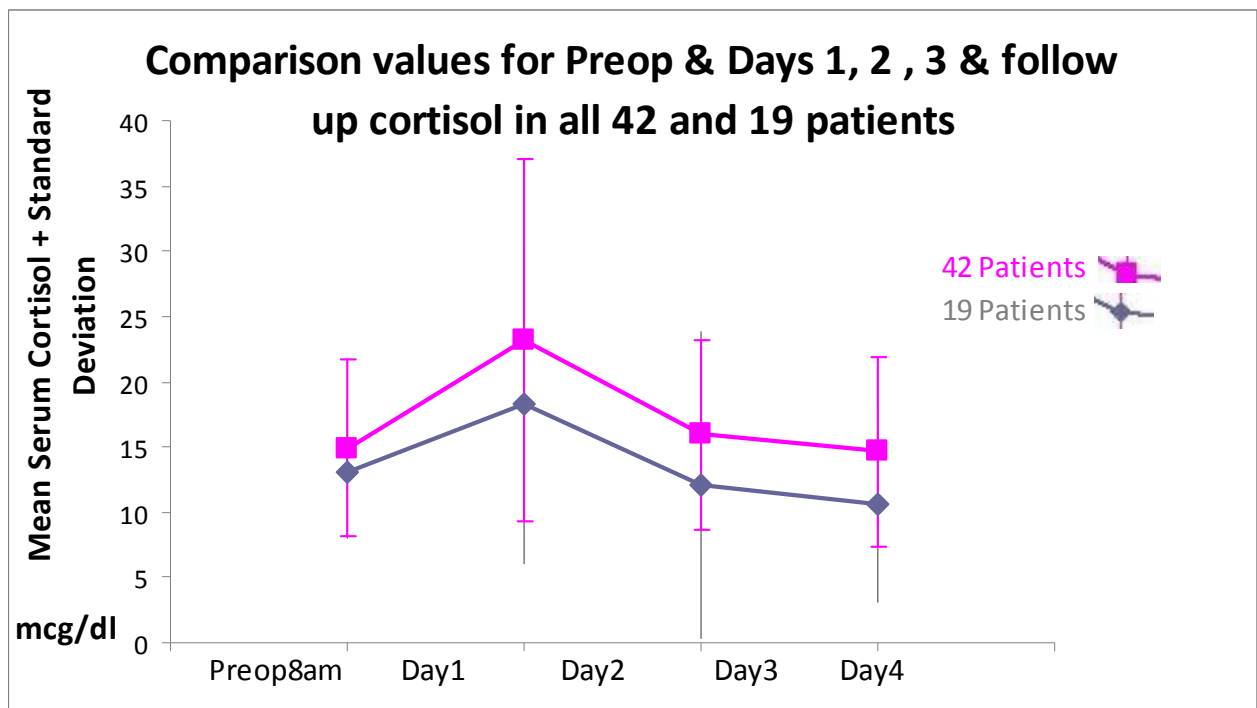
Factors determining steroid requirement in Group 1 (Table 4)

The data from the 61 patients were analyzed for factors that could predict steroid requirement postoperatively (Table 4). There was no significant difference in the preoperative hypothyroidism, apoplexy nor the intraoperative CSF leak. There was a higher incidence of smaller tumors with in the 42 patients who did not require steroids. (p=0.09)

The requirement of Synacthen test influencing the requirement of perioperative steroid cover were also analysed and among the 61 patients it was found that 11 of 19(58%) patients who required steroids and 26 of 42(62%) patients who did not require steroids were identified to have a normal HPA axis preoperatively based on the Synacthen test with no significant difference between them. It was also noticed that there was a significantly (p=0.001)higher instance of radical tumor excision in the 19 patients who required steroids(100%) versus that in the remaining 42 patients who did not require steroids(55%) which could suggest possibility of a decreased percentage of normal gland preservation during surgery.

Table 4: Comparison of the preoperative and postoperative factors within Group 1 between the 19 patients who required steroids and the 42 patients who did not require steroids

	Steroids given (19 patients)	**Steroids not given (42 patients)**	**P Value**
Gender-males	**8**	**19**	**1.00**
Apoplexy	2	8	0.47
Preoperative hypothyroidism	5	3	0.0941
Synacthen test	11	26	0.78
Small tumors(Microadenomas)	8 (3)	28 (4)	0.094
Intraoperative CSF leak	8	11	0.24
Radical excision	19	23	0.0001
Gland preserved	19	40	0.52
Postoperative Diabetes insipidus	1	1	0.06

Fig. 13 Demonstrates on a graph the number of patients who required steroids in the immediate postoperative period and the status of the 19 patients at 3-6 months follow up.

8 patients were lost to follow up and steroids could be stopped for 5 patients and 6 required to be continued on steroids.
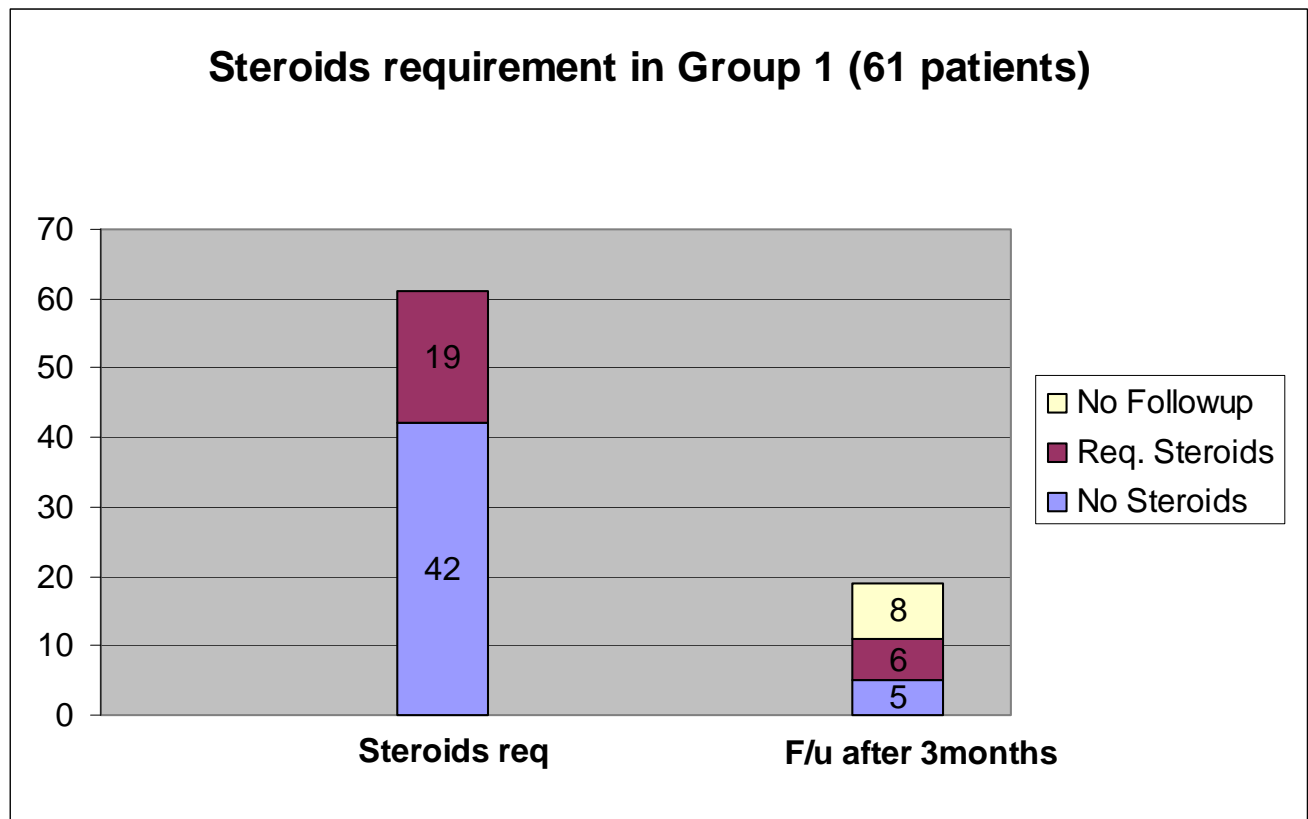
Fig 14 Shows the reasons why hydrocortisone was administered in the 19 patients. Sixteen patients developed hyponatremia of which 11 were symptomatic. Out of the 19 patients, only 5 patients had a low serum cortisol<3.6 mcg/dl. There was an overlap of the incidence of symptoms and hyponatremia among the 19 patients.
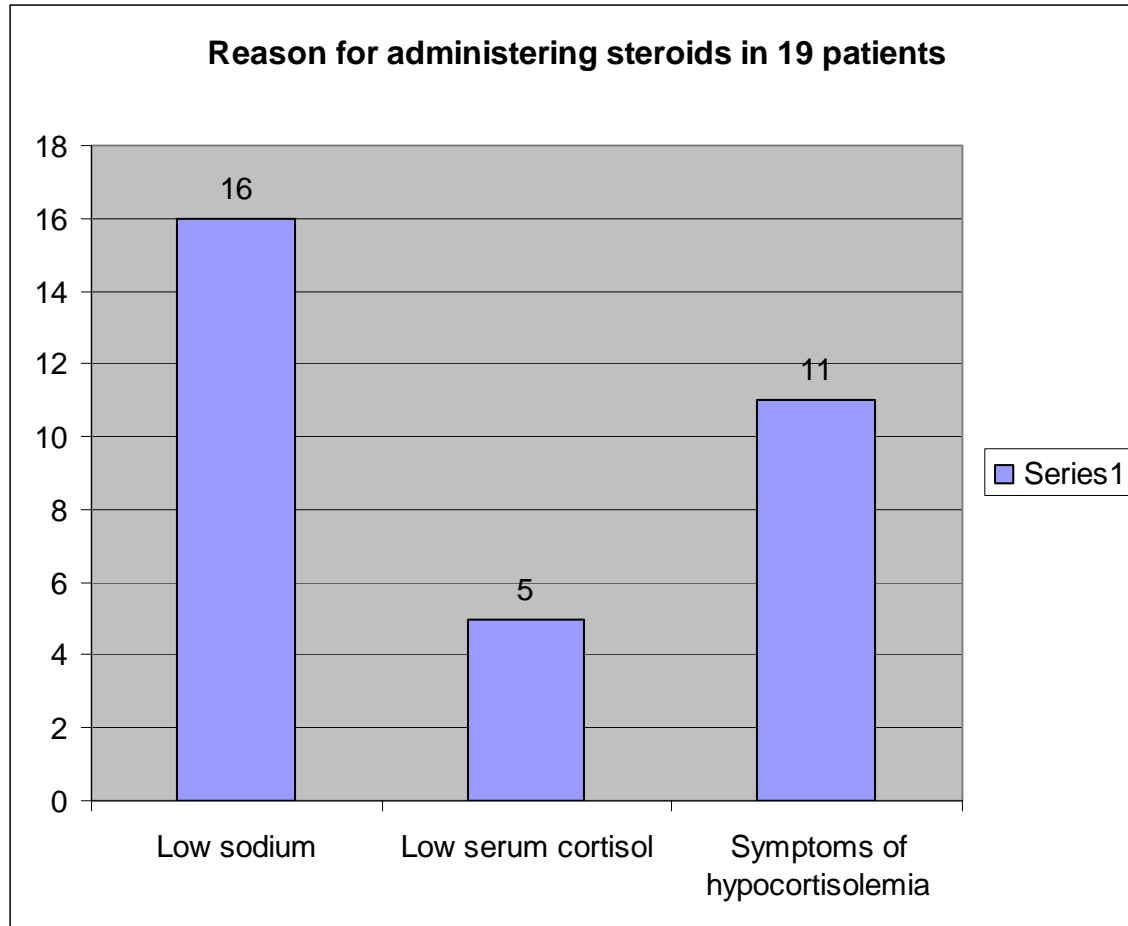
Outcomes at 3-6 months follow up in Group 1(Fig 13)

All these 61 patients were followed up between 3-6 months after surgery. All the 42 patients who did not require perioperative steroids remained asymptomatic with normal serum cortisol level and did not require long term steroids. Of the 19 patients who were discharged on steroids, 6 required long term steroids at follow up. Steroids could be withdrawn in 5 of these patients as their serum cortisol level was normal. Eight patients were lost to follow-up.

DISCUSSION

Factors associated with preoperative hypocortisolemia

We had analysed the following factors as size of tumor, hypothyroidism, apoplexy, age of the patient and type of tumor and studied the correlation with the incidence of preoperative hypocortisolism.

In our study, there was a significant difference in the incidence of small tumor (microadenomas and Hardy's A and B) versus large tumors (Hardy's C, D and invasive adenomas within group 1 (p=0.001) and group 2 (<0.001) axis. There was also significant difference noted between the incidence of small tumors in groups 1 (36) versus group 2 (11) , p=0.001. and also for large tumors in group 1 (25) versus group 2 (33) respectively (p<0.001) (Table 1).

Other authors have also found that the size of the adenoma influences the occurrence of hypocortisolemia/ hypo-pituitarism in the pre and postoperative period. A macro adenoma (>10 mm) was found more likely to compromise normal pituitary function resulting in secondary adrenal insufficiency. [36]

Pituitary apoplexy causes sudden destruction of the normal pituitary tissue due to infarction or hemorrhage into the pituitary. Apoplexy usually spares the posterior pituitary and solely affects the anterior pituitary. [37] We found no significant difference in the incidence of apoplexy among Group 1 patients who required postoperative steroids and who did not require steroids (Table 7).

Our evidence of preoperative hypopituitarism was based on a normal 8AM serum cortisol level. 24 patients had a normal cortisol level > 16 mcg/dl. 52 patients had a cortisol level <16 mcg/dl and underwent the Synacthen test. 37 of them passed with a serum cortisol >20mcg/dl and 15 patients failed. This is important because mere documentation of a random cortisol level < 16 mcg/dl does not necessarily indicate hypocortisolemia since 37 out of 52(71%) patients passed the Synacthen test. The incidence of preoperative hypocortisolism in our study was 19%.

In a study by Cozzi et al including 72 patients undergoing transsphenoidal resection of non-functioning pituitary adenomas, 14 patients (19.4%) had hypocortisolemia pre-operatively as defined by an 8am serum cortisol level less than 8 mcg/dl and they were given perioperative steroids.[23] Since a definitive test such as Synacthen or an Insulin tolerance test was not done preoperatively in this study the incidence of preoperative hypocortisolemia might have been underestimated. Hence the requirement of a standard test to identify patients with a normal HPA axis is required. In one of the studies by Oelkers et al[19], 13 out of 57 (22.8%) patients had an abnormal response to the short Synacthen test and 14 of 57(24.56%) patients had an abnormal response using the Insulin hypoglycaemia test.

Assessment of immediate postoperative cortisol response

The conventional protocol has been to administer high dose steroid cover in the perioperative period for patients undergoing transsphenoidal resection of pituitary adenomas. [1] Udelsman et al[26] had earlier proved that supra-physiological doses of steroids did not offer any significant advantage during the surgical stress in adrenalectomised primates.

In a study by Nicholas et al[29] it was shown that a normal immediate postoperative HPA axis would be able to identify patients who will have normal HPA axis function at follow up later. The ability of immediate postoperative cortisol levels >15 mcg/dl (done 60-80 minutes after the surgery) to predict normal HPA axis function in future was assessed by standard analytical methods with a sensitivity of 98% and a positive predictive value of 99%.

In another study, the cortisol level cortisol level on the morning after surgery in 83 patients undergoing transsphenoidal resection of pituitary adenomas were done and demonstrated that levels ≥ 15 μg/dl are predictive of normal long-term HPA function assessed by a definitive test done 1-3 months later with a sensitivity of 80.5%, specificity of 66.7% and a positive predictive value of 96.9%[35].

In a study by Zada et al[27], the cortisol index was calculated retrospectively for assessment of the cortisol stress response following transsphenoidal pituitary surgeries in 52 patients. Cortisol index was estimated from the difference between the postoperative day 1 8am cortisol and the preoperative basal cortisol.   It was seen in the study that there was a significant difference (p<0.005) between the mean cortisol index in patients who required perioperative steroids (-2.8mcg/dl) and mean cortisol index in patients who did not require steroids (+14.4mcg/dl).   From the mean cortisol index, he found that there was an 87% increase in cortisol in the immediate postoperative period in those who did require steroids as compared to the 56% postoperative surge on Day 1 in our study. This implies an appropriate cortisol surge during surgery in all these patients.

The safe level of serum cortisol on postoperative days 1,2 and 3 following surgery for patients in whom steroids were withheld have been analysed and a guideline has been put forward in the study by Inder et al[22] and it has been found safe to withhold steroids in patients with an 8 AM serum cortisol > 16 mcg/dl on the days 1,2 and 3. In patients with a serum cortisol between 9-16 mcg/dl it is safe if the patient is asymptomatic and no hyponatremia. With cortisol between 3.6-9 mcg/dl, a definitive test can be done and steroids given only during periods of stress. Definite steroid replacement needs to be given if 8 AM cortisol levels were below 3.6 mcg/dl.

In our study, the patients in whom steroids were withheld were monitored using a serum 8AM cortisol and for hyponatremia and clinical deterioration. There are studies supporting the use of serum cortisol in the immediate postoperative period as a predictor of HPA axis in the long term.

Our findings indicate that 42 out of the 61(69%) patients in whom steroids were withheld perioperatively did not have any problems postoperatively and subsequently at follow up.

Nineteen patients required perioperative steroids either due to clinical symptoms,11 patients (58%), hyponatremia, 16 patients (84%) or a serum cortisol<3.6 mcg/dl, 5 patients (26%). (Appendix 2).

Five of the 19 patients had definite hypocortisolemia with a cortisol < 3.6 mcg/dl of which 3 developed symptoms and 2 were asymptomatic. 8 other patients had a serum cortisol < 16 mcg/dl but > 3.6 mcg/dl of which 5 patients were symptomatic and also had hyponatremia, 2 had hyponatremia alone and one patient had become symptomatic but no hyponatremia. The 2 patients who had a low serum cortisol alone < 3.6 mcg/dl had their tumor size 2cm and 5 cm respectively. Hence the incidence of true hypocortisolemia would include the 5 patients who had a serum cortisol level < 3.6mcg/dl and also the 8 patients who had either developed hyponatremia or clinical features of hypocortisolism with a serum cortisol< 16 mcg/dl. This would amount to a true incidence of 13 patients(21%). Hence the possibilities considered for the hypocortisolemia in these patients postoperatively could be either inadequate preservation of the adenohypophysis or an infarction of the gland postoperatively. The remaining 6 of the 19 patients who had hyponatremia with or without symptoms were able to produce a good cortisol response> 16 mcg/dl and might have benefitted from an evaluation for other causes of hyponatremia as SIADH or a cerebral salt wasting syndrome.

16 patients developed hyponatremia of which 10 patients had a serum cortisol level < 16 mcg/dl on postoperative days as described in Fig 10. The cortisol index for Day 1 was calculated for these 10 patients and it was also noticed that 6 patients had a postoperative surge of cortisol on day 1 after surgery and the remaining 4 patients had a drop in the serum cortisol with a negative cortisol index. (Appendix 2). It was observed that the mean cortisol index was 6.5 mcg/dl for these 10 patients. This as compared to the study by Zada et al[27] where the mean cortisol index estimated retrospectively for the patients who required steroids which was -2.8 mcg/dl suggesting that the actual number of patients who required steroids might have been lower than this group of 19 patients who were required steroids.

It was also noticed in our study that of the 16 patients who developed hyponatremia, 10 patients developed a delayed hyponatremia (which is on day 7 or later) indicating that even though the immediate postoperative cortisols were normal on days 1,2 and 3, a delayed hypocortisolemia could still occur. The causes considered for this could be an infarcting residual adenohypophysis or an insufficient preservation of the adenohypophysis. But other causes of delayed hyponatremia need to consider too as SIADH and CSW since the first three days postoperatively were uneventful.

All these 19 patients were continued on steroids at discharge for benefit of doubt. At a follow up 3-6 months after surgery of these 19 patients who required steroids in the immediate postoperative period, 5 patients became off steroids at 3-6 months follow up while 6 patients were continued on steroids and 8 lost follow up. This might suggest the possibility of either a transient postoperative hypocortisolemia or a possibility of an SIADH/Cerebral salt wasting syndrome.

Hyponatremia in the postoperative period

The incidence of hyponatremia in the Groups 1 and 2 were 22.9% and 20.45% respectively. This almost equal incidence of hyponatremia in the 2 Groups suggests that withholding steroids might not be responsible for the hyponatremia and hence a detailed evaluation should be done to identify the appropriate management of postoperative hyponatremia to avoid over treatment with postoperative long term steroids. This puts down the fact that there were other causes of hyponatremia which need to be considered along with hypocortisolism. This also suggests a detailed evaluation to distinguish between syndrome of inappropriate antidiuretic hormone secretion and cerebral salt wasting syndrome which could also form major causes of hyponatremia in the postoperative period in patients undergoing surgery for pituitary adenomas.

Steroids and incidence of diabetes insipidus

A pituitary adenoma, regardless of the size, rarely causes diabetes insipidus (DI) before surgical intervention[36]. Hence steroids are capable of unmasking diabetes insipidus in the postoperative period in patients undergoing surgery for pituitary adenomas. In our study, there was a significant increase in the incidence of diabetes insipidus in patients who received perioperative steroids (Group 2),9.09% as compared to the patients in Group 1 who did not receive postoperative steroids,3.27% (Table 2).

The preservation of normal adenohypophysis during surgery is the ultimate factor determining preservation of the HPA axis. Hence when the surgeon recognizes that he is not able to preserve the adenohypophysis during surgery, postoperative steroids should be given irrespective of the immediate postoperative cortisol levels.

Based on the above data, we identify the incidence of preoperative hypocortisolemia to be 19% which would help filter the patients who might benefit from withholding steroids. This would also stem from the use of a reliable definitive test for the assessment of the HPA axis preoperatively as the Synacthen test. This would also avoid labelling patients as hypocortisolemic based on the 8 Am serum cotisol alone but who can produce an appropriate response to Synacthen test.

The true incidence of hypocortisolemia from our study was 21% (13 patients) including those who had a definite low serum cortisol<3.6 mcg/dl(5 patients) and those 8 patients with a cortisol<16 mcg/dl but with hyponatremia or became symptomatic. Hence the remaining 6 of 19 patients who required steroids postoperatively with hyponatremia could have been evaluated for other causes and long term steroids prevented. We recommend withholding of steroids perioperatively in a clinical set up where the patients would be on continous monitoring and hypocortisolemia was picked up early and to better give the routine steroid cover for the rest since 21% patients carried the risk of hypocortisolemia as per our study.

The incidence of hyponatremia in the Groups 1 and 2 were almost similar indicating that patients on steroids too can develop hyponatremia due to other causes as SIADH and CSW. Hence hypocortisolemia if not strongly considered as the cause of hyponatremia when the serum cortisol levels rose to > 16 mcg.dl, evaluation for hyponatremia need to be done to avoid long term steroids unnecessarily.

There has a mean postoperative cortisol surge of 56% in our study with a mean positive surge I the 19 patients who required steroids too indicating that further trials need to be considered to determine the cut off for the % surge considered appropriate for an intact HPA axis.

HPA axis in the long term

In our study, in the first follow up visit 3-6 months after the surgery, all 42 patients who did not receive perioperative steroid cover remained off steroid supplementation at 3-6 month follow up and of the 19 patients who received steroids in study Group 1, 5 did not require steroid supplementation at 3-6 month follow up and 6 were continued on steroids while 8 patients lost to follow up.

CONCLUSION

1) Incidence of preoperative hypocortisolemia- 19%

2) Preservation of adenohypophysis at surgery was- 100%

3) Incidence of definite postoperative hypocortisolemia – 8% (5/61 patients)

4) Incidence of hyponatremia was 84%

5) There was a documented 56% surge of cortisol on Day 1 following surgery in the 61 Group 1 patients with a maximum surge of 111%.

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APPENDIX I

INFORMED CONSENT

SUBJECT NAME

DATE OF BIRTH/AGE

1) I confirm that I have read and understood the information sheet dated.............for the above study and have and the opportunity to ask questions.

2) I understand that my participation in the study is voluntary and that I am free to withdraw at any time. without giving any reason, without my medical care or legal rights being affected.

3) I understand that the institution and the regulatory authorities will not require my permission in the future to look into my health records in respect to this study or any further research in relation to it, even if I withdraw from this trial. I understand that my identity will not be revealed in any information released to third parties or published.

4) I agree not to restrict use of any data from this study provided it is only for scientific purposes.

5) I agree to participate in this study.

Signature of the patient   Signature of the parent / Guardian / Relative

                                             Name & relationship

Signature of the doctor   Name of the doctor
                                             Date:

INFORMATION SHEET

The patients included in this study are those who have been planned for surgeries involving the pituitary gland.

The pituitary gland in the brain produces hormones one of which is steroid. After pituitary surgery the levels of these steroids in the blood may come down. Hence we give steroids in injection form to all patients undergoing surgeries of the pituitary gland.

But steroids have their own side effects like it might cause increased production of urine, increased thirst and dehydration and causing abnormal levels of certain electrolytes in blood. This can be a difficult problem after surgery. It might also cause rise in blood sugars, delayed healing of wound, rise in blood cholesterol and decrease in bone strength when given for a long time. Also by giving steroids for all patients undergoing pituitary surgeries, we will not be able to test immediately whether the pituitary gland has recovered its normal function after the removal of the tumour.

Hence this study is aimed to give steroids only to those who need them. The blood levels of steroids are checked before the surgery, if the levels are low, steroids are given during the surgery. If blood steroid levels are normal there is evidence that patient will not require steroid cover during surgery. After the surgery steroid levels are monitored for 3 days.

At any point of time, if there is a reduction in blood levels of steroids or the patient has symptoms, steroids will be given immediately.

It is also to be informed that this method of giving steroid medicines only if required has been accepted and is being practised in other countries (USA, Australia).

APPENDIX II

PERIOPERATIVE DATA IN STUDY GROUP 1 (61 Patients)

SNO	Hospital number	Age	Gender	Diagnosis	Hardys_grade	Date of surgery	Preop_cortisol8am	Synacthen Done	PostSynacthen cortisol	Apoplexy	Extent of excision	hypophysis preser	DI	Postop_Cortisolday1	Postop_Cortisolday2	Postop_Cortisolday3	Cortisolfollowup
1	099936F	27	M	Non Functional	C	21-Feb-12	9.9	Yes	24.85	Yes	Radical	Yes	No	15.15	1.91	5.7	12.79
2	955979D	37	M	GH	A	21-Jun-11	11.4	Yes	28.69	Yes	Radical	Yes	No	13.44	16.14	7.25	16.08
3	099870F	30	F	GH	B	12-Jan-12	10.36	Yes	21.08	No	Radical	Yes	No	22.73	10.77	5.34	6.51
4	664565D	53	M	Non Functional	B	03-Nov-10	20.68	No		No	Radical	Yes	No	25.71	4.57	18.82	13.11
5	885104D	50	F	Non Functional	B	07-Jun-11	20.19	No		No	Radical	Yes	No	21.02	6.46	7.06	0
6	193625F	32	M	Non Functional	C	30-May-12	9.43	Yes	22.52	No	Radical	Yes	No	28.34	17.64	11.3	12.36
7	142723F	39	F	GH	B	11-Jun-12	11.8	Yes	24.41	No	Radical	Yes	No	30.08	28.05	15.12	11
8	141727F	27	M	GH	A	16-Mar-12	12.99	Yes	22.81	No	Radical	Yes	No	5.95	21.3	8.19	0
9	812862D	40	F	GH	A	25-May-11	9.78	Yes	33.88	No	Radical	Yes	No	25.85	5.75	13.1	9.09
10	762194D	44	F	GH	C	25-Oct-10	6.95	Yes	22.62	No	Partial	Yes	No	25.79	12.76	15.22	12.22
11	271159F	28	F	Non Functional	B	07-Sep-12	19.81	No		No	Partial	Yes	No	16.95	10.93	9.02	18.42
12	087359F	35	M	GH	micro	02-Mar-12	24.65	No		No	Radical	Yes	No	6.4	13.61	12.93	0
13	331910F	34	M	Non Functional	C	13-Nov-12	7.1	Yes	22.9	Yes	Radical	Yes	No	19.9	9.69	10.25	0
14	964180D	31	F	GH	B	04-Aug-11	6.88	Yes	23.27	Yes	Partial	Yes	No	13.92	19.59	10.25	18.36
15	977989D	55	M	Non Functional	C	12-Aug-11	18.23	No		No	Radical	Yes	No	28.36	14.44	17.26	12.36
16	019188F	47	F	GH	B	06-Dec-11	17.03	No		No	Radical	Yes	No	13.2	21.37	15.85	0
17	197621F	36	F	GH	A	20-Jul-12	4.29	Yes	29.26	No	Radical	Yes	No	10.47	14.1	5.6	12.75
18	991943D	29	M	GH	A	25-Oct-11	6.01	Yes	21.03	No	Partial	Yes	No	13.18	14.53	7.91	11.38
19	926428D	57	M	Non Functional	C	19-Jul-11	10.81	Yes	24.35	No	Partial	Yes	No	21.88	1.38		7.05
20	056222F	37	F	Non Functional	C	10-Nov-11	13.78	Yes	23.8	No	Partial	Yes	No	33.2	26.9	20.5	17.49
21	938672D	61	M	GH	C	22-Jun-11	12.36	Yes	33.06	No	Partial	No	No	14.06	8.68	28.29	8.55
22	165953F	46	F	Non Functional	C	10-Apr-12	14.21	Yes	25.2	No	Radical	Yes	No	5.58	5.78	10.93	0
23	745702D	50	F	GH	Micro	15-Nov-10	6.17	Yes	25.02	No	Radical	Yes	No	10.68	5.73	14.49	9.33
24	297575F	61	F	Non Functional	C	08-Oct-12	16.43	No		No	Radical	Yes	No	0	0	0	0
25	052880F	36	F	GH	C	07-Dec-11	10.4	Yes	24.6	No	Radical	Yes	No	44.02	33.26	18.82	13.13
26	682313D	39	M	Non Functional	micro	26-Nov-10	5.39	Yes	24.05	No	Partial	Yes	No	26.05	16.49	10.86	0
27	877898D	63	F	Non Functional	C	11-Feb-11	14.53	Yes	29.9	No	Partial	Yes	No	47.27	31.23	25.45	0
28	884187D	59	M	Non Functional	B	08-Jun-11	14.09	Yes	26.66	No	Radical	Yes	No	22.96	13.15	9.23	15.23
29	344331F	40	F	GH	A	13-Dec-12	9.1	Yes	29.02	No	Partial	Yes	No	36.28	16.91	13.95	0

30	164732F	36	M	GH	B	07-Aug-12	22.2	No		No		Partial	Yes	No	16.94	23.7	23.37	22.96
31	001082F	30	M	Non Functional	C	30-Aug-11	19.04	No		No		Radical	Yes	No	33.9	42.71	23.6	14.05
32	899179D	59	M	Non Functional	B	13-Jun-11	19.14	No		No		Radical	Yes	Yes	12	4.04		0
33	956745D	27	M	GH	E	27-Jun-11	18.92	No		No		Partial	Yes	No	1.88			6.54
34	914364D	55	M	Non Functional	C	20-Apr-11	17.19	No		No		Radical	Yes	No	15.19	6.15	7.5	13.85
35	670599D	47	M	GH	micro	02-Jun-10	21.4	No		No		0	Yes	No	17.8	17.9	12.13	13.37
36	088178F	30	M	GH	A	24-Jan-12	9.63	Yes	27.31	No		Partial	Yes	No	14.32	8.27	8.29	21.67
37	890089D	36	F	Non Functional	C	10-Mar-11	24.29	No		Yes		Radical	Yes	No	17.66	25.32	13.56	
38	969191D	29	F	GH	B	27-Sep-11	9.77	Yes	23.86	No		Partial	Yes	No	14.93	10.8	6.17	11.96
39	007323F	39	M	GH	E	03-Jan-12	9.72	Yes	24.2	No		Partial	Yes	No	10.1	0	0	12.65
40	258320F	27	M	GH	A	21-Nov-12	20.1	No		No		Partial	Yes	No	30.05	12.91	17.92	19.58
41	992206D	62	M	Non Functional	B	08-Aug-11	6.37	Yes	29.85	No		Partial	Yes	No	12.28	13.87	9.63	8.05
42	357578B	37	F	GH	B	21-Nov-11	23.77	No		No		Radical	Yes	No	36.4	19.2	19.46	4.55
43	751305D	33	F	GH	B	19-Oct-10	9.98	Yes	26.17	Yes		Partial	Yes	No	31.63	12.09	9.5	6.28
44	772715D	24	M	Non Functional	C	16-Dec-10	16.63	No		No		Partial	Yes	No	0	0	0	12.48
45	085878F	44	M	Non Functional	B	27-Jan-12	13.41	Yes	36.1	No		Radical	Yes	No	37.8	23.53	15.6	7.19
46	726302D	29	F	GH	B	30-Aug-10	21.93	No		Yes		Partial	Yes	No	15.95	20.72	21.04	10.16
47	793545D	36	F	Non Functional	C	20-Oct-10	18.34	No		No		Partial	Yes	Yes	28.31	19.58	11.46	9.69
48	175641F	46	F	Non Functional	C	02-May-12	12.36	Yes	24.4	No		Partial	Yes	No	12.1	4.6	3.26	0
49	355697F	42	M	GH	A	03-Jan-13	10.24	Yes	28.7	No		Radical	Yes	No	13.9	15.22	12.85	10.81
50	138544F	43	F	GH	A	23-Mar-12	17.74	No		No		Radical	Yes	No	19.29	7.8	6.12	0
51	172765F	46	M	Non Functional	D	20-Apr-12	11.73	Yes	25.67	No		Radical	Yes	No	43.61	29.6	23.71	12.12
52	795815D	30	F	GH	C	09-Nov-10	14.59	Yes	20.8	Yes		Partial	Yes	No	17	18.16	18.2	12.53
53	963423D	46	F	GH	Micro	29-Mar-12	23.29	No		No		Radical	Yes	No	41.7	12.01	22.67	10.7
54	763465D	25	F	GH	C	20-Sep-10	6.8	Yes	23.54	No		Radical	Yes	No	18.16	17.19	15.21	0
55	855540C	26	F	GH	A	22-Feb-11	36.52	No		No		Partial	Yes	No	75	22.94	23.91	12.6
56	799431D	23	F	GH	B	10-Nov-10	18.42	No		Yes		Radical	Yes	No	5.6	13.02	20.62	19.94
57	822299D	45	F	Non Functional	C	30-Nov-10	13.75	Yes	24.8	No		Radical	Yes	No	23.74	4.5	2.5	0
58	751089D	42	F	GH	C	16-Sep-10	18	No		Yes		Partial	Yes	No	24.8	12.14	12.07	14.86
59	146661C	52	F	GH	micro	11-Aug-11	9.88	Yes	21.88	No		Radical	Yes	No	14.05	18.73	32.59	13.54
60	874610D	31	M	GH	A	04-May-12	10.35	Yes	29.42	No		Radical	Yes	No	16.02	22.36	13.1	
61	709269D	50	F	GH	B	28-Jun-10	10.29	Yes	25.97	No		Partial	Yes	No	49.59	25.48	30.58	30.58

PERIOPERATIVE DATA FOR GROUP 2 PATIENTS (44 PATIENTS)

SNO	Hospital number	Age	Gender	Diagnosis	Hardys_ grade	Date of surgery	Preop_cortisol8 am	Apoplexy	Extent of excision	Diabetes insipidus	Hyponatremia	Hyponatre miaday
1	760015D	47	F	GH	C	03-Dec-10	7.62	No	Partial	No	No	
2	005174F	51	M	Non Functional	B	17-Nov-11	6.97	Yes	Partial	No	Yes	3
3	925277D	55	M	Non Functional	D	24-Jun-11	0.6	No	Partial	No	No	
4	901535C	31	M	Non Functional	B/E	01-Feb-11	2.72	No	Partial	Yes	No	
5	891454D	63	M	Non Functional	C	14-Apr-11	12.04	No	Partial	No	Yes	11
6	884800D	29	M	Non Functional	C	10-Jun-11	9.84	No	Partial	No	Yes	7
7	879119D	25	F	GH	D	25-Feb-11	25.33	No	Partial	No	No	
8	857213D	35	M	Non Functional	B	03-Mar-11	3.37	No	Partial	No	No	
9	839927D	24	F	GH	E	24-May-11	14.08	No	Partial	No	No	
10	828220D	56	M	Non Functional	C	09-Aug-11	2.68	No	Partial	No	No	
11	932947D	50	F	Non Functional	B	06-Aug-11	13.54	No	Radical	No	No	
12	781342D	32	M	GH	D	16-Mar-11	14.62	No	Partial	No	Yes	3
13	935676D	39	M	Non Functional	C	07-Jun-11	10.8	No	Partial	No	No	
14	734903D	37	M	GH	B	07-Sep-10	6.39	No	Radical	Yes	No	
15	671091D	45	M	GH	micro	09-Sep-10	6.55	No	0	No	Yes	7
16	549217C	46	F	Non Functional	C	24-Nov-11	1.15	No	Partial	Yes	No	
17	437590D	47	F	Non Functional	C	30-Jun-10	14.28	Yes	Partial	No	No	
18	071882F	29	M	GH	B	09-Dec-11	7.12	No	Radical	No	No	
19	058446F	63	M	Non Functional	B	11-Nov-11	8.08	No	Radical	No	Yes	5
20	058312F	31	F	GH	B	08-Dec-11	4.28	No	Partial	No	No	
21	056280F	26	M	GH	C	05-Dec-11	5.52	Yes	Partial	No	No	
22	022366D	57	M	GH	A	04-Nov-11	4.76	No	Radical	No	No	
23	811388D	25	M	GH	B	16-Feb-11	3.42	Yes	Partial	No	No	
24	036786F	44	F	Non Functional	C	11-Jun-12	0	No	0	No	No	
25	305276F	41	F	GH	C	29-Sep-12	16.23	Yes	0	Yes	No	
26	292428F	36	F	Non Functional	C	26-Sep-12	2.3	No	0	No	No	
27	285618F	25	M	GH	C	27-Sep-12	13.03	No	0	Yes	No	
28	235139F	32	F	GH	C	10-Sep-12	4.5	No	0	No	No	
29	092528C	66	M	Non Functional	C	04-Sep-12	7.18	Yes	0	No	No	
30	190054F	34	F	Non Functional	C	21-Aug-12	4.44	No	0	No	No	

31	260258F	50	F	Non Functional	C	14-Aug-12	0	No	0	No	No	
32	904624D	25	M	Non Functional	B	24-Jul-12	0	Yes	0	Yes	No	
33	926022D	48	M	Non Functional	C	12-Oct-11	12.03	No	Radical	No	Yes	7
34	215440F	23	M	Non Functional	C	22-Jun-12	10.46	No	0	No	No	
35	325427F	45	M	Non Functional	D	15-Nov-12	0.92	No	0	Yes	Yes	6
36	183864F	54	M	Non Functional	C	28-May-12	10.2	No	0	No	No	
37	162533F	40	F	Non Functional	C	15-May-12	8.7	No	0	No	No	
38	186791F	41	M	Non Functional	C	07-May-12	19.27	Yes	0	Yes	No	
39	100232F	39	F	Non Functional	C	15-Mar-12	4.71	No	0	No	Yes	1
40	088305F	48	M	Non Functional	C	05-Jan-12	5.18	No	0	No	No	
41	984692D	55	M	Non Functional	C	01-Nov-11	1.5	No	Partial	Yes	No	
42	982386D	34	M	Non Functional	C	18-Aug-11	25.47	No	Partial	No	No	
43	967645D	44	F	Non Functional	C	23-Jun-11	4.8	No	Partial	No	No	
44	230682F	35	F	GH	C	04-Jul-12	9.6	Yes	0	No	No	

APPENDIX III

STUDY PROFORMA

Serial no:

Date

Name

Age/ Sex   Hospital number

Diagnosis / Previous surgery

Functioning / Non functioning

If functioning, type

Hardy's grade

Comorbidities

Duration of symptoms

H/O of Apoplexy

Preoperative cortisol levels (8 am)

Other Harmonal levels   T4   TSH   FTC

                                   FSH   LH   Prolactin

                                   HGH   IGF-1

Synacthen test   Yes   No

Post Synacthen serum cortisol, if done

Eligible for the study   Yes   No

1

Date of surgery

Extent of tumour excision

Pituitary gland seen during surgery

Gland preserved   Yes   No   Could not comment

Introperative complications, if any

Serum cortisol levels in **mcg/100ml** on the following postoperative days

Day 1	Day 2	Day 3	Day 7	6 months

Serum sodium and potassium
levels in **mEq/L**

	Preop	Day 1	Day 2	Day 3
Sodium				
Potassium				

Post op DI   Yes (Transient/Permanent)   No

Symptoms of hypocortisolemia,   Yes   No

Symptoms   Persistent vomiting   Hyponatremia   Hypotension

Delayed hyponatremia   Yes   No

Cause   Hypocortisolemia/ cerebral salt wasting/ SIADH

Serum cortisol level

Steroid supplementation   Yes   No

2

Follow up (3-6 months) :

H/o hypocortisolemia crisis :   Yes   No

Treatment -   on steroids / off steroids

If on steroids- prednisolone :   5mg od / 2.5 mg od / 5mg on A/D

If off steroids – 8am cortisol: post synacthen cortisol:

Long term steroid :   required / not required.