Balkan Med J 2011; 28: 338-340 • DOI: 10.5174/tutfd.2009.03067.4

Anesthetic Management of a Pediatric Patient with Arginase Deficiency

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ABSTRACT

Arginase deficiency is an autosomal recessive disorder of the urea cycle in which a defect in conversion of arginine to urea and ornithine leads to hyperammonemia. Patients with urea cycle disorders may show increased protein catabolism due to inadequate intake of energy, protein and essential amino acids; infections, fever and surgery. A 12-year-old girl with arginase deficiency, ASA II who weighed 40 kg was scheduled for bilateral adductor, quadriceps and gastrocnemius tenotomies. She had mental retardation, spasticity and flexion posture of thelower limbs. Metabolic homeostasis was restored with appropriate diet. Successful anesthetic management allowed the patient to be discharged 48 hours after surgery. Increased levels of arginine and ammonia during or after surgery may lead to serious complications such as hypotension, cerebral edema, convulsions, hypothermia and spasticity. Thus special attention must be given to metabolic homeostasis and nutrition of the patients with arginase deficiency in the perioperative period. Primary goals should be to minimize stress levels by effective anxiolysis, provide an adequate amount of protein-free energy with proper fluid management and to obtain an effective preemptive and postoperative analgesia. In addition to a high level of knowledge, successful anesthesia requires professional communication among nursing staff, dietitians, pediatric metabolism specialist, surgeon and anesthesiologist.

Key Words: Arginase deficiency, spasticity surgery, anesthetic management

Received: *20.07.2009* ***Accepted:*** *17.11.2009*

Introduction

Arginase deficiency is a rare congenital autosomal recessive disorder of the urea cycle (1). A defect in the conversion of arginine to urea and ornithine results in increased blood levels of arginine and ammonia (1). Arginase deficiency causes a neurological syndrome characterized by progressive spastic quadriparesis, psychomotor growth retardation and epileptic seizures (2). Peak ammonia levels are typically lower than those of other urea cycle disorders, but may occasionally be excessive in the presence of accelerated endogenous catabolism (1, 3). In a healthy individual, amino acids that are not utilized for protein synthesis are eliminated through several biochemical pathways and excess nitrogen is converted to urea. Patients with urea cycle disorders may show increased protein catabolism due to inadequate intake of energy, protein or essential amino acids; infections, fever, surgery, strenuous physical activity or labour (4). Anesthesia of an arginase-deficient patient may be complicated by serious problems including hypotension, cerebral edema and epileptic seizures. Paucity of relevant information in the literature poses several challenges in the anesthetic management of these patients. Few cases of arginase-deficiency have been described in the literature, one of which was related to anesthetic management (3, 5). In this report, we presented the anesthetic management of a pediatric patient with arginase deficiency.

Case Report

A 12-year-old female child, ASA grade II who weighed 40 kg was scheduled for bilateral adductor, quadriceps and gastrocnemius tenotomies. She was diagnosed to have arginase deficiency when she was 3 years old. She had mental retardation, spasticity and flexion posture of the lower limbs. Metabolic homeostasis was restored with a specific diet for urea cycle disorders, which includes essential amino acids, arginine-free dietary supplements involving a malt dextrin preparation. The preoperative level of ammonia of the patient (24 μmol/L) was within reference range (9-33 μmol/L). Neither she nor her family reported a history of an anesthesia-related problem. Quadriceps tenotomy was performed 7 years previously with no complication.

Oral intake of solid food was stopped eight hours before surgery. Clear fluid intake was stopped four hours before surgery. Premedication was achieved with 0.05 mg kg^{-1} intravenous (IV) midazolam and 0.1mg kg^{-1} IV ondansetron half an hour prior to induction of anesthesia. Under standard monitorization, anesthesia was induced with 0.006 mg kg^{-1} alfentanil and 5.6 mg kg^{-1} IV thiopental. Laryngeal mask airway (LMA, 2.5 size) was placed at the second attempt. Anesthesia was maintained with sevoflurane 1.5% in N_2O:O_2 (50%: 50%). Preemptive analgesia was provided with "0.5 mg kg^{-1} IV meperidine" and "0.25 mg kg^{-1} IV tenoxicam" administered just

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before the initiation of the surgical incision. Throughout the procedure, the patient's systolic blood pressure, heart rate, and end-tidal carbon dioxide concentration ranged between 100-110 mmHg, 80-100 bpm, and 30-35 mm Hg, respectively. In total 400 mL 1/3 mixed fluid and 250 mL dextrose 5% were administered during the 4 hour procedure. The glucose level was measured as 181 mg dL^{-1} during hourly capillary glucose monitoring and 2 units of regular insulin were administered intravenously. The level of capillary glucose ranged between 130-180 mg dL^{-1}. the patient was ventilated through volume control throughout the procedure, and partial oxygen saturation remained above 98%. At the end of surgery, a caudal block with 0.5 mL kg^{-1} bupivacaine was performed to provide postoperative analgesia. The patient recovered uneventfully 4 hours after induction of anesthesia.

She developed a tendency to sleep during postoperative follow-up. Her serum ammonia level was 92 µmol/L, which was three times the upper limit of reference range; and arginine measured 337 µmol/L (reference values are 113-197 µmol/L) in the blood sample taken 10 minutes after recovery. Careful attention was paid at every step of the procedure, including preoperative assessment, intraoperative monitoring and postoperative care to avoid hypotension, convulsion or hypothermia. The patient had only slight pain when she was discharged to the orthopedics clinic after a 4 hour follow-up in the post anesthetic care unit.

IV fluid was changed to 10% dextrose on the recommendation of the pediatric metabolism specialist. An oral nonsteroidal anti-inflammatory agent was given for her pain. A blood sample taken 24 hours after surgery showed significant decrease in serum levels of ammonia (48 µmol/L) and arginine (209 µmol/L). Concurrently, the patient's general condition improved and her pain was relieved. Serum levels of ammonia (27 µmol/L) and arginine (147 µmol/L) returned to normal range and the patient was discharged 48 hours after surgery.

Discussion

Arginase deficiency is an inherited metabolic disorder caused by severe deficiency of liver arginase activity. It is the most infrequent form of urea cycle disorders, with an incidence of less than 1 in 100,000 individuals (6). Arginase-deficient patients show far less severe symptoms and experience fewer hyperammonemic crises. Tissue accumulation of arginine is the biochemical hallmark of hyperargininemia. Although ammonia is a potent neurotoxin, it is not considered to be responsible for brain damage in the affected children, since the tissue concentration of ammonia is only slightly increased in this disorder. Hyperargininemic patients may present with severe neurological symptoms and brain damage, but its pathophysiology is not yet well understood. Increase of tissue concentration of ammonia, which is expected to cause metabolic alterations in the brain, is mild in this disorder and not consistent among affected children. Increased levels of arginine and/or its metabolites in the brain have been implicated in neurological alterations observed in this disease (7). Current treatment of arginase deficiency includes protein restriction, supplementation of essential amino acids other than arginine and use of sodium benzoate or sodium phenylbutyrate to eliminate nitrogen independent of the urea cycle and to direct excess nitrogen to alternative pathways (8).

Increase of arginine and ammonia levels during or after surgery may lead to serious complications such as hypotension, cerebral edema, convulsions, hypothermia and spasticity in patients with arginase deficiency, thus special attention must be given to their metabolic homeostasis and nutrition in the perioperative period.

In addition to increased energy requirements provoked by surgery, patients are at risk of inadequate energy intake due to preoperative fasting. Patients may also be told to stop all medications while fasting.

In an animal study, Delwing et al. demonstrated that acute administration of arginine provoked a significant inhibition of pyruvate kinase activity, an enzyme crucial for glucose metabolism and energy production in the brain, hippocampus, cerebral cortex and striatum (9). Since, glucose is critical for the development and function of the brain, reduced energy may cause an overall failure of metabolism that impairs cellular functions and induces brain damage through distinct mechanisms, including secondary excitotoxicity (10). Because of the increased arginine levels in patients with arginase deficiency, glucose intake should be well organized. Therefore, the dietician and anesthesiologist should work in close cooperation with the surgical team to avoid decompensation before, during or after surgery. The patient must be admitted to hospital at least 24 hours before surgery and intravenous glucose and lipid emulsions should be administered, if required. The surgical team must be advised to give the patient a dose of N-scavenging drug before surgery, and to double the dose after surgery if required (4). Considering these, we believe that an 8 hour pre-operative fasting period in these patients is too long. Particularly, patients similar to our case should have a minimal fasting period and if possible, clear oral fluids should be continued until 2-3 hours before surgery. Increased levels of serum ammonia after surgery indicates that 5% dextrose and 1/3 mix fluid used for IV fluid therapy failed to provide sufficient energy. Depending on the patient's age and metabolic status, at least 10% dextrose should be administered and total parenteral nutrition should be considered during and after surgery to provide the energy needed if surgery is prolonged or the patient's condition is more severe. Postoperative enteral nutrition should be commenced as soon as possible (4).

Arginine stimulates nitric oxide, thus increased levels may cause vasodilatation and exacerbate the hypotensive effects of most intravenous and inhalational agents (11). Since ammonia levels were not remarkably increased, no hypotension was observed in our case; however arginine levels may increase up to 5-10 times of normal in affected individuals. Adequate fluid should be supplied to avoid hypotension, and an adrenergic agonist should be readily available.

Patients with high levels of arginine have a tendency to develop cerebral edema. Hyper-ammoniemia responds to prompt hydration with intravenous fluids as well as sodium benzoate and sodium phenylbutazone. Perioperative fluid management is crucial (4, 12), and excessive fluid may cause cerebral edema, while fluid deficit will hinder management of

hyper-ammoniemia. We did not observe any symptoms related to cerebral edema with our fluid management.

Patients with arginase deficiency may experience epileptic seizures. We did not observe any epileptic activity with the agents used for induction and maintenance of anesthesia, which included midazolam, thiopental, sevoflurane and nitrous oxide. These medications can be used safely, although sevoflurane may rarely show epileptic effects. Agents that may trigger convulsions, such as ketamine, should be avoided. Despite the enzyme stimulating effects of carbamazepine, antiepileptic drugs show additive effects with anesthetic agents. That's why, there is also some literature expressing that the titration induction of a single agent may be helpful in assessing the anesthetic requirement for maintenance of anesthesia (5).

Muscle relaxants may be dangerous and show unpredictable effects in patients with paresthesia and/or spasticity. Thus, we chose to use LMA without a myorelaxant as the most appropriate choice. We preferred LMA in our case, without a neuromuscular blocker and experienced no problems. Stress response to anxiety before anesthesia, tissue damage and pain during surgery, and postoperative pain may increase catabolism. Subsequently, catabolism may cause protein degradation and increase ammonia/arginine levels. Adequate sedation and analgesia should be achieved to minimize this response. We used IV midazolam, which is an effective anxiolytic, however oral midazolam given on the night preceding surgery may be a good alternative to reduce the anxiety that occurs during that time.

Narcotic analgesics and non steroid anti inflammatory drugs (NSAID) may be used in combination for intra-operative and post-operative analgesia. If a painful procedure is carried out, epidural or IV continuous techniques of patient controlled analgesia protocols or central block techniques can be used. We used a narcotic and NSAID in combination for preemptive analgesia and a caudal block for acute postoperative analgesia. Our case did not report significant pain.

In conclusion, patients with arginase deficiency require meticulous anesthesia, as do all patients with urea cycle disorders, to avoid mortality and morbidity. Primary goals may be listed as minimizing stress levels by an effective anxiolysis, providing sufficient amount of protein-free energy and intravenous fluid, along with effective preemptive and postoperative analgesia. In addition to a high level of knowledge, successful anesthesia requires professional communication among the nursing staff, dietician, pediatric metabolism specialist, surgeon and anesthesiologist.

Conflict of Interest

No conflict of interest was declared by the authors.

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