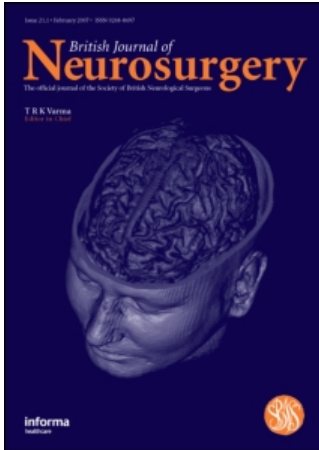


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ORIGINAL ARTICLE

Hydrocortisone dose and postoperative diabetes insipidus in patients undergoing transsphenoidal pituitary surgery: a prospective randomized controlled study

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Abstract

We report the results of a prospective randomized controlled trial, which looked at the incidence of postoperative diabetes insipidus (DI) following the use of three different hydrocortisone protocols, and the results of a study, on the incidence of DI and cortisol response in patients not given hydrocortisone. In study 1, 114 patients with pituitary macroadenoma were randomized into three groups: conventional dose (inj. hydrocortisone 100 mg IV 6-hourly for 3 days); intermediate dose (inj. hydrocortisone 100 mg IV 6-hourly on day 1, 100 mg IV 8-hourly on day 2, and 100 mg IV 12-hourly on day 3); low dose protocol (inj. hydrocortisone 25 mg IV 6-hourly on day 1, 25 mg IV 8-hourly on day 2 and 25 mg IV 12-hourly on day 3). Radical excision was achieved in 92 patients. The incidence of DI with the conventional dose was 52%, intermediate dose, 36% and low dose, 24% ($p = 0.025$). Study 2 included 16 consecutive patients with Hardy's grade A & B pituitary adenoma. These patients were randomized to receive (Group I) or not receive (Group II) hydrocortisone. Patients in Group II demonstrated normal cortisol response intraoperatively and no patient developed features of hypocortisolism; the incidence of DI in this group was 14%. The low dose hydrocortisone protocol reduced the incidence of DI by 46% when compared with the conventional dose hydrocortisone protocol. In patients with grade A and B tumour with normal preoperative cortisol levels, the use of perioperative hydrocortisone can be avoided.

Key words: *Diabetes insipidus, hydrocortisone, pituitary surgery.*

Introduction

Diabetes insipidus (DI) is a common problem encountered following transsphenoidal pituitary surgery. The reported incidence of temporary DI^{1–4} following surgery ranges from 10 to 66% and the incidence of permanent DI^{3–7} ranges from 0.4 to 15%. DI following pituitary surgery contributes to patient morbidity, prolongs their hospital stay and increases cost of treatment.

Anti-diuretic hormone (ADH) in addition to its action on the renal collecting ducts, is also known to act on the pituitary gland as a potent corticotrophin releasing factor (CRF). Intravenous hydrocortisone and dexamethasone are used for steroid cover during transsphenoidal pituitary surgery. In patients with poor ADH reserve, these exogenous steroid preparations are known to inhibit ADH release and precipitate DI.⁸ This inhibitory effect may be dose dependent. Audrey *et al.*⁸ had observed that large

doses of corticosteroids suppress arginine vasopressin (AVP) secretion. They noted that in patients on high doses of corticosteroids, a greater increase in plasma osmolarity is required for an equivalent stimulation of AVP release.

Symreng *et al.*⁹ studied adrenal function in long-term steroid treated patients undergoing major elective surgery. They observed that the low-dose hydrocortisone regimen (25 mg at induction of anaesthesia followed by a continuous infusion of hydrocortisone 100 mg during the next 24 h) was sufficient for substitution therapy during surgery and in the early postoperative phase. Udelsman *et al.*¹⁰ examined the effects of different doses of glucocorticoids on haemodynamic adaptation during surgical stress in adrenalectomized primates and concluded that there is no apparent advantage in supraphysiological glucocorticoid prophylaxis during surgical stress in primates. Neurosurgical literature, however, still recommends high dose peri-operative corticos-

teroid cover for patients undergoing transsphenoidal pituitary surgery.¹¹

In our institution, the conventional steroid protocol for patients undergoing transsphenoidal pituitary surgery, consisted of 100 mg intravenous hydrocortisone given on the night prior to surgery, followed by 100 mg given every 6 h for the next 72 h. In a retrospective analysis, we observed that 55% of our patients on this regime, developed DI in the post-operative period (unpublished data).

The present study was undertaken to determine the relationship between perioperative hydrocortisone dose and the incidence of postoperative DI. A recent study¹² found that patients with Cushing's disease could be operated on without hydrocortisone cover. We, therefore, prospectively evaluated a group of patients with normal basal cortisol, who received transsphenoidal pituitary surgery with and without perioperative hydrocortisone cover.

Patients and methods

Study 1

A randomized controlled trial was undertaken using three different hydrocortisone dose protocols for patients undergoing transsphenoidal pituitary surgery. One-hundred-and-fourteen consecutive patients were randomized 1 day prior to surgery into one of three groups. All patients had a central venous catheter inserted for assessment of the status of hydration. Patients with polyuria also had a urinary catheter inserted, for accurate assessment of hourly urine output. Blood pressure, vital signs and electrolytes were closely monitored in the Neurosurgical ICU. Any patient who developed hypotension, hyponatraemia or clinical deterioration was to be immediately changed over to the conventional hydrocortisone protocol.

Group 1: conventional dose hydrocortisone protocol

These patients received hydrocortisone 100 mg intravenously every 6 h for 72 h, starting from the night prior to surgery.

Group 2: intermediate dose hydrocortisone protocol

These patients received hydrocortisone for 72 h starting from the time of induction of anaesthesia. They received 100 mg intravenously every 6 h on day 1, every 8 h on day 2 and every 12 h on day 3 following surgery.

Group 3: low dose hydrocortisone protocol

These patients received hydrocortisone for 72 h starting from the time of induction of anaesthesia. They received 25 mg intravenously every 6 h on day

1, every 8 h on day 2 and every 12 h on day 3 following surgery.

Diabetes insipidus was diagnosed when all three of the following criteria were fulfilled:

- polyuria (urine output > 500 ml/h for three consecutive hours);
- serum sodium > 145 meq/l* [serum sodium was used as a measure of serum osmolarity, as we find that serum osmolarity measurements are unreliable in our facility (M. S. Seshadri, unpublished observation)];
- urine osmolarity < 300 mosm/kg.

Study 2

After receiving approval from the Institutional Review Board, 16 consecutive patients with Hardy's tumour grade A and B, were randomized into two groups before surgery. They included patients with the following types of tumours: acromegaly (seven), non-functioning tumours (five) and prolactinoma (four).

The inclusion and exclusion criteria for this study are mentioned in Table I. The baseline cortisol values of these patients is given in Table II.

Group I patients were given hydrocortisone according to the low dose protocol in Study 1 (inj.

TABLE I. Inclusion and exclusion criteria (Study 2)

	Inclusion criteria	Exclusion criteria
Age	15–55 yrs	< 15 or > 55 yrs
8 a.m. cortisol*	> 7 µg/dl	< 7 µg/dl
4 p.m. cortisol*	> 2 µg/dl	< 2 µg/dl
Hardy's tumour grade	A and B	C, D and E
Features of apoplexy	Absent	Present
Steroid therapy	Not on steroids	On steroids

*Serum cortisol normal range.

8 a.m.: 7–25 µg/dl (193–690 nmol/l).

4 p.m.: 2–9 µg/dl (55–248 nmol/l).

Conversion factor X 27.6.

TABLE II. Baseline cortisol levels of patients (Study 2)

	Group I (with hydrocortisone) Baseline serum cortisol (µg/dl)		Group II (without hydrocortisone) Baseline serum cortisol (µg/dl)	
	8 a.m.	4 p.m.	8 a.m.	4 p.m.
1	16.2	6	19.52	8.47
2	15.5	8.6	15.27	-
3	12.59	4.13	12.3	4
4	12	11.3	13.75	7.79
5	7.25	5	14.4	6.6
6	10.2	8.43	12.33	4.47
7	16.28	6.7		
8	15.72	9.06		
9	17.48	-		

hydrocortisone 25 mg IV 6-hourly on day 1, 25 mg IV 8-hourly on day 2 and 25 mg IV 12-hourly on day 3), while patients in Group II did not receive hydrocortisone.

In Group I patients, serum cortisol was estimated 6 h following surgery. In Group II patients (i.e. those who did not receive hydrocortisone), serum cortisol was estimated at the following time points:

- at induction of anaesthesia;
- towards the end of surgery;
- 6 h following surgery;
- at 8 a.m. on the day following surgery;
- at 4 p.m. on the day following surgery.

These patients were closely monitored in the Neurosurgical ICU. Their blood pressure was continuously monitored. Serum electrolytes were monitored at 6-hourly intervals, and a strict record of their fluid intake and output was maintained.

Group II patients who developed low blood pressure, hyponatraemia and low cortisol levels ($< 10 \mu\text{g/dl}$), documented on two consecutive occasions, were to be given inj. hydrocortisone and considered to have failed the treatment.

Fluid management

The perioperative fluid management was guided by CVP, urine output and serum sodium values. The intravenous fluid administration was adjusted based on the hourly urine output. Four-hourly urine output + 100 ml would be replaced over the next 4 h. One-hundred millilitres were added every 4 h to take care of insensible water loss. If the serum sodium decreased to less than 135 mmol/l or if CVP was less than 5 cm, the rate of IV fluid administration was adjusted appropriately. If the serum sodium increased to more than 145 mmol/l and if urine osmolarity was $< 300 \text{ mosm/kg}$ treatment for diabetes insipidus was initiated with inj. pitressin and the rate of fluid administration was reduced appropriately to avert iatrogenic hyponatraemia.

Postoperative imaging

Contrast-enhanced CT of the head was performed on the seventh postoperative day to determine the extent of tumour removal.

Statistical analysis

True Epistat 5.3 (Epistat Services, Richardson, TX) a medical statistics software package, was employed to organize data and perform statistical analysis. Differences between the different groups were analysed using the χ^2 test and p value < 0.05 was considered as significant.

Results

Study 1

During the study period 114 patients with pituitary macroadenoma underwent transsphenoidal pituitary surgery. Thirty-two patients were allotted to Group 1 (conventional dose hydrocortisone protocol), 30 to Group 2 (intermediate dose hydrocortisone protocol) and 52 to Group 3 (low dose hydrocortisone protocol). Table III, shows the extent of surgery in relation to the grade of tumour. Only at the end of surgery could we determine which patient had undergone total tumour excision and which patient had undergone partial tumour excision. This resulted in unequal numbers in the three groups.

Radical excision (confirmed by postoperative contrast-enhanced CT) was possible in 23/32 in Group 1, 28/30 in Group 2 and 41/52 in Group 3. Thus, radical excision of tumour was achieved in 92 of the 114 patients (81%) with pituitary macroadenoma. These 92 patients were those included in the final analysis. Details of these 92 patients has been included in Table IV. All the three groups were comparable in sex distribution, age, type of tumour and hormonal profile.

The incidence of DI in all the 92 patients with pituitary macroadenoma following radical excision of tumour is shown in Table V.

Of the 32 patients who developed DI, 19 had a serum sodium levels $> 150 \text{ mmol/l}$ at the time of diagnosis.

With the low dose protocol, the incidence of DI was reduced by 46% as compared with the conventional dose protocol ($p = 0.025$). None of the patients assigned to the low dose hydrocortisone protocol needed to change over to the conventional dose.

Overall, 32 (35%) patients developed DI following radical excision of pituitary macroadenoma. In 25 (78%) patients, DI resolved¹⁻⁴ prior to their discharge from hospital.

Seven (22%) patients [conventional dose (one), intermediate dose (two) and low dose (four)] continued to have DI at the time of discharge. Polyuria in these seven patients was well controlled with carbamazepine.^{13,14} They were advised to continue carbamazepine 300mg per day till review. At 6 months follow-up, DI had resolved in three

TABLE III. Tumour grade and extent of surgery (Study 1)

Tumour grade	Partial excision	Radical excision	Total
A	2	22	24
B	6	22	28
C	7	30	37
D	3	5	8
E	4	13	17
Total	22	92	114

TABLE IV. Demographic details of patients who underwent radical excision of tumour (Study 1)

	Group 1 (23) Conventional dose (%)	Group 2 (28) Intermediate dose (%)	Group 3 (41) Low dose (%)
Sex			
Male	16 (70)	14 (50)	30 (73)
Female	7 (30)	14 (50)	11 (27)
Age			
Range (years)	16–57	16–57	16–66
Mean (years)	39	39	41
Type of tumour			
Non functioning	9 (39)	13 (46)	21 (51)
GH secreting	–	4 (14)	7 (17)
Prolactinoma	11 (48)	6 (21)	7 (17)
ACTH secreting	2 (9)	5 (18)	4 (10)
FSH secreting	1 (4)	–	1 (2)
TSH secreting	–	–	1 (2)
Hormonal status			
Normal profile	7 (30)	11 (39)	19 (46)
Partial hypopituitarism	10 (43)	11 (39)	17 (41)
Pan hypopituitarism	6 (26)	6 (21)	5 (12)
Tumour grade			
A	4 (17)	7 (25)	10 (24)
B	8 (35)	4 (14)	11 (27)
C	5 (22)	12 (43)	13 (32)
D	1 (4)	2 (7)	2 (5)
E	5 (22)	3 (11)	5 (12)

TABLE V. Incidence of DI following radical excision of pituitary macroadenoma (Study 1)

Hydrocortisone protocol	No. of patients (92)	No. with DI
Conventional dose	23	12 (52%)
Intermediate dose	28	10 (36%)
Low dose	41	10 (24%)*

Low dose versus intermediate dose $p=0.308$.

*Low dose versus conventional dose $p=0.025$.

patients and carbamazepine was stopped, the other four required long-term treatment with carbamazepine for control of symptoms. The incidence of permanent DI^{3–7} following transsphenoidal radical excision of tumour was only 4%.

Study 2

This study looked at the cortisol response and the incidence of DI in patients who underwent transsphenoidal pituitary surgery without the use of hydrocortisone.

The mean serum cortisol level, 6 h after surgery in patients who received inj. hydrocortisone IV 6-hourly on day 1 (Group I) was 28 $\mu\text{g}/\text{dl}$.

The serum cortisol response (mean \pm SD) at various time points, in patients who did not receive inj. hydrocortisone (Group II) is as follows:

At induction of anaesthesia	8.5 \pm 3 $\mu\text{g}/\text{dl}$
Towards the end of surgery	18 \pm 2.5 $\mu\text{g}/\text{dl}$
6 h after surgery	26.5 \pm 3.5 $\mu\text{g}/\text{dl}$

8 a.m. on the second postoperative day	14.5 \pm 1 $\mu\text{g}/\text{dl}$
4 p.m. on the second postoperative day	16 \pm 5 $\mu\text{g}/\text{dl}$

It is evident that the cortisol values 6 h after surgery are quite similar in the two groups. None of the nine patients in Group I developed DI, while one patient in Group II, who had undergone second stage surgery for acromegaly developed partial transient DI. No Group II patient developed hypotension or hyponatraemia during or after surgery.

Discussion

High doses of parenteral steroids administered in the perioperative period, suppress ADH release and contribute to the high incidence of DI following transsphenoidal pituitary surgery. These observations have been confirmed in previous studies by Audrey *et al.*⁸ who observed that large doses of corticosteroids suppress AVP secretion, so that a greater increase in plasma osmolarity is required for an equivalent stimulation of AVP release. As a corollary, Boykin *et al.*¹⁵ showed that glucocorticoid deficiency is associated with increased hypothalamic synthesis and pituitary release of vasopressin.

For patients who had been on long-term corticosteroid therapy, in contrast to empirical high dose corticosteroid substitution regimes, a low dose substitution regimen was first proposed by Kehlet & Binder¹⁶ in 1973. Subsequently, in 1976, Kehlet¹⁷ reported that the total increment of cortisol in association with major surgery was in the range of 75–150 mg for the first 24 h. During the subsequent 2–3 days cortisol production declined and returned

to control levels, in uneventful cases. These observations are similar to those reported earlier by Hardy and Turner¹⁸ and Hume *et al.*¹⁹. Kehlet¹⁷ then proposed that a bolus dose of hydrocortisone 25 mg at the induction of anaesthesia followed by 100 mg as a continuous infusion for the following 24 h is sufficient to avoid adrenal insufficiency. These observations were subsequently confirmed by Symreng *et al.*⁹ in patients with prolonged hypothalamic-pituitary-adrenal (HPA) axis suppression due to long-term glucocorticoid therapy.

Based on the above studies, we hypothesized that hydrocortisone 25 mg given intravenously every 6 h would provide adequate steroid cover for the stress of transsphenoidal pituitary surgery. In our prospective, randomized single blind study, a dose-response relationship was noted, between the dose of hydrocortisone and the incidence of postoperative DI. The lowest incidence of postoperative DI was seen with the low dose hydrocortisone protocol.

Our Study 2 showed that patients with normal basal cortisol levels and not given hydrocortisone, are able to mount a graded cortisol response to stress. The peak cortisol response was found to occur 6 h following surgery and was similar to the values observed by Jasani *et al.*²⁰ Our study demonstrates that in patients with normal basal serum cortisol levels, the HPA axis responds normally to the stress of transsphenoidal pituitary surgery and the serum cortisol values in these patients match the serum cortisol values obtained with the low dose hydrocortisone protocol. The only patient who developed transient DI was an acromegalic who was subjected to a second surgical procedure, and this by itself is a risk for developing DI.

To our knowledge, there have been no similar studies in the past. Simmons¹² studied the cortisol response of 27 patients with Cushing's disease, operated on without steroid cover. He remarks that exogenous steroid medications are not required for patients with Cushing's disease until remission is determined. Our study extends these observations to patients with other pituitary tumours who have normal basal cortisol values.

Our study suggests that intraoperative hydrocortisone cover is not required for patients with normal basal cortisol levels. In patients who need hydrocortisone cover, use of the low dose regimen significantly decreases the incidence of postoperative DI.

Conclusion

In patients with pituitary macroadenoma who are subjected to transsphenoidal radical excision of tumour, the low dose hydrocortisone protocol reduces the incidence of postoperative DI by 46% when compared with the conventional dose hydrocortisone protocol.

Patients with normal basal cortisol levels, who were not given hydrocortisone, in Study II show normal and appropriate intraoperative and perioperative cortisol response in relation to the stress of transsphenoidal pituitary surgery, indicating that the HPA axis functions normally in these subjects in this situation. In view of the small number of patients studied, this study lacks sufficient power to detect any difference between the two groups, in terms of the incidence of postoperative DI. Larger number of patients will need to be studied, to see if avoidance of hydrocortisone intra- and postoperatively will further reduce the incidence of postoperative DI.

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