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ORIGINAL ARTICLE

General anesthesia for congenital adrenal hyperplasia: a single institution's experience

Sema Şanal Baş

Department of Anaesthesiology and Reanimation, M.D, Eskişehir Osmangazi University Faculty of Medicine Büyükdere, 26040, Eskişehir, Turkey

Corresponding author: Sema Şanal Baş, Department of Anaesthesiology and Reanimation, M.D, Eskişehir Osmangazi University Faculty of Medicine Büyükdere, 26040, Eskişehir, Turkey. E-mail: drsemasa@gmail.com

Keypoints

- Propofol, rocuronium and remifentanil is the suitable anesthetics to be administered during the surgical procedures in the patients with congenital adrenal hyperplasia for the anesthesia induction.
- Sevoflurane which is the most recommended anesthetic in the literature for the congenital adrenal hyperplasia pediatric patients for the maintenance of the anesthesia after the induction.
- Congenital adrenal hyperplasia patients should be closely monitored in terms of bradycardia and hypotension who are under the risk of adrenal insufficiency during and after surgical operations.

Abstract

Introduction

The goals of the perioperative approach for the patients with childhood Congenital Adrenal Hyperplasia (CAH) are not similar at most centers. In this study, the effectiveness of the anesthetic method and our peroperative steroid treatment applied to pediatric patients with CAH undergoing surgical procedures was evaluated.

Materials and methods

In the study CAH who were undergo elective pediatric surgery were included retrospectively. Propofol, lidocaine, remifentanil and rocuronium were given intravenously for induction. Anesthesia was maintained using sevoflurane and remifentanil. All the patients were administered 3 times with 10 mg/m2 of intravenous methylprednisolone before the operation.

Results

15 patients (8 male, 7 female) with CAH experiencing salt wasting due to 21 hydroxylase deficiency were included in the study. During the operation, the additional steroid administration was necessary for 6 (40%) out of 15 patients due to bradycardia, hypotension and fever. All of these 6 patients were administered an additional dose of 1 mg/kg of methylprednisolone.

Discussion and Conclusion

We are of the opinion that the morbidities likely to develop in the cases with CAH who are under the risk of adrenal insufficiency may be precluded by the closely monitoring during and after the operation and by the administration of an additional steroid doses.

Keywords

Adrenal hyperplasia, congenital diseases, pediatric anesthesia

Introduction

Congenital adrenal hyperplasia (CAH) is an autosomal recessive hereditary disease arising from a genetic defect of one of the five enzymes which take part in cortisol synthesis from cholesterol inside adrenal cortex. Its incidence in the world is about 1:15000. Most encountered form of CAH is 21-hydroxylase deficiency, which has

90% incidence. 21-hydroxylase enzyme catalyses the transformation of progesteron to deoxycorticosterone and 17-hydroxyprogesterone to 11-deoxycortisol (1-2).

Pediatric CAH patients have similar perioperative approach in many of the centers in the world, nevertheless their treatment protocols may be varied according to each specific surgical intervention during which they undergo (3-9). However, there is no evidence-based data regarding any perioperative approach within this context. We aim here to present our perioperative approach to 21-hydroxylase deficient pediatric CAH patients who are scheduled for various surgical operations. We present our general anesthesia management, efficacy of our perioperative steroid treatment and possible adverse events.

Materials and methods

15 CAH (salt-losing deficiency due to 21-hydroxylase defect) pediatric patients are retrospectively included in our study. Hospital ethical committee approved our study. All the patients' diagnoses, previous therapies, operation types, perioperative and post-operative adverse events have been extracted from hospital files and documents. Patients were under treatment of hydrocortisone 15-17 mg/m^2/day (three times a day) and fludrocortisone acetate 0,2 mg/day dosage. The fasting times for the children were set as 2 hours for clear liquid, 4 hours for breast milk and 6 hours for infant formula or solid food. All patients are hospitalized one day before surgery. Pre-operative visit and informed consent is completed. Premedication included per oral 0,3 mg/kg midazolam. All patients received methyl prednisolone 10 mg/m^2/dose at the night before surgery. Also, same doses of methyl prednisolone are administered to each patient just before general anesthesia induction, and during the ongoing operation. Weight-appropriate continuous iv fluids with 5% dextrose and 0.9 % NaCl were used during surgery. Propofol 2-4 mg/kg iv, lidocaine 0,5-1 mg/kg, remifentanil 0,5-1 µg/kg, rocuronium 0.45-0.6 mg/kg were administered for induction. Anesthesia maintenance involved 4 liter/minute 50% air with 50% oxygen, and sevoflurane inhalation (MAC 1-1.3), together with iv remifentanil infusion 0.05-0.2 mcg/kg/minute (infused until the end of surgery). Perioperative heart rate, mean blood pressure (MAP), peripheral oxygen saturation (SpO_2), end-tidal carbondioxide ($etCO_2$) and body temperature values are recorded and monitorised. Infra-red non-touch fore-head thermometer is used to detect and record body temperature before induction, during operation and at the recovery room.

If hypotension and bradycardia are detected simultaneously, extra dose of steroids (1 mg/kg methyl-prednisolone) are given iv concomitantly. Blood glucose, Na, and K level were measured before, during, and after surgery.

The study was approved by the Local Ethics Committee of our hospital, and informed consents were provided from all participants and/or their parents and/or legally responsible persons. All study procedures were performed in accordance with the Helsinki Declaration of 1975, as revised in 2008.

The analysis of data was performed using SPSS for Windows 23 package software. In addition to descriptive statistical methods (mean and standard deviation), Student's t-test and the Mann-Whitney U-test were used to compare quantitative data. The results were evaluated at 95% confidence intervals, with a significance level of $p < 0.05$.

Results

Of the 15 cases, 7 of them are girls and 8 of them are boys. Ages varied between 2-120 months. Body weights varied between 4-40 kg. Heights varied between 52-128 cm. All cases have (21OHD) salt-losing CAH diagnoses. Different surgical operations are scheduled.

These (elective) surgeries are not emergency procedures in our patients.

7 patients are subjected to vaginal reconstruction, 3 patients are subjected to hypospadias, 2 patients are subjected to cystoscopy, 1 patient is subjected to testicular biopsy, 1 patient is subjected to central catheter insertion, and 1 patient is subjected to circumcision.

Mean operation durations are 133±76 minutes, anesthesia durations are 154±83 minutes, recovery durations are 8,8±1,3 minutes. During operation, mean heart rate is

121±16 beats/minute, MAP is 54.2±5.5 mm/Hg, etCO2 is 32.8±4.5 mm/Hg and saturation is 99±0,7 %.

Before the induction, infra-red non-touch fore-head thermometer is used to detect and record body temperature of all patients, their average body temperature was 36,6±0,1 C^0, the average body temperature during the operation was 37±0,1 C^0 and the average body temperature in the recovery unit was 37,1±0,5 C^0. During the operation, 6 of the 15 patients (40%) needed extra dose of steroids administrations because of bradycardia, hypotension and/or fever. 4 patients needed atropine. Extra dose of steroids administrations are recorded about 42±32 minutes after the start of initial surgical incision. The patients had no tachycardia. Urinary output was normal. There is no recorded problem with blood glucose, Na or K level before, during and/or after surgery. In only one patient with elevated body temperature during the operation, (although the cause of fever could not be determined) the body temperature values returned to the normal range upon the administration of additional dose of iv methyl-prednisolone. Only one of the patients needed blood transfusion during the vaginal reconstruction operation. After erythrocyte suspension (10 ml/kg) transfusion, additional dose of steroid is administered during the operation. Post-operative analgesia involved 15 mg/kg paracetamol and 1 mg/kg tramadol iv infusions. No mortality is recorded.

Discussion and Conclusion

There is no randomized controlled study in the literature about anesthesia management of pediatric patients with congenital adrenal hyperplasia. Published data and the information is limited; usually single case reports in the form of case presentations (1,9). Our study aims to present 21-hydroxylase deficient pediatric CAH patients undergoing various surgical procedures, who received same general anesthesia management and steroid treatment. We believe this study is worth presenting, since there is no any similar previous study published in literature.

Congenital adrenal hyperplasia (CAH) is an autosomal recessive inherited disease resulting from the deficit of one of the five enzymes necessary for the synthesis of cortisol from cholesterol. The deficient enzyme is 21-hydroxylase (P450c21) in 90 % of CAH cases. The clinical symptoms emerge upon excess testosterone and dihydrotestosterone in the peripheral tissues as a result of the excessive increase in the secretion of ACTH caused by the lack of cortisol which is not produced enough. Due to the enzyme deficiency, the conversion of progesterone and 17-OHP, and of the adrenal androgens lead to CAH. Since the enzyme 21-hydroxylase is also essential for aldosterone synthesis, the synthesis of aldosterone is also disrupted; the salt wasting (losing) may lead to specific symptoms which accompany the clinical picture in the case of complete lack of this enzyme (2,3). The usual salt wasting type is the complete lack of the enzyme 21-hydroxylase and the synthesis of aldosterone is also deficient in addition to cortisol. 75% of the CAH cases are of this type (1-3). In accordance, all of our patients in our study group had this type of salt wasting form of 21-hydroxylase deficiency.

The literature consists very limited data; only sporadic case reports of pediatric CAH patients undergoing general anesthesia. There is no published controlled study of these patients which evaluate or assess steroid treatment, morbidity and mortality during general anesthesia management procedures. In the literature, there are different case reports of doses and administrations of steroids. Replaced amount of cortisol-steroid in CAH is not similar to the amount of physiological secretion of cortisol. Furthermore, the individual differences in the drug metabolism and the gene polymorphism of the glucocorticoid receptors cause difficulties in achieving the optimum hormonal control (7-10). During stressful situations (for example surgery, trauma, severe sickness), 2 or 3 times more than physiological doses are needed and should be administered. In order to prevent adrenal crisis in stressful conditions like severe sickness, surgical intervention or trauma, daily hydrocortisone doses might be increased 3 or 6 times; administration routes are mainly intramuscular (im) or intravenous (iv) (2,3,6-11). Accordingly, we administered methylprednisolone 3 times at 10

mg/m^2/dose to our patients; one night before the operation, in the morning of operation, and during the operation. In addition, we had to administer an additional steroid dose after we observed symptoms of adrenal insufficiency in 6 out of 15 patients. We suggest that adrenal insufficiency is at such high frequency because of the above-mentioned reasons as well as the use of methylprednisolone instead of hydrocortisone and the administration of the same drug dose in the surgical procedures with different durations of surgeries.

It is stated in the literature that adrenomedullary function is also disrupted in CAH patients with adrenal cortex insufficiency, which might be another contributing factor to adrenal crisis especially in the cases proceeding with excessive salt wasting. As a supporting evidence, it is known that 21-hydroxylase deficiency patients proceeding with excessive salt wasting may experience adrenal crisis in the presence of inflammatory disease and other stressful conditions despite sufficient glucocorticoid and mineralocorticoid replacement (1-3,7-9). Even though we administered adequate doses of steroids to all the patients before and after the surgery, significant proportion of our patients showed symptoms of insufficiency. This may be because of use of methylprednisolone instead of hydrocortisone as well as affected and disrupted adrenal medulla; therefore they may have both contributed to insufficiency symptoms of our patients.

Although the literature contains various steroid protocols according to the severity and duration of surgery of patients with CAH, there is no any published randomized controlled study about exact amount of steroid needs and/or replacements.

It is estimated that in case of major surgery, cortisol is secreted at a quantity of 75-100 mg in adults and in case of minor surgery, cortisol is secreted about 50 mg in adults. There is no available information about the release of cortisol in pediatric CAH patients during the surgical procedures (1,6-10).

Besides, various steroid protocols with different doses are recommended for the surgical procedures that necessitate general anesthesia, while there are also various treatment protocols developed individually according to the severity and the stress load of each surgery. In this study, we administered a standard dose in a small number of patients with CAH, in a manner independent from the duration and severity of the surgical procedure. The small number of our cases as well as same steroid dose protocol to all patients were the major limitations of our study.

As a situation not reported previously in the literature, one of our cases developed fever of unknown etiology after the caudal epidural anesthesia (for postoperative analgesia of hypospadias operation). Interestingly, improvement of the patient upon the subsequent administration of standard steroid dose, made us think that it may be acute adrenal insufficiency. In literature, there is only one case report about the application of the caudal epidural anesthesia in a patient with CAH (12). This caudal method is recommended in CAH patient group, since no problem (or adverse event) is recorded (12). However, we believe that further randomized controlled studies are needed to confirm such recommendation to become generally accepted. Due to the situation encountered in our study, we think that it would not be appropriate to recommend the use of the caudal epidural anesthesia in all CAH patient groups.

Etomidate is one of the agents used for the induction of anesthesia. It is particularly not recommended in case of adrenal insufficiency because etomidate inhibits the steroid synthesis particularly in the unstable patients with hemodynamic deterioration (1,3,13). Propofol is the most widely used intravenous agent used for the induction of anesthesia. It is easily titrated during the anesthesia care, it has rapid onset and termination of action especially in pediatric patients. The opioids are also frequently preferred for perioperative analgesia purposes during surgical procedures (14). Remifentanil has very rapid onset and termination of action. After cessation of remifentanil infusion, the average extubation time is in the range of 8-13 minutes. Remifentanil may also be preferred in neonates and children for the purpose of sedation and

analgesia during flexible bronchoscopy, endoscopy, cardiac electrophysiological studies, ROP examination (retinopathy of premature) and bone marrow aspiration procedures (15). Sevoflurane is an inhaler agent which is halogenated ether with fluorine. Owing to its low solubility, it has rapid induction and rapid recovery capabilities. It also provides good control over the depth of anesthesia. Sevoflurane is also preferred in pediatric age groups because it is strong inhaled anesthetic allowing rapid recovery. Moreover, it does not depress the myocardial contractility in the children (unlike other halothane and halogenated inhalers) (16). Rocuronium is a commonly used neuromuscular blocker agent with steroid structure. It has intermediate duration of action. It is a non-depolarizing neuromuscular blocking agent with rapid onset of action and optimum duration of action. It was reported that it provides the best intubation conditions in 60-90 seconds after its intravenous administration. Furthermore, its cardiovascular side effects are minimal (17). In literature, we found some information about the suitable anesthetics to be administered during the surgical procedures in the patients with congenital adrenal hyperplasia. Propofol, rocuronium and remifentanil are the agents of choice for our patients; we administered for the anesthesia induction as they are commonly preferred for the anesthesia induction in the pediatric patients and they have relatively less possible side effects. We used sevoflurane, which is the most recommended anesthetic in the literature for the pediatric patients, for the maintenance of the anesthesia after the induction.

Although the modern techniques of anesthesia practice and introduction of novel anesthetics minimize the stress response during surgical interventions, we are of the opinion that CAH patients should be closely monitored. As a result morbidities are still likely to develop in the cases with CAH who are under the risk of adrenal insufficiency during and after surgical operations. Administration of an additional drug, notably steroids, may be considered as an option of treatment.

Ethics approval

Ethical approval from Eskişehir Osmangazi University Ethical Commitee

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