Contemporary approach to preoperative preparation of patients with adrenal cortex hormones dysfunction

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INTRODUCTION

A drenal glands are paired retroperitoneal organs consisting of two parts: cortex and the medulla. These parts are two independent and different endocrine entiti-
es. The statement, dating from Addison’s time, saying that adrenal cortex is necessary for life while medulla is not, is valid nowadays. Surgical extirpation of adrenal glands or functional destruction of the adrenal tissue, demands lifelong substitution with synthetic adrenal hormones, since they are synthesized only in the adrenal cortex. Adrenal medulla is the place of catecholamine synthesis, but these hormones are produced elsewhere in the body, which makes catecholamine substitution unnecessary.

Thirty different steroid hormones are produced in the adrenal cortex, among which the most important are two classes: mineralocorticoids, whose major representative is aldosterone, and glucocorticoids, whose major representative is cortisol.

Cortisol is one of the most important stress hormones, because it has metabolic, catabolic, anti-inflammatory and vasoactive characteristics, thus influencing heart muscle and peripheral vascular tonus. This is achieved through cortisol effect on the catecholamine induced vasoconstriction, on the catecholamine and vasoactive peptide synthesis. Cortisol expresses inotropic effect on the heart and modulatory effect on distribution of free water in the vascular compartments. In the cases of corticosteroid absence stress may cause shock, hypotension, and death.

Aldosterone effects electrolyte balance, primarily modulates potassium and sodium level, through its action on kidneys, gastrointestinal system and sweat glands. Excess of aldosterone causes retention of sodium and urinary loss of potassium, as well as, metabolic alkalosis. Deficite of aldosterone causes opposite effects: loss of sodium, retention of potassium and metabolic acidosis. Excess of potassium stimulates aldosterone release, which on the other hand, will stimulate potassium excretion. Aldosterone is the most important factor in regulation of potassium level in the organism. Deficiency or excess of adrenal cortex hormones, in patients who are planned for surgical treatment (for any reason) demand careful and specific preop-
Preoperative preparation, in order to avoid intraoperative and postoperative complications that may be life threatening.

**Preoperative Preparation of Patients with Deficiency of Hormones Produced in the Adrenal Cortex**

Deficiency of hormones synthesized in the adrenal cortex, if not primarily corrected, will result in adrenal insufficiency (AI), shock and lethal outcome. Prevention of the AI must be included within the preoperative preparation procedure in all patients with inadequate adrenal tissue reserve. This is especially important for all patients who are therapeutically receiving exogenous glucocorticoids. Few weeks after the onset of steroid therapy, atrophic changes in the adrenal glands are evident. Exogenous production of hormones by adrenal glands will start several months after cessation of steroid therapy. Due to all of the above reasons of therapy should be gradual, because adrenal cortex is incapable of prompt stress response. Crisis of hypocorticism usually develops 24 hrs after cessation of steroid therapy. Manifestation of the hypocortical crisis is related to the severity and extent of stress reaction.

Which patients must receive perioperative glucocorticoid supplementation, or stress dose of steroids?

1. Patients with Addison’s disease
   - Addison’s disease or primary AI is rare autoimmune disease (incidence is 110 on 1,000,000 population). Chronic AI will develop after 90% of the adrenal gland tissue has been destroyed. Gradual destruction of the adrenal cortex in the initial phase of the disease, causes decrease in the adrenal reserve, meaning that basal steroid secretion is partially preserved, but increased production of hormones in response to stress is not possible. This means that acute adrenal crisis in these patients (without obvious clinical picture) may be caused by operative stress, trauma or infection, or by any other condition that requires increased corticosteroid secretion. Further development of the disease with subsequent loss of the adrenal cortical tissue will decrease basal glucocorticoid and mineralocorticoid secretion causing clinical manifestation of the AI. Decrease of the cortisol secretion causes increase in ACTH secretion (negative feedback mechanism); therefore increased plasma ACTH level is the earliest and the most sensitive indicator of suboptimal adrenocortical reserve.

2. Patients who had bilateral adrenalectomy. It is also recommended to treat patients after unilateral adrenalectomy, as well as, patients who had surgical procedure on hypophysis.

3. All patients on glucocorticoid therapy instituted one year before surgical procedure, despite the reason, in any dose, and in any form of application (oral, parenteral, inhalatory and even local).

Especially important is to make good preoperative evaluation in those patients who are not able to give us reliable information about the type and doses of medications prior to surgery. Comorbidity that may be treated with steroids is various: bronchial asthma, rheumatoid arthritis, systemic lupus erythematosus, ulcerative colitis, hematological disturbances with thrombocytopenia, immune suppressive therapy, allergy etc.

In order to select patients with increased risk for the development of perioperative AI, diagnostic tests must be performed. Determination of basal values of ACTH and cortisol is important for distinction between primary and secondary AI. In primary AI, basal cortisol level is decreased, and level of ACTH is increased. In secondary AI, basal cortisol values may be normal or even increased, but insufficient to meet the needs of the organism, especially in the state stress. ACTH hormone stimulation test (with 1 µg of natural ACTH or 250 µg of synthetic ACTH) has great diagnostic value due to its ability to distinguish between primary AI, secondary AI, partially secondary AI, and relative AI. If the diagnosis is obscure following these tests, ACTH response is evaluated with test of insulin induced hypoglycemia or with metyrapone test. Normal response upon ACTH stimulation, without stress, is plasma cortisol value equal to or greater than 20 µg/dl, and during period of stress or severe disease, total serum cortisol is increased 2-10 times above upper normal values. Even though there is no absolute value of serum cortisol that could make clear distinction between adequate and insufficient adrenal response, data from the contemporary literature confirm that the threshold for the diagnosis of adequate cortisol response in critically ill is 25 µg/dl.

Regimens for perioperative glucocorticoid supplementation in patients with limited adrenal reserve

Perioperative supplementation of glucocorticoids in patients with limited adrenal reserve depends on the type of surgical procedure, and on the extent of the stress imposed by the procedure. The basic principle is that the dosages for supplementation should not be smaller than the dosages already given to the patient for therapy of the intercurrent disease. It is also recommended that the dosage of glucocorticoids should be doubled 2-3 days prior to the elective surgery. When titrated doses for substitutional therapy it should be kept in mind that daily cortisol production from both adrenal glands in normal conditions (without stress) is 12-30 mg, and this value should be hydrocortisone maintenance dose value. Under the maximal stress adrenal glands may synthesize 200-500mg and according to this, maximal stress dose that may be applied for supplementation is 200-400mg.

There are different protocols, guidelines and recommendations for perioperative supplementation (according to Aron, Clark, and Rosen, shown in the table). Some authors suggest that better hemodynamic stability is achieved if glucocorticoid preparations are given as short infusions, not as IV bolus injections.

Modified protocol according to Aron:

1. Correction of the electrolyte disbalance and arterial pressure, hydration of the patient if necessary.
2. Hydrocortisone (sodium phosphate or sodium succinate) 100mg IM, before entrance in the operating theatre.
3. Hydrocortisone 50 mg IM or IV after the surgical procedure, every 6 hours during next 24 hours.
4. If the postoperative period is satisfactory, dosage should be reduced to 25 mg of hydrocortisone given every 6 hours during next 24 hours, and in the following 3-5 days doses should be gradually decreased to the maintenance level. Fludrocortisone should be given once the patient is capable for oral intake.

5. In the protocol according to Clark the following is recommended:
   a) for minor diagnostic and surgical procedures: hydrocortisone 25-50 mg during the induction phase
   b) for medium sized surgical procedures: hydrocortisone 50 mg for induction phase, and then 25 mg every 6 hours during 24 hours
   c) for major surgical interventions: hydrocortisone 50 mg for induction phase and then every 6 hours during following 48 to 72 hours.

   After this period usual therapeutic dose of required steroids is implemented.

   Roizen recommends (for person whose body weight is 70 kg):
   - for major surgical procedures (maximal stress), application of 200 mg of hydrocortisone during the day.
   - for minor surgical procedure, application of 100 mg of hydrocortisone IV daily.

   Each following day decrease the dosage for 25%, until the patient is capable for oral intake or until maintenance dosage is applicable. This does not apply if complications develop (i.e. infection), in which case dosages are being increased instead of being decreased.

   It is obvious from the above that all of the suggested protocols differ slightly from each other and their common features are:
   1. Minor surgical procedures (hernioplastic, laparoscopic cholecystectomy, knee surgery): 25 mg IV for 1 day
   2. Moderate surgical stress (opened cholecystectomy, partial colon resection): 50-75 mg IV for 1-2 days
   3. Major surgical stress (pancreatoduodenectomy, oesophagectomy, total colectomy, cardiopulmonary bypass, ilio-femoral bypass): 100-150 mg IV per day, for 2-3 days
   4. Patients who develop hypotension, or their condition deteriorates in the period of postoperative recovery, receive maximal stress dose of 200-400 mg IV per day.

   If the adrenal crisis develops after all, prompt response is mandatory. There are several therapeutic protocols used in the acute adrenal crisis (Clauer, Aron). All these protocols require immediate interventions and applications of steroid therapy. Immediate procedures include: maintenance of the airway, breathing and circulation. For correction of dehydration aggressive volume replacement with 5% dextrose in physiologic solution is used. Hypoglycemic and electrolyte disbalance is corrected at the same time. Hypoglycemia is present in 67% of the adrenal crisis cases, and for correction of this condition 50% dextrose is recommended. Electrolyte disbalances seen in the adrenal crisis are: hyponatremia in 88% of cases, hyperkalemia in 64% of cases and hypercalcemia in 6-33% of cases. Steroids are applied immediately. Hydrocortisone 100mg IV is given, which is repeated every 6 hours during first 24 hours. This means that total daily dose on the first day is 400 mg IV, and afterwards it is decreased for 50mg. It is expected that complete stabilization is achieved in the following 4-5 days, enabling dosage adjustment to the maintenance dosage, with addition of mineralocorticoids if necessary.

   In childhood period recommended daily dosages for therapy of adrenal crisis are:
   - Children <12 years of age: 1-2mg/kg IV bolus, then infusion of 25-150mg/24 hours divided into 3-4 doses
   - Children >12 years of age: 1-2mg/kg IV bolus, then infusion of 150-250mg/24 hours divided into 3-4 doses

   However, the newest recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients are (consensus statement from an international task force by the American College of Critical Care Medicine):12
   - Hydrocortisone (daily dose for the adults): 200 mg divided into 4 equal doses or 240 mg in continued infusion
   - Methylprednisolone as the 2nd choice therapeutic agent: 1mg/kg/24h

   Also, all necessary therapeutic measures aimed at treating infections or any other precipitating and complicating condition are instituted as needed. Response to therapy is usually very quick and improvement is seen in the first 12 hours. In patients with severe complications (i.e. sepsis) high doses of cortisol up to 100mg IV every 6 hours are used, until the condition is stabilized. In primary AI, mineralocorticoids (in the form of fludrocortisone) are instituted when the total daily cortisol dose decreases up to 50-60mg/day, while in the acute crisis seen in AI usage of glucocorticoids is sufficient. Intramuscular usage of cortisol acetate is contraindicated in the acute adrenal crisis, due to its slow absorption and conversion into cortisol in the liver which is required for the therapeutic effect. Cortisone acetate also expresses inadequate suppression of the ACTH (inadequate glucocorticoid activity).14

**PREOPERATIVE PREPARATION IN PATIENTS WITH EXCESSIVE PRODUCTION OF THE ADRENAL CORTEX HORMONES**

The most frequent diseases that cause excessive production of the adrenal cortex hormones are Cushing’s syndrome (hypercorticism) and Conn’s syndrome (hyperaldosteronism).

**Cushing’s syndrome**

The most common cause of Cushing’s syndrome is exogenous usage of steroids for the therapeutic purposes. Another cause is the presence of ACTH secreting tumor of the hypophysis and finally the primary lesion of the adrenal glands (ACTH independent). Primary lesions are mostly adenomas of the cortex, micronodular and macronodular hyperplasia, and carcinomas of the adrenal gland.
Cushing’s syndrome causes significant disturbances in the volume of body fluids and in the electrolyte concentration, as well as, changes on different organs and organ systems.\(^1\,^2\)

Following characteristics must be emphasized when we talk about perioperative preparation of the patient with Cushing’s syndrome: electrolyte and acid-base disturbances (hypokalemia, metabolic alkalosis), obesity, hypertension, coronary disease, hyperglycemia, osteoporosis, anemia. Most of the patients have some form of psychological disturbance, and 30% of patients develop steroid psychosis. Increased predisposition toward infection in perioperative period is seen in these patients.\(^1\,^8,^9\)

**Arterial hypertension**, with fluid retention, and increased rennin levels, increased vascular reactivity, if poorly controlled may cause damage to the other organs. Arterial hypertension occurs in 85% of the patients with Cushing’s syndrome. ECG may shows ischemic lesions (high QRS complex and inverted T wave), and these patients need cardiologic evaluation prior to surgery in order to achieve good perioperative regulation of hypertension. Antihypertensive therapy is instituted until the day of the surgical procedure. In the cases of surgical procedures with vital indications spironolactone up to 400mg/day is used; in order to temporarily normalize intravascular circulatory volume through elimination of excessive fluid and preservation of potassium. Depending on the time available for perioperative preparation ACE inhibitors (Captopril 12, 5 to 50 mg/day) or Ca channel antagonists may be used. If the hypertension is poorly regulated then hypertensive crisis with disturbances of cardiac rhythm is likely to develop.\(^1\)

**Hypokalemia and metabolic alkalosis** must be corrected preoperatively even before the vital surgical procedure, with continuous potassium level monitoring during the procedure. Hypokalemia may cause life threatening disturbances of the cardiac rhythm even in the non stressful conditions. Effect of hypokalemia is augmenting during anesthesia and surgery due to stress, anesthetic agent, bleeding etc. Slow IV administration of potassium chloride at a dose of 0, 5 mmol/kg/h or 20-30 mmol/h is used for the correction of hypokalemia together with frequent controls of the serum potassium values and continuous ECG monitoring.\(^\text{20}\)

**Poor glucose toleration and diabetes mellitus** are frequent in this syndrome due to decreased peripheral utilization of glucose, gluconeogenesis, antinsulin activity of glucocorticoids etc. It is necessary to regulate glucose level in the preoperative period, and this is achieved with oral antidiabetic agent, until satisfactory glucose levels are achieved. If vital surgical interventions, or major surgeries, after which patient will not be able to start oral intake for a long time are expected, insulin is used for glucose regulation and the dose is titrated according to the measured values.\(^7\)

**Obesity** of the patient with Cushing’s syndrome, which is found in 80% of cases is important for the anesthesiologist due to the following problems:\(^1^9\)
- position of the peripheral venous line is not easily established
- mask ventilation, laryngoscopy, and intubation are difficult
- intraoperative lung ventilation may be inadequate as well
- it is difficult to change position of the patient on the operating table (especially in the dorsal decubitus position)
- consider liposolubility of inhalatory anesthetics, due to their deposition in the adipose tissue
- careful titration of the amount of IV anesthetics due to their lipophilic and hydrophilic properties, and due to the large volume of distribution in obese patients
- somnolence and sleep apnea are more frequent in obese patients during the postoperative period. Patients with prolonged obstructive sleep apnea, may develop pathologic changes of the right heart due to progression of pulmonary hypertension
- wound healing is prolonged and problematic in these patients
- infections are more frequent
- in these patients tromboembolic complications are more frequent, so these patients need preoperative prevention with low molecular weight heparin.

**Gastroesophageal reflux** is very common in patients with Cushing’s sy and antireflux preoperative therapy with antacids and prokinetics is needed, in order to prevent vomiting, regurgitation, and aspiration. Infections and slow wound healing is also common finding in these patients, therefore placement of IV lines, central venous catheters, urinary catheters must be performed in strictly aseptic conditions. Antibiotic prophylaxis is recommended even for the, so called, "clean" surgical procedures. Steroid psychosis is sometimes so prominent feature, that in some cases psychiatrists make diagnosis of the Cushing’s syndrome. Prolonged usage of the antipsychotic, anxiolytic, and other psychiatric medications may cause psychological and physical dependency and appearance of the apstinential syndrome in the postoperative period. Certain antipsychotic drugs may interact with anesthetics. Especially important is to determine whether the patient is using tricyclic antidepressants and MAO inhibitors in order to make good choice of anesthetics. Osteoporosis must be evaluated preoperatively because fragile, osteoporotic bones might be fractured due to the changes of body position of the patient during surgery. Airway evaluation is needed because of possible problems with laryngoscopy and intubation. These patients might have trouble some mechanical ventilation of the lungs due to obesity, increased resistance, decreased compliance and weak musculature of the respiratory system.\(^1^8\)

**Evaluation of the therapeutic regimens** used for the therapy of the Cushing’s syndrome is important for the preoperative evaluation. Medical therapy used for treatment of Cushing’s syndrome is inhibiting process of steroidogenesis. The most frequently used agents are: mitotane, ketoconazole, metyrapone, aminoglutetimide, etomidate, trifluridone. These drugs are more effective when used in combination because they have synergistic action. Medical therapy must be introduced gradually and with great
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Conn’s syndrome

Conn’s syndrome is caused by the excessive production of the mineralocorticoids in the adrenal cortex. The most important disturbance seen in Conn’s syndrome that must be corrected prior to surgery is disturbances of the electrolyte balance, metabolism and cardiovascular system.

Hypertension is usually severe and resistant to usual therapy.

Increased diastolic pressure is particularly significant for these patients (100-125 mmHg). Heart problems frequently occur: left ventricular hypertrophy (not proportional to the level of blood pressure), angina pectoris, myocardial infarction, heart failure. Peripheral vascular diseases are also common, and they cause retinopathy, nephropathy, peripheral artery disease. Proteinuria is present in 50% of patients with the primary aldosteronism, and 15% of cases have renal insufficiency. Transitory ischemic attacks and cerebrovascular accidents may also occur.

Electrolyte and metabolic disturbances in Conn’s syndrome are: hypokalemia (usually above 3 mmol/l, but might be very severe - even less than 2.5 mmol/l), hypernatremia, metabolic alkalosis, DM. The other manifestations of Conn’s syndrome are neuromuscular symptoms (muscular weakness, tiredness, periodic paralysis, spasms, tetany, paresthesias), polyuria with nocturia. Polyuria and nocturia are caused by the decrease in renal concentrating capacity caused by hypokalemia.

Preoperative evaluation of the operative risk depends on the symptoms of the disease, stage of the hypertension, degree of the hypertension regulation, potassium concentration in serum, acid-base balance, metabolic balance and presence of the organ damages.

Main goals of the preoperative preparation are: regulation of blood pressure and potassium level. Regulation of blood pressure requires combination of several drugs and their doses, depending on the arterial pressure values and comorbid conditions and complications. The first choice therapeutic agent is potassium sparing diuretic Spironolactone given at a dose of 100-400mg/day. Alternative to this agent is Amiloride at a dose of 5-15mg/day or Nifedipine (30-90 mg/day). ACE inhibitors are also used (Captopril) and inhibitors of the angiotensin receptors (Losartan-Na). Short preoperative preparation before urgent/ vital surgical intervention include: fast potassium supplementation (0.5mmol/kg/h), and regulation of hypertension with infusion of vasodilators.

CONCLUSION

Patients with deficient production of the adrenal cortex hormones have limited adrenal reserve and are not able to respond to an increased need for cortisol hormone in the state of stress. In order to prevent development of the adrenal crisis and acute adrenal insufficiency it is important to administer stress doses of glucocorticoids in the course of preoperative preparation. Different surgical procedures impose different levels of increased stress upon the patient. This must be kept in mind when titrating the doses required for perioperative glucocorticoid supplementation.

Excessive production of the hormones in the adrenal cortex whether as a part of Cushing’s syndrome, Conn’s syndrome or some other etiology, will cause numerous disturbances, primarily hypertension and hypokalemia.

Preoperative preparation of these patients require correction of the disbalances, in order to avoid development of complications, among which some might be life threatening.

SUMMARY

Preoperatīvās priepriekas bolesnīcām sa poremēcājumi funkciēs kore nadubrēzē uzlāde bazē ir pašlīdzīgās preoperatīvās evaluācijās vrste un težā poremēcājumā. Ti poremēcājá mēgt būt divvajās: insuficijēce (pretēca, blaga vai izražēna) vai hipertunki (hiperkorticizm un/i hiperaldosteronizm).

Ukoliko s u pitanju bolesnici sa limitiranom adrenalnom rezervom (Adisonova bolest, terapijska primena glukokortikoida idr.), onda je takvim bolesnicima potrebna supstitucija kortikosteroida, kako u preoperatīvom privremp ce, tako i u celom perioperativom period. Dože za supstituciju prilagodjavaju se težini oseanalne insuficijencije i težini (veličini) planirane hirurške intervencije.

Bolesniki sa Kušingovim sindromom (ili drugim oblicima hiperkorticizma), kao i bolesnici sa Konovim sindromom ( ili drugim oblicima hiperaldosteronizma) imaju četvrt niz poremēcājumi funkcije organa koji su od značaja za preoperatīvnu priepremu, anesteziju i ishod hirurške lečenja. Zajednički imenitelj za ova dva sindrom je hidroelektroliti disbalans, sa hipokalijemijom kao dominantnim poremēcājumom i metabolicka alkaloza, kao i izražena hipertenzija. Poremēcājuni vezi sa hipertunkcijom adrenalnog korekta se moraju korigovati preoperatīvno kako ne bi došlo do komplikacija, a kada je u pitanju hipokalimija, ona se obaveznim pre ishod komplikacija, a kada je u pitanje hitne hirurške intervencije jer može rezultirati teškom srčanom aritmijom u toku operacije.

Ključne reči: preoperatīvās prieprema, korticīl, aldosteron, Adisonova bolest, Kušingov sindrom
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