A New Perioperative Glucocorticosteroid Replacement Therapy for Cushing's Syndrome

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Abstract

Background: To evaluate the safety and effects of a new perioperative glucocorticosteroid replacement therapy for Cushing's syndrome.

Methods: A simple method of glucocorticosteroid replacement therapy as follow was adopted for 83 cases of Cushing's syndrome patient which were diagnosed before the operation: No glucocorticosteroid was used before operation, but during adrenal adenoma resection 100 mg hydrocortisone was given by intravenous injection and another 200 mg hydrocortisone was given on the day of surgery. On day 1 and day 2 postoperative, 100 mg/12h and 100 mg/24h hydrocortisone were given by intravenous injection respectively. Prednisone(10mg/8h) was given from the day 2 postoperative by oral administration, then 5mg was reduced once a week until a maintenance dosage (5mg) was reached. Clinical symptoms were observed, plasma cortisol and 24h urine cortisol levels were intermittently measured post-operation to evaluate the safety and the curative effect of this new glucocorticosteroid replacement therapy.

Results: Adrenal insufficiency and steroid withdrawal syndrome did not occur with all patients. Compared with the concentration of urine cortisol preoperation, it was significantly decreased on the day 7 postoperative. Plasma cortisol concentration was significantly decreased on day 6 postoperative compared with preoperative. All the patients were followed up to 6 months, plasma cortisol and 24h urine cortisol levels were all normal.

Conclusions: This new glucocorticosteroid replacement therapy was safe, simple, and effective.

Methods

Clinical data

From July 2015 to July 2018, 83 CS patients(21 male, 62 female)who were referred to our hospital for adrenal gland surgery were considered for this study. We reviewed the computerized database of the patients. The ages of these patients are ranged from 22 to 61 and the median age is 33. The course of the disease is from 1.5 months to 51 months. Seventy-eight patients were diagnosed as adrenal adenoma and 5 patients were diagnosed as ACTH-independent macronodular adrenal hyperplasia(AIMAH). All the patients had different degrees of centripetal obesity, moon face, sanguine temperament looks, skin purple striae, and other typical signs of CS. Presurgery, the plasma cortisol is 42.03 ± 16.11 ug/dl (normal value, 15 ± 10 ug/dl) and 24 h urine cortisol is 733.26 ± 388.26 ug/24 h (normal value, 70 ± 40 ug/24 h). All patients underwent CT, and plain CT scan of adrenal show unilateral or bilateral adrenal tumor or nodule, and enhancement scanning of the unnormal site of the adrenal show obviously enhanced.

Laboratory Examination

With all patients, the cortisol circadian rhythm disappeared; Low-dose dexamethasone suppression test and high-dose dexamethasone suppression test can not be inhibited.

Surgical Method

All the patients underwent adrenal resection by the posterior retroperitoneoscopic approach. Seventy-eight adrenal adenoma patients underwent adrenal adenoma resection; Five cases ACTH-undependent adrenal nodular hyperplasia patient underwent total adrenalectomy with the side of obvious hyperplasia. Postoperative pathology confirmed consistent with preoperative diagnosis (Fig-1).

Hormone Replacement Therapy

All the patients did not administrate glucocorticoid before surgery, 100 mg hydrocortisone was given during adrenal resection by intravenous injection,and another 200 mg hydrocortisone was given by intravenous injection on the day of surgery. On day 1 and day 2 postoperative, 100 mg/Q12h and 100 mg/Qd of hydrocortisone was given by intravenous injection respectively. Prednisone(10 mg, Tid) was given from the second day postoperative by oral administration, then 5 mg was reduced every one week until a maintenance dosage (5 mg) was reached. When the levels of plasma cortisol and urine cortisol were normal, the glucocorticosteroid replacement therapy was stopped.

Plasma cortisol and 24 h urine cortisol levels were measured on the day 1, 2, 6, and 7 postoperative during hospitalization, respectively. The blood pressure, heart rate, electrolyte levels, and clinical symptoms of the patients were monitored. All the patients were followed up to 6 months, plasma cortisol and 24 h urine cortisol levels were measured on the month 1, 3, 6 postoperative.

Statistical analysis

The results are presented as mean ± standard deviation. Statistical analysis was performed with SPSS version 17.0 using the T-tests. $P < 0.05$ considered as a significant level.

Results

All the patients had a successful operation. The symptoms of adrenal insufficiency including weakness, fatigue, anorexia, weight loss, nausea, and vomiting were not observed. Mortality was zero. Plasma cortisol and 24 h urine cortisol levels were measured on the day 1, 2, 6, and 7 postoperative during hospitalization, respectively. Compared with preoperative, plasma cortisol levels on the day 1 and 2 postoperative slightly decreased but no statistical significance; Urine cortisol levels significantly rised ($P < 0.05$) respectively on the day 1 and 2 postoperative, and decreased on the day 6 postoperative to a level slightly lower than the levels of preoperative. On the day 7 postoperative, plasma cortisol and urine cortisol levels were all significantly reduced compared with preoperative ($P < 0.05$) (Table 2). All the

patients discharged from our hospital on the day 7 postoperative, and operative incisions well recovered. Plasma cortisol and urine cortisol levels were all significantly decreased on the month 1, 3 and 6 month postoperative compared with preoperative. On the month 6 postoperative, the levels of cortisol in plasma and urine were all normal (Table 3).

Discussion

In the present study, we have adopted a new perioperative glucocorticosteroid replacement therapy for 83 cases of CS patient, and by 6 months of the follow-up survey, we have proved this new therapy is safe, simple, and effective.

Glucocorticosteroid productions play an important role in maintaining the normal physiological function of the heart and circulatory system, and it is regulated by the hypothalamus and pituitary gland, together with the adrenal cortex, called the hypothalamus-pituitary-adrenal axis[8]. CS patients have a high level of cortisol and surgery is the first line for the treatment. Adrenalectomy always associated with an

Table 1
 Patient demographics and adrenal lesionlaterality/multifocality

Gender:		
M	21	(25)
F	62	(75)
Mean ± SDage/median (range)	33.8 ± 18.6/33.2	(22–61)
No. side (%):	38	(46)
Rt	45	(54)
Lt		
No. laterality (%):	61	(73)
Unilat	22	(27)
Bilat		

increased complication rate and long operating times for CS is associated with a significant number of clinical manifestations reflecting the exposure of tissues to high cortisol levels[9, 10]. The prevalence of hypertension in CS is approximately 70%[11, 12], and CS patients always with high cardiovascular risk[13]. A lot of studies have proved the retroperitoneoscopic approach is fast and safe for patients with CS[14]. In this study, all patients received a successful operation by retroperitoneoscopic approach. After adrenalectomy, much less of cortisol is secreted than preoperative, and the hypothalamus-pituitary-adrenal axis and contralateral adrenal can not compensate in a short time which will cause adrenal insufficiency. Postoperative adrenal insufficiency is an important issue as postoperative management of CS patients whose function of contralateral adrenal or pituitary gland is suppressed[15]. For that,

postoperative corticosteroid supplementation is considered mandatory in CS patients. Besides the principal indication of treatment, appropriate levels of perioperative and postoperative doses remain questionable. High dosages of corticoids were always used as a standard in earlier studies that sometimes causing severe complications, such as infectious, reduce bone mineral density, unfavorable metabolic effects and an increased risk of cardiovascular disease[14, 16]. On the contrary, low dosages of corticoids would cause adrenal crisis and threaten the patient's life. So, an appropriate dose for postoperative corticosteroid supplementation plan is needed[15].

Table 2
Comparisons of plasma cortisol and urine cortisol levels within peroperative period (± sd)

Plasma cortisol (ug/dl)	**Urine cortisol (ug/24 h)**	
Preoperation	42.03 ± 16.11	733.26 ± 388.26
Day 1 postoperative	37.63 ± 12.32	1754.12 ± 849.26*
Day 2 postoperative	35.49 ± 10.81	1201.63 ± 597.39*
Day 6 postoperative	17.58 ± 7.92*	633.17 ± 396.28
Day 7 postoperative	14.83 ± 6.68*	392.43 ± 212.66*

* $p < 0.05$

statistical difference compared with CNEI + PBS gruop ($P < 0.05$), statistical difference compared with CNEI + hUCB-MSCs group($P < 0.05$), #statistical difference compared with Sham + PBS group($P < 0.05$).

Furuta. etc. have reported a postoperative corticosteroid supplementation plan as that on the day of surgery, the day 1 and 2 postoperative, 30 mg/Qh100 mg/Q12h and 100 mg/QD hydrocortisone was given by intravenous injection, respectively; From the day 2 postoperative, 20 mg/Q6h hydrocortisone is given by oral administration and then reduced to a maintenance dosage[6]. Although this plan can avoid adrenal crisis, too much glucocorticosteroid is used. In China, the adrenal disease treatment guidelines advised a postoperative corticosteroid supplementation plan as that 2 mg dexamethasone is given by intramuscular injection on the day before operation; 2 mg dexamethasone is given about half an hour before operation by intramuscular injection; Then 100200 mg hydrocortisone is given by intravenous injection during operation and post-operation respectively. From the day 1 postoperative, 2 mg dexamethasone is administrated by intramuscular injection every 6 h, then the dose is gradually reduced to a maintenance dosage [17]. This plan is too complex and with poor compliance. The half-life of cortisol in plasma is 80 to 120 min, and 70% of the cortisol which is secreted by the body or given by intravenous injection will be cleared in 24 h. Based on the above theories, we attempt to build a new, simple, and effective glucocorticosteroid replacement therapy plan for CS patients in this study. Considering the CS patients always have a sanguine temperament and thinning skin and intramuscular injection of glucocorticoid will cause subcutaneous ecchymosis even

Table 3
Comparisons of plasma cortisol and urine cortisol levels within the postoperative follow-up period (± sd)

Plasma cortisol (ug/dl)	Urine cortisol (ug/24 h)	
Preoperative	42.03 ± 16.11	733.26 ± 388.26
Month 1 postoperative	16.07 ± 7.86*	182.26 ± 79.45*
Month 3 postoperative	14.12 ± 8.55*	90.64 ± 59.81*
Month 6 postoperative	13.25 ± 6.23*	71.26 ± 38.72*
* $p < 0.05$		
statistical difference compared with CNEI + PBS group ($P < 0.05$), ※statistical difference compared with CNEI + hUCB-MSCs group($P < 0.05$), # statistical difference compared with Sham + PBS group($P < 0.05$).		

infection, so glucocorticoid administration method of intramuscular injection is not adopted in this plan.

On the day 1 postoperative, the urine cortisol levels of the patients were significantly increased compared with preoperation. Excessive secretion of cortisol by surgical stress and ultra physiological doses of intravenous glucocorticoid hormone replacement therapy are the reasons for that. In the normal condition, 15 ~ 30 mg/d cortisol was secreted, but it could reach to 150□400 mg/d by surgical stress[17]. The plasma cortisol levels begin to gradually decrease from the day 2 postoperative, and it significantly lower than the levels of preoperative on the day 6 postoperative. In addition, 24 h urine cortisol levels of all patients were higher than the normal level perioperative. From the above datas, the dose of glucocorticoid used in this new glucocorticosteroid replacement therapy is proved to be enough for the patients.

No adrenal crisis, operative incision infection, and other postoperative complications happened, and all the patients discharged from hospital on the 7th post-surgery day. Six months postoperative, all the patients were all within normal plasma cortisol and urine cortisol levels. So, this new perioperative period glucocorticosteroid replacement therapy is safe and effective for CS patients.

Conclusion

This new perioperative glucocorticosteroid replacement therapy could significantly reduce the dosage of glucocorticoid used for CS patients, thus reducing the happening of complications induced by glucocorticoid, alleviate patient's suffering and pain, and improve the patient's quality of life.

Abbreviations

CS
Cushing’s syndrome; ACTH:adrenocorticotropic hormone;

AIMAH
ACTH-independent macronodular adrenal hyperplasia

Declarations

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Not applicable

Author Contributions

Involved in study design and conduct(L.W.&L.M.L.); Data collection, management, analysis (.L. W.& L. Y.,), and interpretation (Y.X.Y.); and manuscript preparation, review, or approval (L.W.,L.Y.&Z.C.).

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Availability of data and materials

The original data files [confidential patient data] and statistical analyses are available from the corresponding author upon reasonable request. Requests for access to the study data can be submitted via email to wlianggn@163.com

Ethics approval and consent to participate

This study was carried out in accordance with the recommendations of the ethics commission of the Tianjin Medical University General Hospital with written informed consent from all patients. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

Consent for publication

Consent for publication was obtained from all patients.

Competing Interests

All authors declare no competing financial interests.

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Figures

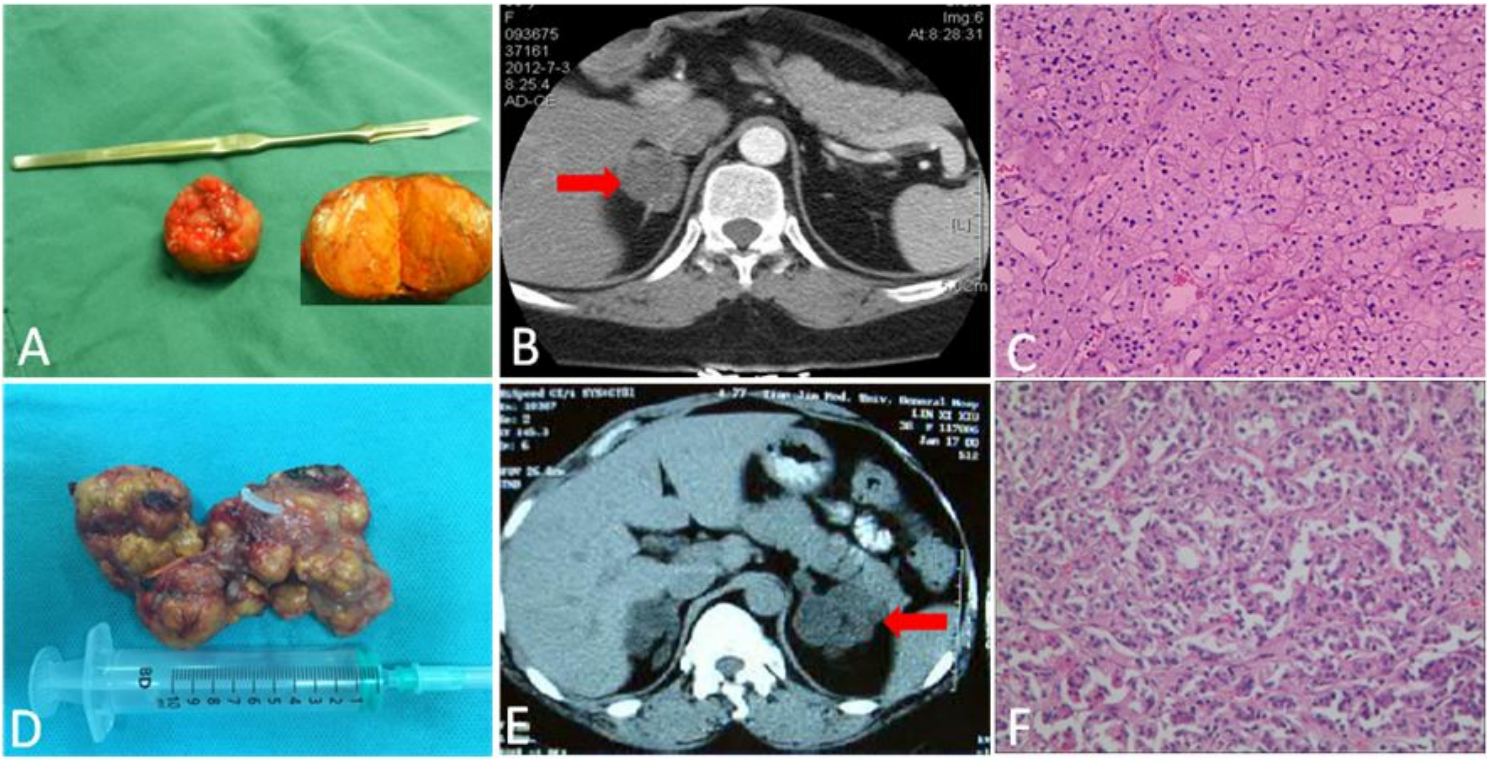

Figure 1

A and D show the tissue of adrenal adenoma and AIMAH, respectively; B and E show the axial section of CT scan of adrenal adenoma and AIMAH(red arrows), respectively; C:microscopic examination revealed thatadrenal pathology was micronodular adrenal