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Hormone Replacement Therapy after Unilateral Adrenalectomy

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Abstract

Unilateral adrenalectomy is widely performed for the treatment of both hormonally active and inactive adrenal tumors; however, the need for postoperative hormone replacement therapy (HRT) remains controversial. This study aimed to evaluate the necessity, duration, and clinical relevance of glucocorticoid replacement after unilateral adrenalectomy based on functional recovery of the hypothalamic–pituitary–adrenal (HPA) axis.

A prospective cohort study with elements of retrospective analysis included 108 patients who underwent minimally invasive unilateral adrenalectomy between 2018 and 2025. Hormonal status was assessed preoperatively, in the early postoperative period, and at 1, 3, and 6 months after surgery. Morning serum cortisol, ACTH, and electrolytes were measured, with dynamic testing performed when indicated. Glucocorticoid replacement therapy was prescribed individually based on laboratory results and clinical presentation.

Glucocorticoid replacement therapy was required in 46 patients (42.6%) in the early postoperative period, while 62 patients (57.4%) maintained adequate cortisol levels without replacement. The need for HRT was strongly associated with tumor functional status: replacement therapy was necessary in 84.6% of patients with corticosteromas, 50.0% with aldosteromas, and 42.9% with pheochromocytomas, compared with only 22.2% of patients

with hormonally inactive tumors. In most cases, HRT was transient, with normalization of morning cortisol allowing discontinuation of therapy in 37.0% of patients at 1 month, 63.0% at 3 months, and 82.6% at 6 months. Persistent adrenal insufficiency beyond 6 months occurred in only 7.4% of the total cohort and exclusively among patients with hormonally active tumors.

The study demonstrates that routine hormone replacement therapy after unilateral adrenalectomy is not universally required. Instead, individualized management based on systematic hormonal monitoring allows safe prevention of adrenal insufficiency while avoiding unnecessary long-term glucocorticoid exposure, thereby optimizing postoperative outcomes and patient quality of life

Key words: Adrenalectomy; Hormone Replacement Therapy; Adrenal Insufficiency; Hypothalamic-Pituitary-Adrenal Axis; Cortisol

Unilateral adrenalectomy is a standard surgical approach for the treatment of a wide spectrum of adrenal gland disorders, including hormonally active adenomas, pheochromocytomas, corticosteromas, aldosteromas, as well as non-functioning tumors with a potential risk of malignancy [1, 2]. Over recent decades, advances in imaging techniques, anesthetic management, and minimally invasive surgical technologies have led to a significant reduction in perioperative mortality and complication rates, resulting in an increasing number of patients who have undergone unilateral adrenalectomy and require long-term endocrine follow-up [1, 3, 4].

Traditionally, it has been assumed that after removal of one adrenal gland, the contralateral gland is able to fully compensate for the loss of hormonal function, making hormone replacement therapy (HRT) unnecessary or only temporarily required [5]. However, accumulating clinical evidence indicates that such compensation is not always complete or timely, particularly in patients with prolonged preoperative corticosteroid hypersecretion, concomitant endocrine disorders, advanced age, or significant comorbidities [4, 6]. In these patients, transient or persistent adrenal insufficiency may develop, substantially affecting the postoperative course, quality of life, and long-term prognosis [6, 7].

Particular clinical attention is required for patients with autonomous cortisol secretion, including subclinical hypercortisolism [8]. In this group, prolonged suppression of the hypothalamic–pituitary–adrenal axis leads to functional atrophy of the contralateral adrenal gland, markedly increasing the risk of postoperative acute or chronic adrenal insufficiency.

Even in the absence of overt clinical manifestations in the early postoperative period, latent glucocorticoid deficiency may become evident during intercurrent illnesses, surgical interventions, or psycho-emotional stress [8, 9].

Hormone replacement therapy after unilateral adrenalectomy remains a matter of debate [4, 10, 11]. On the one hand, excessive and unjustified administration of glucocorticoids is associated with the risk of iatrogenic hypercortisolism, metabolic disturbances, osteoporosis, and cardiovascular complications. On the other hand, underestimation of the risk of adrenal insufficiency may result in adrenal crises, which pose a direct threat to the patient's life. In this context, an individualized approach to the indications, dosage, and duration of HRT, based on hormonal profiles, functional testing, and clinical characteristics of the patient, is of paramount importance.

Current clinical guidelines propose various algorithms for the management of patients after unilateral adrenalectomy; however, these recommendations are not always uniform and are often based on limited evidence [12, 13]. Existing discrepancies concern both the necessity of routine hormone replacement therapy and the criteria for its discontinuation. This underscores the need to summarize contemporary data on functional recovery of the hypothalamic–pituitary–adrenal axis, the role of dynamic hormonal testing, and clinical markers of adrenal compensation. Thus, hormone replacement therapy after unilateral adrenalectomy represents an important interdisciplinary issue at the intersection of endocrinology and surgery. A comprehensive analysis of indications, pathophysiological mechanisms, and clinical outcomes of its use is necessary to optimize postoperative patient management, reduce the risk of complications, and improve long-term treatment outcomes.

The aim of this study was to evaluate the effectiveness of hormone replacement therapy after unilateral adrenalectomy.

Materials and Methods. The study was designed as a prospective cohort observation with elements of retrospective analysis and aimed to assess the necessity, duration, and clinical appropriateness of hormone replacement therapy following unilateral adrenalectomy. The research was conducted at the Odesa Regional Clinical Hospital between 2018 and 2025. The study material was formed on the basis of clinical data used in a dissertation devoted to the surgical treatment of adrenal gland pathology.

Included in the analysis were 108 patients who underwent unilateral adrenalectomy for adrenal tumors. The cohort was predominantly female, with 89 women (82.4%) and 19 men (17.6%). Patient age ranged from 29 to 68 years, with a mean age of 44.2 ± 1.3 years. Tumors were located on the left adrenal gland in 47 patients (43.5%) and on the right in 61 patients

(56.5%). Neoplasm size ranged from 1.7 to 9.5 cm in maximum diameter, with a mean of 3.6 ± 0.2 cm.

According to functional activity, patients were divided into two main groups. Hormonally active tumors were diagnosed in 72 patients (66.7%), including pheochromocytoma in 35 cases (32.4%), aldosteroma in 24 cases (22.2%), and corticosteroma in 13 cases (11.1%). Hormonally inactive tumors (incidentalomas) were identified in 36 patients (33.3%). All patients underwent a complete preoperative clinical, laboratory, and instrumental assessment and were followed by an endocrinologist for at least 6 months after surgery.

Surgical treatment consisted of minimally invasive unilateral adrenalectomy performed via a transabdominal or retroperitoneal approach depending on anatomical features, tumor size, and location [14]. The surgical approach was not analyzed as an independent factor because the primary objective of the study was to evaluate contralateral adrenal function and to substantiate the need for postoperative hormone replacement therapy.

Hormonal status was assessed preoperatively, in the early postoperative period (postoperative days 3–7), and at 1, 3, and 6 months after adrenalectomy. Morning (08:00) serum cortisol, adrenocorticotropic hormone (ACTH), and electrolyte concentrations (sodium, potassium) were measured [15]. In the presence of clinical or laboratory signs of adrenal insufficiency, 24-hour urinary cortisol determination and a short synthetic ACTH stimulation test were additionally performed [16].

Glucocorticoid hormone replacement therapy was prescribed on an individual basis, taking into account morning cortisol levels, clinical signs of adrenal insufficiency, and the results of dynamic hormonal testing. In most cases, hydrocortisone was used in physiological doses with subsequent gradual titration and evaluation of the possibility of discontinuation as hypothalamic–pituitary–adrenal axis function recovered. The duration of replacement therapy and dose adjustments were guided by laboratory parameters and the clinical condition of the patients [13, 17].

The primary study endpoints were the frequency of glucocorticoid replacement therapy after unilateral adrenalectomy, its duration, and the time to recovery of hypothalamic–pituitary–adrenal axis function. In addition, the association between the need for replacement therapy and tumor type, as well as the incidence of transient and persistent adrenal insufficiency, was analyzed.

The study was conducted in accordance with contemporary bioethical requirements [18]. All participants provided written informed consent. Statistical analyses were performed

using standard methods of variation statistics [19]. Quantitative variables are presented as mean values with the standard error of the mean. Intergroup comparisons were performed using parametric or nonparametric tests depending on data distribution. Differences were considered statistically significant at $p < 0.05$.

Results showed that unilateral adrenalectomy was associated with multidirectional changes in hypothalamic–pituitary–adrenal axis function, which depended substantially on tumor hormonal activity, the duration of preoperative hypersecretion, and the individual compensatory capacity of the contralateral adrenal gland. As early as the postoperative period, a decrease in morning cortisol levels was observed in a considerable proportion of patients; however, the magnitude and clinical significance of this decrease varied.

Among all 108 patients, glucocorticoid replacement therapy was initiated in 46 patients in the early postoperative period, representing 42.6% of the cohort. In the remaining 62 patients (57.4%), cortisol levels remained within reference or subnormal ranges without clinical manifestations of adrenal insufficiency, allowing replacement therapy to be withheld. Nevertheless, even in this group, transient fluctuations in hormonal parameters were observed, indicating the need for dynamic monitoring.

A clear association between replacement therapy and tumor type was identified. The highest need for hormone replacement therapy was observed in patients with corticosteromas: 11 of 13 patients (84.6%) received replacement therapy, reflecting marked suppression of the hypothalamic–pituitary–adrenal axis due to prolonged autonomous cortisol secretion before surgery. In patients with aldosteromas, replacement therapy was required in 12 of 24 cases (50.0%), whereas in the pheochromocytoma group it was required in 15 of 35 patients (42.9%). The lowest rate of replacement therapy was observed among patients with hormonally inactive tumors, in whom glucocorticoid replacement was indicated in only 8 of 36 patients (22.2%).

Analysis of hormonal dynamics demonstrated that, in most patients requiring replacement therapy, cortisol secretion by the contralateral adrenal gland gradually recovered. One month after surgery, normalization of morning cortisol was documented in 17 of 46 patients (37.0%) receiving replacement therapy. By three months, this number increased to 29 patients (63.0%), and by six months to 38 patients (82.6%), enabling stepwise glucocorticoid dose reduction and complete discontinuation of replacement therapy in the majority.

Persistent adrenal insufficiency requiring continuation of glucocorticoid replacement beyond six months after adrenalectomy was identified in 8 patients, accounting for 7.4% of the entire cohort and 17.4% of those who initially received replacement therapy. All such

patients belonged to the hormonally active tumor group, with corticosteromas predominating. No cases of persistent adrenal insufficiency were recorded among patients with hormonally inactive tumors.

Clinical manifestations of adrenal insufficiency in the early postoperative period included general weakness, orthostatic hypotension, nausea, decreased appetite, and varying degrees of hyponatremia. No severe adrenal crises were observed, which is likely attributable to timely hormonal monitoring and early initiation of replacement therapy. During follow-up, clinical symptoms regressed in parallel with recovery of hormonal function, as confirmed by laboratory indicators.

Comparative analysis showed that the risk of postoperative adrenal insufficiency was significantly higher in patients with prolonged preoperative cortisol hypersecretion, larger tumor size, and older age. In contrast, neither the side of adrenalectomy nor the minimally invasive surgical approach had a significant effect on the need for, or duration of, glucocorticoid replacement therapy.

These findings indicate that hormone replacement therapy after unilateral adrenalectomy should not be regarded as a routine component of postoperative care, but rather as a tool for individualized correction of transient or persistent hypothalamic–pituitary–adrenal axis dysfunction. The need for glucocorticoid therapy in nearly half of patients in the early postoperative period is consistent with contemporary concepts of limited recovery speed of contralateral adrenal function, particularly after prolonged preoperative hormonal suppression. At the same time, the predominantly temporary nature of replacement therapy, with discontinuation feasible in most patients within six months, confirms the substantial compensatory potential of adrenal tissue provided adequate clinical monitoring is ensured.

The strong dependence of replacement therapy frequency and duration on tumor type underscores the pivotal role of the preoperative hormonal milieu in the development of postoperative adrenal insufficiency. The highest risk in corticosteroma patients is pathophysiologically justified, as autonomous cortisol secretion causes chronic ACTH suppression and functional atrophy of the contralateral adrenal gland. In this cohort, even the absence of prominent clinical symptoms cannot be interpreted as evidence of adequate compensation, necessitating proactive hormonal surveillance. Conversely, the lower frequency of replacement therapy in pheochromocytoma and hormonally inactive tumor groups supports the view that routine prophylactic glucocorticoid administration in these cases is unjustified and may contribute to iatrogenic complications.

The present data also prompt reconsideration of the diagnostic value of clinical manifestations in postoperative adrenal insufficiency. The nonspecific nature of symptoms such as general weakness or orthostatic reactions, particularly in the early postoperative period, limits their diagnostic utility without laboratory confirmation. Accordingly, regular measurement of morning cortisol and dynamic assessment using stimulation tests are of key importance, allowing timely identification of subclinical adrenal insufficiency and prevention of adrenal crises.

Based on the results, several practical recommendations can be formulated regarding postoperative clinical monitoring and hormone replacement therapy after unilateral adrenalectomy. Hormonal monitoring should be performed in all patients irrespective of tumor functional status and should include measurement of morning cortisol within the first 3–7 postoperative days, as well as repeated assessments at 1, 3, and 6 months. In patients with corticosteromas or evidence of prolonged preoperative hypercortisolism, standard monitoring should be supplemented by a short synthetic ACTH stimulation test to objectively assess the reserve capacity of the hypothalamic–pituitary–adrenal axis.

Initiation of glucocorticoid replacement therapy should be considered in the presence of laboratory evidence of insufficient cortisol secretion, especially when combined with clinical symptoms, or in cases of reduced hormonal reserve on dynamic testing. In corticosteroma patients, early initiation of replacement therapy with subsequent stepwise dose titration is appropriate, whereas in patients with hormonally inactive tumors therapy should be prescribed only when clear indications are present. The duration of replacement therapy should be individualized and reassessed at each follow-up point based on clinical presentation and hormonal parameters.

A critical aspect is gradual tapering and discontinuation of glucocorticoids after objective confirmation of recovery of contralateral adrenal function, since unnecessarily prolonged replacement therapy may delay endogenous recovery and increase the risk of iatrogenic hypercortisolism. Patients with persistent adrenal insufficiency require long-term endocrine follow-up, education regarding stress-dose adjustment, and timely modification of therapy during intercurrent illnesses.

Thus, the results confirm that effective postoperative management after unilateral adrenalectomy requires an integrated approach combining early laboratory monitoring, judicious individualized use of glucocorticoid replacement therapy, and regular reassessment of hypothalamic–pituitary–adrenal axis function. The proposed recommendations are aimed at

minimizing the risks of both insufficient and excessive hormonal replacement, ultimately improving postoperative outcomes and patient quality of life.

Conclusions:

1. The study demonstrated that after unilateral adrenalectomy, glucocorticoid hormone replacement therapy was required in 46 of 108 patients (42.6%), whereas in 62 patients (57.4%) the function of the contralateral adrenal gland provided adequate cortisol levels without the need for hormonal supplementation, indicating the absence of a universal need for routine replacement therapy after unilateral adrenal removal.

2. The frequency and duration of replacement therapy significantly depended on tumor functional status: replacement therapy was indicated in 84.6% of patients with corticosteromas, 50.0% with aldosteromas, and 42.9% with pheochromocytomas, while among patients with hormonally inactive tumors the need for replacement therapy occurred in only 22.2%, highlighting the key role of preoperative hormonal suppression of the hypothalamic–pituitary–adrenal axis.

3. Follow-up showed that replacement therapy was transient in most patients: normalization of morning cortisol with the possibility of complete discontinuation was achieved in 37.0% at 1 month, 63.0% at 3 months, and 82.6% at 6 months after surgery, whereas persistent adrenal insufficiency requiring continuation beyond 6 months was documented in only 7.4% of the total cohort.

4. Timely laboratory monitoring and individualized initiation of glucocorticoid replacement therapy prevented adrenal crises in 100% of cases and enabled safe discontinuation of glucocorticoids in the vast majority of patients, supporting the clinical value of an algorithm-based approach to postoperative management after unilateral adrenalectomy.

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