SURGICAL TREATMENT OF PHEOCHROMOCYTOMA

Salimova Dildora Erkinovna
Scientific adviser: Assistant of the Department of Endocrinology, Samarkand State Medical University
Abjalilova Fotima
Malikova Marjona
Buronova Fotima
Zokirova Feruza
Students of the Samarkand state Medical University

Annotation: *This review article briefly summarizes modern ideas about aspects of preoperative preparation, surgical treatment and follow-up of patients with adrenal pheochromocytomas. The main component of preoperative drug preparation is the use of alpha-blockers. The need for their use in all patients is increasingly being challenged, particularly in patients without significant hypertension, and a growing number of publications demonstrate positive results from surgery without the use of alpha-blockers, advocating an individualized approach and their use only for certain indications. In surgical treatment, minimally invasive endoscopic methods of adrenalectomy have become widespread: laparoscopic and retroperitoneoscopic, including the use of their single-port modifications. The key aspect of surgery for pheochromocytomas in the past - the earliest possible intersection of the central vein - with the development of surgical techniques and anesthesia, has ceased to be a mandatory rule for successful adrenalectomy. Despite the significant impact of crossing this vessel on intraoperative hemodynamics, surgical tactics with its later crossing have their justifications and do not lead to worse treatment results.*

Keywords: *pheochromocytoma; alpha-blocker; adrenalectomy; central vein of the adrenal gland; adrenal resection.*

INTRODUCTION

Pheochromocytoma/paraganglioma (PC/PG) is a rare neuroendocrine tumor of chromaffin tissue capable of overproducing catecholamines. The main stage of treatment for FCC/PG is their surgical removal. The incidence of FCC/PG development is relatively low - approximately 1 per 100,000 people per year; among patients with arterial hypertension, their prevalence is 0.2–0.6% [1], which causes doctors to have little awareness of the methods of treating this pathology outside specialized centers. The low prevalence of FCC/PG makes it difficult to carry out large studies, and therefore most publications on this issue are based on small samples of clinical observations, their data, as well as the opinions of the authors, vary. FCC is a special case of paraganglioma of the adrenal gland. The main type of treatment for FCC is adrenalectomy with tumor. This

review article contains a summary of current data regarding preoperative preparation and surgical treatment of FCC.

Preoperative preparation of patients with fcc. Surgical removal of FCC is associated with perioperative complications such as the development of hypertensive crisis, tachyarrhythmia, and uncontrolled hemodynamics [1]. The intra- and postoperative prognosis is influenced by the functional state of target organs suffering from catecholamine intoxication, primarily the heart, kidneys, and brain, and therefore one of the tasks of preoperative preparation is to increase their functional reserves [2]. As preoperative preparation for all patients with FCC/PG, the use of α1-blockers is recommended in order to improve intraoperative hemodynamic control [3, 4]. Despite the pathophysiological validity and expected clinical effectiveness of this therapy, a number of authors doubt the need for its use for all patients with FCC [5–7]. There are a number of studies that describe the results of successful treatment of patients with FCC without the use of preoperative preparation with alpha-1 adrenergic blockers [8–12]. In a study by Groeben H. et al. (2017) of a large cohort of patients with FCC/PG, when comparing intraoperative hemodynamics and postoperative complications of a group of 110 patients with preliminary alpha blockade and 166 patients without it, no significant differences were found [8]. At the same time, Castinetti F. et al. note the presence of additional negative consequences of preoperative therapy with α-blockers, in addition to standard side effects, in the form of the development of postoperative hypotension and, as a consequence, the need for longer vasopressor therapy [13]. Thus, in a recent large retrospective multicenter cohort study, Groeben H. et al. (2020) showed an even higher number of specific complications associated with unstable hemodynamics in the group of patients receiving α-blockers compared to the group of patients who did not undergo this preoperative preparation [1]. In this regard, a number of authors have suggested the possible ranking of patients by risk level in order to determine the need for alpha-blocker therapy [8, 13, 14–16]. Castinetti F. et al. (2022) offer their methods for selecting patients who need this preparation, in which the clinical picture, the degree of increase in metanephrine levels and other factors play a role [13]. However, due to the lack of large randomized studies confirming the effectiveness and safety of surgical removal of catecholamine-producing tumors without prior pharmacological preparation, the standard tactics enshrined in clinical guidelines remains the routine administration of α1-blockers to all patients with FCC/PG [3, 4]. In preoperative preparation, β-blockers can also be used to control heart rate, but it is important to remember that their use is possible only after prior use of α1-blockers for at least 3 days [4, 14, 17].

Choice of surgical access to the adrenal gland. The open adrenalectomy technique was first performed in 1926 independently by the Swiss surgeon Cesar Roux and the American surgeon Charles Mayo [18]. Despite the fact that almost 100 years have passed since the first such operation was performed, the technique is still used, but currently it is resorted to only when it is impossible to perform the operation using minimally invasive

techniques, which is usually associated with the large size of the tumor, adhesion to surrounding organs, invasion into neighboring organs and tissues or other reasons. The largest size of pheochromocytoma for the use of endoscopic techniques was most often called 5–6 cm, but at the moment there are many publications confirming the safety and effectiveness of endoscopic techniques in removing tumors of larger sizes [19–21]. One of the significant factors is the personal experience of the surgeon and the operating team as a whole.

Intraoperative tactics in relation to the central vein of the adrenal gland. Crossing the central vein is one of the important stages of performing adrenalectomy for adrenal tumors, however, it is in chromaffin tumors that it becomes key. When the outflow of blood through the central vein of the adrenal gland ceases during FCC, there is a sharp decrease in the flow of catecholamines from the tumor into the systemic circulation, which has a significant effect on hemodynamics, the management of which requires experience, high qualifications and skill of the anesthesiological team. The surgical technique at the initial stages of development consisted of cutting the central vein as early as possible [36]. This tactic brought good results and was convenient for laparotomic or laparoscopic approaches, in which the desired vein is located quite superficially. When using the retroperitoneal approach, the central vein is located behind the adrenal gland, and therefore, its intersection often requires preliminary partial mobilization of the adrenal gland, especially the lower pole with the vessels approaching it in this area [37]. Walz MK, one of the founders of the retroperitoneoscopic approach, claims that later intersection of the central vein with this approach does not negatively affect intraoperative hemodynamics in a patient who has undergone preoperative preparation with α-blockers. In the surgical protocol he described, the earliest possible intersection of the adrenal vein is not a prerequisite for a successful outcome of surgical treatment.

Organ-saving operations on the adrenal glands. The standard scope of surgical intervention for FCC is adrenalectomy with tumor. Removal of one adrenal gland, as a rule, does not lead to the development of chronic adrenal insufficiency and does not require lifelong hormone replacement therapy [42]. However, in some cases, it is necessary to prescribe glucocorticoid hormones after unilateral adrenalectomy for FCC, especially in cases of simultaneous co-secretion of cortisol by the tumor before surgery [43]. In patients with bilateral FCC and the presence of hereditary syndromes associated with their development, such as multiple endocrine neoplasia syndrome (MEN) type 2, neurofibromatosis type 1 (NF-1), von Hippel-Lindau syndrome (VHL), it is possible to perform adrenal resection with the purpose of preserving glucocorticoid and mineralocorticoid secretion [3,4]. A number of hereditary mutations in FCC are associated with a high risk of metastasis, and therefore organ-conserving operations are performed in the presence of defects in the SDHB, SDHD, MAX, TMEM127, HRAS, CSDE1 and MAML3 genes

not recommended [44, 45]. Preservation of adrenal tissue in patients with MEN type 2 and VHL syndromes, as well as NF-1, leads to an increase in the incidence of relapse, which patients should be warned about, however, studies have shown that the incidence of FCC metastases does not increase and the survival of patients does not decrease [46].

Postoperative care. In the early postoperative period, mandatory monitoring of the patient's basic hemodynamic parameters is required. European clinical guidelines from 2014 indicate the need for continuous monitoring of blood pressure levels in the first 24–48 hours after surgery [3]. The need for this control is beyond doubt, but there are different approaches to it. While some medical centers do routinely perform 24-hour continuous monitoring of the blood pressure level of patients in the intensive care unit after removal of FCC, there are many centers in which postoperative monitoring can be carried out outside the intensive care unit. According to the authors' observations, daily monitoring in the intensive care unit does not reduce the mortality of this category of patients, and therefore is not mandatory [1]. Due to the risk of metastasis and recurrence of FCC after surgical treatment, international and Russian clinical guidelines state the need for at least 10 years of postoperative follow-up [3, 4, 15]. The existing PASS and GAPP scores for assessing the metastatic potential of FCC have limited prognostic power [52].

Conclusion. The widespread use of sensitive laboratory tests and the use of such radiation diagnostic methods as computed tomography and magnetic resonance imaging have led to an increase in the intravital detection of FCC, including small tumors. This fact created an urgent need to improve surgical methods for treating catecholamine-producing tumors, the emergence of surgical technologies using minimally invasive approaches, and improvement of anesthesia. Despite the fact that according to the WHO histological classification of the 2017 revision, FCC/PG are classified as malignant neoplasms, the development of genetic research methods has led to a discussion of the possibility of performing organ-conserving operations in patients with identified hereditary mutations. Most conclusions and recommendations were made based on data from multicenter cohort studies and meta-analyses, since the rarity of the pathology determines the absence of large randomized studies in this area.

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