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Effectiveness of unilateral laparoscopic adrenalectomy in ACTH-independent hypercortisolaemia and subclinical Cushing's syndrome — a retrospective study on a large cohort

Skuteczność jednostronnej adrenalektomii laparoskopowej w hiperkortyzolemii i subklinicznym zespole Cushinga niezależnych od ACTH — badanie retrospektywne na dużej kohorcie

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Abstract

Introduction: To assess the effectiveness of early unilateral laparoscopic adrenalectomy in ACTH-independent and subclinical hypercortisolaemia.

Material and methods: We conducted a unicentric, retrospective study. Between 2010 and 2015, 356 laparoscopic adrenalectomies were performed in the Department of General and Endocrine Surgery of the MUW. Hypercortisolaemia was found in 50 (14%) patients, while overt hypercortisolaemia was found in 31 patients. In the hypercortisolaemia group, ACTH-dependent hypercortisolaemia was diagnosed in five (10%) and ACTH-independent hypercortisolaemia in 25 patients (50%). One patient with overt hypercortisolaemia had cancer of the adrenal cortex. The remaining 19 (38%) patients had subclinical Cushing's syndrome. For our study, we compared patients with ACTH-independent hypercortisolaemia (n = 25) with those with Cushing's syndrome (n = 19). Patients with ACTH-dependent hypercortisolaemia (n = 5) and the patient with cancer of the adrenal cortex (n = 1) were excluded.

Results: Patients from both groups (n = 44) underwent a unilateral transperitoneal adrenalectomy. Good early outcomes were observed in 42 patients (93.3%). In one patient, an additional laparoscopic surgery was necessary on postoperative day 0 due to bleeding. In another patient, on day 22 post-surgery, we found an abscess in the site of the excised adrenal gland, which was drained under laparoscopic guidance. In three patients (6.8%) with substantial obesity, temporary respiratory insufficiency of varying degrees occurred. We did not observe any thromboembolic complications. All patients with overt hypercortisolaemia and nine patients with subclinical hypercortisolaemia had secondary adrenal insufficiency postoperatively.

Conclusions: Transperitoneal unilateral laparoscopic adrenalectomy is an efficient and safe treatment option in patients with ACTH-independent hypercortisolaemia, both overt and subclinical. **(Endokrynol Pol 2018; 69 (4): 411–415)**

Key words: *Cushing's syndrome, ACTH-independent Cushing's syndrome, subclinical Cushing's syndrome*

Streszczenie

Wstęp: Celem pracy była ocena skuteczności wczesnej jednostronnej adrenalektomii laparoskopowej w niezależnej od ACTH i subklinicznej hiperkortyzolemii.

Materiał i metody: Przeprowadzono jednoośrodkowe, retrospektywne badanie. W latach 2010–2015 wykonano 356 adrenalektomii laparoskopowych w Klinice Chirurgii Ogólnej i Endokrynologicznej Warszawskiego Uniwersytetu Medycznego (WUM). Hiperkortyzolemię stwierdzono u 50 pacjentów (14%), natomiast jawną hiperkortyzolemię u 31 pacjentów. W grupie pacjentów z hiperkortyzolemią, hiperkortyzolemię ACTH-zależną zdiagnozowano u pięciu (10%) pacjentów, natomiast ACTH-niezależną u 25 (50%) pacjentów. U jednego z pacjentów z jawną hiperkortyzolemią stwierdzono raka kory nadnerczy. U pozostałych 19 (38%) pacjentów stwierdzono subkliniczny zespół Cushinga. Dla celów niniejszego badania, porównano pacjentów z ACTH-niezależną hiperkortyzolemią (n = 25) z pacjentami z zespołem Cushinga (n = 19). Z badania zostali wykluczeni pacjenci z ACTH-zależną hiperkortyzolemią (n = 5) oraz pacjent z rakiem kory nadnerczy (n = 1).

Wyniki: Pacjentów z obu grup (n = 44) poddano jednostronnej adrenalektomii przezotrzewnowej. Dobre wczesne wyniki leczenia zaobserwowano u 42 pacjentów (93,3%). U jednego z pacjentów konieczna była dodatkowa operacja laparoskopowa z powodu krwawienia w 0. dobie pooperacyjnej. U innego pacjenta, w 22. dobie pooperacyjnej, wykryto ropień w miejscu wyciętego gruczołu nadnerczowego,

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który został odsączony pod kontrolą laparoskopową. W przypadku trzech pacjentów (6,8%) ze znaczną otyłością, wystąpiła przejściowa niewydolność oddechowa o różnym stopniu nasilenia. Nie zaobserwowano żadnych powikłań zakrzepowo-zatorowych. U wszystkich pacjentów z jawną hiperkortyzolemią oraz u dziewięciu pacjentów z subkliniczną hiperkortyzolemią stwierdzono wtórną niewydolność nadnerczy po operacji.

Wnioski: Jednostronna laparoskopowa adrenalektomia przezotrzewnowa jest skuteczną i bezpieczną opcją leczenia pacjentów z ACTH-niezależną hiperkortyzolemią, zarówno jawną jak i subkliniczną. **(Endokrynol Pol 2018; 69 (4): 411–415)**

Słowa kluczowe: *zespół Cushinga, ACTH-niezależny zespół Cushinga, subkliniczny zespół Cushinga*

Introduction

Since the pioneering work of Harvey Cushing (1869–1939) on the physiology and pathology of the pituitary gland and its influence on the exocrine function of the adrenal cortex, a rapid development of treatment options for patients with associated dysfunctions has evolved. Most prominent, despite their rare incidence (2–3 individuals per million) are hypercortisolaemia, Cushing's disease (CD), and Cushing's syndrome (CS). Hypercortisolaemia is three times more prevalent in women than in men [1]. It can be endogenous or exogenous; the former being seen in Cushing's syndrome, Cushing's disease, and ectopic cortisol-secreting endocrine tumours. The latter is associated with prolonged glucocorticoid use (e.g. in patients with autoimmune diseases) [2]. The incidence of endogenous Cushing's syndrome is reported as low; however, this is due to under-evaluation of patients with uncontrolled diabetes mellitus, obesity, or hypertension. Underestimation could be avoided by screening for Cushing's syndrome in therapy-resistant diabetes or hypertension. So far, however, most cases of adrenal tumours still prevail as incidental findings on radiographies. With the rapid development of radiological techniques and increasing availability and use of these, incidentalomas are becoming more frequent. Subclinical Cushing's syndrome has been reported in 5–10% of these patients.

Symptoms of hypercortisolaemia — obesity, hypertension, diabetes, hyper- and dyslipidaemia, osteoporosis, etc. — often impair the quality of life, which is especially abominable in patients with unrecognised long-term hypercortisolaemia [3]. There is even a correlation proven between hypercortisolaemia and depression. Laparoscopic adrenalectomy (LA) has emerged as the golden standard of care for cortisol-producing adrenal adenomas < 5 cm and has overruled open adrenalectomy (OA). Also, recent studies reported LA to be beneficial in patients with subclinical Cushing's syndrome, leading to a reduction of life-impacting symptoms, such as arterial blood pressure, and increased body weight and fasting glucose levels. Thus, there is a need to validate the trend of performing LA as symptomatic treatment for ACTH-independent hypercortisolaemia and subclinical Cushing's syndrome — the disease variants where standard drug treatment is not effective and a laparotomic surgery approach is too radical.

While LA is recommended for cortisol-producing adrenal adenomas < 5 cm, there is, however, controversy in the surgical field of whether LA is also safe for large tumours. Data on specifically large tumour LA are scarce and so it remains to the surgeons' discretion which approach (LA or OA) is chosen. Whether LA is a safe and efficient therapeutic approach for patients with adrenal tumours > 5 cm and ACTH-independent hypercortisolaemia and subclinical Cushing's syndrome is also still unclear. One of the mostly feared complications is postoperative hypocortisolism; therefore, data with long-term follow-up are imperative.

The aim of our retrospective, unicentric, long-term follow-up study, was to address those knowledge gaps and assess the safety and the effectiveness of laparoscopic adrenalectomy as a treatment of hypercortisolaemia in specific subgroups of ACTH-independent hypercortisolaemia and subclinical Cushing's syndrome, with tumours smaller and larger than 5 cm.

Material and methods

We retrospectively analysed outcomes of laparoscopic adrenalectomies performed between 2010 and 2015 in the Department of General and Endocrine Surgery, MUW, in patients with clinically and biochemically confirmed hypercortisolaemia (preoperatively, all patients underwent an endocrine work-up). Of a total of 356 laparoscopic adrenalectomies performed due to adrenal tumours, 147 (41.3%) specimens were positive for adenomatous hyperplasia or individual adrenal cortical adenomas in histopathological findings. Of those, 50 patients (34%) had confirmed hypercortisolaemia/ /Cushing's syndrome (CS): 39 (78%) women and 11 (22%) men, aged 28–72 years (mean: 48.7 years). Five patients (10%) had ACTH-dependent hypercortisolaemia, 26 (52%) patients ACTH-independent hypercortisolaemia, and the remaining 19 (38%) patients had subclinical Cushing's syndrome. Typical symptoms in the studied group included hypertension (40 patients, 90.9%), obesity (25, 56.8%), and type 2 diabetes (23, 52.3%). In all cases, the presence of tumours was

confirmed preoperatively on radioimaging (US, CT, MRI, PET); the tumour size ranged from 23 to 90 mm (mean 36 mm) and the density between 5 and 30 jH. In 13 (29.5%) patients, we found bilateral adrenal enlargement (adrenal thickness > 10 mm).

Overt hypercortisolaemia was defined as the presence of typical symptoms — hypertension, obesity, diabetes, osteoporosis, depression — confirmed by at least two screening tests (short dexamethasone suppression test, urine free cortisol excretion, or late-night saliva or serum cortisol). ACTH-independent hypercortisolaemia was diagnosed at ACTH levels < 5 pg/mL, and ACTH-dependent hypercortisolaemia was diagnosed at ACTH levels > 20 pg/mL. Subclinical hypercortisolaemia was diagnosed in patients without evident symptoms, while the cortisol level in the dexamethasone suppression test was > 5 mg/dL and the level of ACTH was < 5 pg/mL.

All surgeries were performed under general anaesthesia, using a transperitoneal approach with four ports. Trocars were introduced along the costal margin, starting from the midline to the tip of rib XII, on both sides. Dissection was performed with a harmonic knife, and a simple retractor was used to create a triangular operating field that allowed for mobilisation of the liver, spleen, and pancreatic tail in the peritoneal space. Following clipping of the adrenal arteries and veins, the adrenal gland was removed from the peritoneal cavity with a laparoscopic bag. In six patients with large tumours (diameter > 50 mm), we enlarged the entrance site for trocars in the abdominal wall (mini-laparotomy), which was then stitched up. Cortisol levels were measured in all patients on postoperative day 0, 10 hours after the intervention. Depending on the cortisol level, hydrocortisone substitution for a mean period of two weeks was administered. At cortisol level < 5 mg/dL, hydrocortisone was given at a dose of 20–30 mg daily.

For the statistics, analysis of interest data distribution in both groups was conducted with Fisher Exact Test. All calculations were performed with the package Statistica 13.0.

Results

All patients underwent laparoscopic transperitoneal adrenalectomy; conversion to open surgery was not necessary in any case. We analysed early treatment outcomes in a total of 44 patients: in patients with subclinical Cushing's syndrome (n = 19, 43.2%) and in patients with ACTH-independent hypercortisolaemia (n = 25, 56.8%). In the first group (subclinical Cushing's syndrome), tumour size ranged from 8 x 33 mm to 67 x 72 mm (mean: 26 x 42 mm), as measured on CT, MRI, US, or postoperative samples. The mean tumour size in patients with ACTH-independent hypercortisolaemia was 30 x 38 mm. Thirteen patients (29.5%) who had a subtle enlargement of the contralateral adrenal gland preoperatively (thickness greater than 10 cm, i.e. twice the normal size) were followed up on an outpatient basis Surgery duration ranging from 75 min to 210 min (mean: 130 min). We performed right adrenalectomy in 20 (45.5%) patients and left adrenalectomy in 24 (54.5%) patients. In the ACTH-independent hypercortisolaemia group, secondary adrenal insufficiency appeared significantly more often ($p < 0.0001$). Further characteristics on the surgeries and the postoperative period for both groups are presented in Table I.

Table I. *Characteristics of the laparoscopic transperitoneal adrenalectomy the postoperative period of patients with ACTH-independent hypercortisolaemia and with subclinical hypercortisolaemia*

Tabela I. *Charakterystyka laparoskopowej adrenalektomii przezotrzewnowej i okresu pooperacyjnego u pacjentów z ACTH-niezależną hiperkortyzolemią i subkliniczną hiperkortyzolemią*

	Side	ACTH-independent CS	Subclinical CS	P
Mean surgery duration (min)	Right	120	90	Insignificant
	Left	150	126	Insignificant
Bleeding/blood transfusions	Right	x	x	Insignificant
	Left	x	1	Insignificant
Use of haemostatic glue	Right	x	x	Insignificant
	Left	1	3	Insignificant
Suppurative complications	Right	x	x	Insignificant
	Left	1	x	Insignificant
Number of conversions		x	x	Insignificant
Number of re-operations		2	x	Insignificant
Respiratory insufficiency		3	x	Insignificant
Thromboembolic complications		x	x	Insignificant
Secondary adrenal insufficiency		25	9	P < 0.0001

In the postoperative period, only two patients (4.5%) needed a further intervention: one patient due to a bleeding and one patient due to an abscess in the excised adrenal gland. Bleeding from the adrenal area was stopped laparoscopically with a fibrin sealant (TISSEL). The abscess in the site of the excised adrenal gland (left) was drained laparoscopically.

In the postoperative period, subacute respiratory insufficiency with dyspnoea and fever (up to 38°C) occurred in three obese patients. Radiographically, these

Table II. *Symptoms and diagnostic parameters in patients with ACTH-independent hypercortisolaemia and subclinical Cushing's syndrome*

Tabela II. *Objawy i parametry diagnostyczne pacjentów z ACTH-niezależną hiperkortyzolemią i subklinicznym zespołem Cushinga*

Symptoms	ACTH-independent Cushing's syndrome	Subclinical Cushing's syndrome	Total	P
Diabetes	8	15	23	P < 0.003
Hypertension	23	17	40	Insignificant
Obesity	15	10	25	Insignificant
Depression	4	2	6	Insignificant
Tumour size on CT [mm]	35 x 42	32 x 46		Insignificant
Adenoma*	14	12	26	Insignificant
Adenomatous hyperplasia*	11	7	18	Insignificant
Cancer of adrenal cortex	1	0	1	Insignificant

*based on histopathology

episodes were associated with atelectasis in the lower lung lobes. Respiratory rehabilitation and antibiotics led to complete symptom resolution. All patients enrolled in the study received thromboembolic prophylaxis with low-molecular-weight heparin and graduated compression stockings. The duration of follow-up in both groups was similar, ranging from two to four weeks. Table II summarises the leading symptoms and diagnostic parameters in patients with ACTH-independent hypercortisolaemia and subclinical Cushing's syndrome. Strikingly, diabetes appears significantly more often in patients treated for subclinical Cushing's syndrome.

Discussion

Hypercortisolaemia occurs rarely, usually as part of Cushing's diseases or Cushing's syndrome. Based on epidemiological studies, its incidence is slightly higher than one per million. More commonly, hypercortisolaemia is found in patients with incidentally detected adrenal tumours on imaging studies performed for other indications. Notably, hypercortisolaemia causes approximately 1% of secondary hypertension cases and is found in over 5% of patients with obesity, hypertension, and osteoporosis [1, 4, 5]. Among patients treated for adrenal tumours in our centre, we detected hypercortisolaemia in only 14% of cases. The ratio of overt ACTH-dependent hypercortisolaemia to ACTH-independent and subclinical hypercortisolaemia was 1:9.

Thus far, literature acknowledges adrenalectomy, including the least invasive, laparoscopic approach, as the golden standard with therapeutic benefits in patients with CS [6, 7]. Unilateral laparoscopic adrenalectomy is associated with good long-term outcomes in over 80% of CS patients. However, there is a risk of hypercortisolaemia recurrence, commonly in patients with contralateral adrenal gland enlargement preoperatively or on follow-up [8, 9, 10]. In our study, a slight enlargement of the contralateral adrenal gland was found in as many as 13 patients. According to our protocol, we removed significantly enlarged adrenal glands and monitored for recurrence of hypercortisolaemia on follow-up. Based on long-term observation (several years postinterventionally), recurrence of hypercortisolaemia was rarely detected. When the recurrence occurred, the contralateral adrenal gland was also removed. Such an approach is justified by other studies, and our results correlate with those indicating that, in the long-term, recurrence of hypercortisolaemia after unilateral adrenalectomy is seen in approximately 20% of patients [11, 12].

All patients in our centre underwent unilateral transperitoneal adrenalectomy, and conversion to open surgery was not necessary in any patient. In one patient (2.3%), we observed sustained bleeding post surgery, which was stopped laparoscopically. In another patient (2.3%), on day 22 post surgery, we laparoscopically drained an abscess that had formed in the site of the excised adrenal gland. Respiratory complications were the most frequent ones (three patients, 6.8%), which correlated radiographically with atelectasis of the lower pulmonary lobes and pneumonia. These complications developed in patients with ACTH-independent hypercortisolaemia and substantial obesity and older age. Possibly due to the strictly conducted antithrombotic prophylaxis, we did not record any thromboembolic complications. The antithrombotic prophylaxis included low-molecular-weight heparin (1 mg/kg) and graduated compression stockings during the surgery. Patients with hypercortisolaemia are at an increased risk of thromboembolic complications due to the direct pro-thrombotic effects of cortisol and other indirect prothrombotic effects caused by cortisol-related metabolic derangements. Another factor that increases the risk of thromboembolic complications is compression of large veins due to pneumothorax related to laparoscopic adrenalectomy [13, 14].

Our results also further correlate with other reports stating that the general morbidity following laparoscopic adrenalectomy ranges from 0 to 8% [9] and conversion to open surgery occurs in 2–4.2% of cases [7, 15]. Limiting factors in our study were the small sample size (although bigger than in studies so far) and

the retrospective character. Our results are enforced by the long follow-up, which meant that long-term complications could be recorded. Further prospective studies are warranted.

Conclusions

Laparoscopic adrenalectomy is an efficient, safe, and effective curative approach for adrenal tumours in patients with ACTH-independent hypercortisolaemia and subclinical Cushing's syndrome. The symptoms can mostly be eliminated permanently, while the complication rate and duration of hospitalisation is low. The approach can be implemented with the same success and safety profile to large tumours > 5 cm.

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