J Anesth (2007) 21:72–75
DOI 10.1007/s00540-006-0449-y

Journal of
Anesthesia

Anesthetic management of a patient with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) during laparotomy

Nobuko Sasano, Yoshihito Fujita, MinHye So, Kazuya Sobue, Hiroshi Sasano, and Hirotada Katsuya

Department of Anesthesiology and Medical Crisis Management, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8622, Japan

Abstract
A 53-year-old man with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) underwent a gastrectomy. We administered bicarbonated Ringer's solution, which has a physiological concentration of bicarbonate. The level of serum lactate did not increase significantly, and metabolic acidosis did not occur throughout surgery or for 3 h after surgery. Aggressive warming was needed to maintain normothermia, presumably because the mitochondrial respiratory chain, which is responsible for thermogenesis, is impaired in MELAS patients. It is important to maintain normothermia in MELAS patients in order to avoid further mitochondrial metabolic depression.

Key words MELAS · Bicarbonated Ringer's solution · Normothermia · Mitochondria

Introduction

Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is a multisystem disorder caused by mitochondrial dysfunction. Some anesthetic considerations have been proposed [1,2]. To prevent the exacerbation of lactic acidosis, it is very important to maintain normal serum glucose levels, adequate oxygen balance, stable cardiovascular function, and good gas exchange [1]. Although the selection of intravenous fluids has not received much attention, administration of lactated solution should be avoided, because the metabolism of lactate is impaired in MELAS patients. Acetated Ringer's solution can be used for the MELAS patient during surgery. However, it is likely that acetate metabolism is also decreased in MELAS patients, because acetate is metabolized in the citric acid cycle, which is suppressed in MELAS patients. We present here a MELAS patient who underwent a gastrectomy during which he was given bicarbonated Ringer's solution.

Address correspondence to: N. Sasano
Received: June 5, 2006 / Accepted: September 14, 2006

Case report

A 53-year-old man presented with an advanced gastric cancer and was scheduled for a gastrectomy. He had a medical history of diabetes mellitus type 1 of more than 20 years' duration, and sensorineural hearing loss for 10 years. Also he had begun having episodes of dizziness and limb weakness in his thirties. At the age of 45, he underwent muscle biopsy and genetic testing at another hospital, and was diagnosed at that time with MELAS.

Physical examination revealed that the patient had short stature (147 cm), cachexia, and severe muscle wasting (body weight of 30 kg). He could not walk on his own and showed no tendon reflexes. He did not present with ophthalmoplegia. Laboratory data showed anemia (hemoglobin [Hb], 9.9 g/dl), hyperglycemia (glucose, 191 mg/dl), a low creatine kinase (CK) level (CK, 29 U/l), and normal liver function. A pulmonary function test revealed decreased vital capacity (2000 ml; 63%) and normal forced expiratory volume (FEV) 1.0%, of 88%. His ECG was normal, and ultrasound cardiography examination showed good contractility in the left ventricle, with mild tricuspid regurgitation.

On the day of the surgery, the patient was given 70 ml·h^{-1} of acetated Ringer's solution, including 5% glucose for the purpose of providing glucose and extracellular fluid. No premedication was administered. In the operating room just before the start of anesthesia, his blood pressure was 82/50 mmHg and his heart rate was 70 bpm. A radial artery catheter was inserted, and an arterial blood sample was taken. Bicarbonated Ringer's solution (Bicarbon Injection; Ajinomoto, Tokyo, Japan) was then administered intravenously.

An epidural catheter was inserted at T8/9 under local anesthesia. After a test dose of 2 ml 1% lidocaine was given, loss of cold sensation at the level of T7-10 was confirmed, and continuous epidural administration of 0.375% ropivacaine at a rate of 5 ml·h^{-1} was begun. After pre-oxygenation, the patient was given 50 μg fentanyl and 30 mg propofol and was paralyzed with 3 mg vecuronium. Two minutes later, adequate depth of anesthesia and muscle relaxation were confirmed by a value of 40 on the Bispectral Index (BIS; Aspect Medical Systems, Newton, MA, USA) monitor and by a score of 0 in the train-of-four (TOF) response, respectively. The patient's trachea was then intubated. Anesthesia was maintained by continuous epidural administration of ropivacaine and propofol infusion, which was titrated to maintain BIS between 40 and 60. During the surgery, bicarbonated Ringer's solution was given, and acetated Ringer's solution including 5% glucose and insulin were administered intravenously to maintain blood glucose levels between 120 and 200 md/dl. Arterial blood was sampled every hour to measure arterial blood gas, electrolytes, hemoglobin, glucose, lactate, and citrate (Table 1). Dopamine at 2–8 μg·kg^{-1}·min^{-1} was needed to maintain systolic blood pressure at 80 to 110 mmHg, which was the patient's regular blood pressure in the ward. The surgical procedure was uneventful, and the total amount of blood loss during surgery was 127 ml. The patient received 1300 ml of bicarbonated Ringer's solution, 400 ml of acetated Ringer's solution including 5% glucose, and transfusion of 260 ml of packed red blood cells (RBCs). The total urinary output was 1410 ml. The lactate levels did not change significantly throughout the operation, whereas citrate slightly increased (Table 1). Operating time was 2 h and 20 min, and the total amount of vecuronium used was 4 mg. Twelve minutes after propofol was discontinued, the patient emerged from anesthia, and the neuromuscular blockade was reversed by 2 mg of neostigmine together with 1 mg of atropine. Because the patient showed mild hypercarbia (Pa_{CO_2}, 55 mmHg) and also required inotropics, he was transferred to the intensive care unit. Three hours after surgery, his trachea was successfully extubated. He was transferred to the surgical ward the next day.

Discussion

Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is a multisystem disorder clinically characterized by (1) encephalopathy, frequently manifesting as dementia, seizures, or both; (2) evidence of mitochondrial dysfunction in the form of lactic acidosis, ragged-red fibers, or both; and (3) stroke-like episodes [3]. It is one of the most common maternally inherited mitochondrial diseases. An A > G mutation in the transfer $RNA^{LEU(UUR)}$ gene at position 3243 in mitochondrial DNA accounts for approximately 80% of MELAS cases. Electron transport chain defects have been assigned at complex I and IV [4]. Five percent to 21% of MELAS patients have diabetes mellitus [4]. Interestingly, maternally inherited diabetes mellitus and deafness (DAD) has exactly the same point mutation, i.e., the 3243 A > G, as MELAS. It appears that if the mutation load is high (>85%), MELAS results, while a lower mutation percentage (5%–30%) is associated with DAD [5].

Some anesthetic considerations for MELAS patients have been proposed [1,2]. Because a case of malignant hyperthermia in a patient with mitochondrial myopathy has been reported [6], we avoided the use of succinylcholine and volatile anesthetics. Succinylcholine should also be avoided because MELAS patients sometimes present with peripheral neuropathy, i.e., axonal loss and demyelination [4], raising a possible risk of succinylcholine-induced hyperkalemia [1]. Neuromuscular blockade should be administered carefully, using small incremental doses, because some reports

Table 1. Arterial blood gas analysis; lactate; and serum concentrations of citrate, hemoglobin, and glucose before anesthesia induction, and 1 h, 2 h, and 3 h later, and 3 h after surgery

	Before	1 h	2 h	3 h	3 h after surgery
$F_{I_{O_2}}$	0.21	0.5	0.5	0.5	0.5
pH	7.39	7.51	7.42	7.34	7.36
Pa_{CO_2} (mmHg)	39	30	38	45	43
Pa_{O_2} (mmHg)	95.5	209	217	226	234
HCO_3^- (mmol·l^{-1})	23.1	23.7	24.3	23.9	23.6
Base excess (mmol·l^{-1})	–1.1	1.2	0.4	–1.5	–1.1
Lactate (mg·dl^{-1})	29.0	23.0	23.0	29.0	31.0
Citrate (mg·dl^{-1})	2.6	3.1	3.7	3.3	2.6
Hb (g·dl^{-1})	7.7	8.6	11.4	11.7	11.7
Glucose (mg·dl^{-1})	181	172	190	165	126

Normal ranges: lactate, 4–16 mg·dl^{-1}; citrate, 1.3–2.6 mg·dl^{-1}

have described prolonged effects of neuromuscular blocking agents in patients with mitochondrial diseases [1]. In the present patient, we successfully provided epidural anesthesia together with propofol infusion and a small amount of vecuronium under close monitoring with BIS and TOF.

Consideration should be given to the selection of intravenous fluids. Because lactate metabolism is impaired in MELAS patients, and a case report described rapid increases in plasma lactate level after the administration of lactated Ringer's solution [7], administration of lactated solution should be avoided [8]. Saline 0.9% is used for patients with MELAS or other mitochondrial diseases during surgery [2,8]. If, however, serious lactic acidosis occurs, administration of sodium bicarbonate in an attempt to correct acidosis only exacerbates the hyperlactatemia without significant pH improvement [9]. Therefore, intravenous fluid with some alkalinizing agent is preferable, especially in major surgery, in order to prevent or minimize acidosis. Acetated Ringer's solution is one choice. However, because acetate is metabolized in the citric acid cycle, which is impaired in MELAS patients, it is likely that acetate metabolism is also depressed in MELAS patients and that acetated Ringer's solution may not work effectively as an alkalinizing agent.

In cases of metabolic disturbance, bicarbonated Ringer's solution has been reported to be more effective to maintain pH than acetated or lactated Ringer's solution, because the bicarbonate is physiological and does not require a metabolic process to exert the alkalinizing effects [10]. In a case report, the authors described that they made bicarbonated Ringer's solution, and administered it to a patient with mitochondrial encephalomyopathy [11]. Recently, a bicarbonated Ringer's solution (Bicarbon Injection) that has physiological concentrations of bicarbonate and electrolytes has been introduced in Japan (Table 2). This fluid, however, includes citrate to prevent the precipitation of calcium carbonate and magnesium carbonate. Citrate inhibits phosphofructokinase-1 in glycolysis [12], which may deteriorate the energy status of MELAS patients. Our measurement of serum citrate levels revealed a slight increase, which was accounted for by citrate in both the bicarbonated Ringer's solution and the transfused packed RBCs. The serum concentration of citrate in packed RBCs with mannitol-adenine-phosphate preservative, which contains much less citrate than citrate-phosphate-dextrose preservative, is much higher (186 md/dl) than that in bicarbonated Ringer's solution (31.5 md/dl). It is not known how blood citrate levels affect the levels of citrate in cytosol. It seems, however, that this slight elevation in citrate concentrations in blood does not significantly depress glycolysis. This is because citrate inhibits phosphofructokinase-1 significantly when ATP levels are high, which is unlikely in MELAS patients. In addition, ADP and AMP, the levels of which are high in the cells of MELAS patients, stimulate phosphofructokinase-1 as well as other enzymes in both glycolysis and the citric acid cycle [12].

Table 2. Composition of the bicarbonated Ringer's solution ($mEq \cdot l^{-1}$)

Na^+	135
K^+	4
Ca^{2+}	3
Mg^{2+}	1
Cl^-	113
HCO_3^-	25
$Citrate^-$	5

It is very important to maintain normothermia during surgery, because hypothermia depresses mitochondrial function [13] and, moreover, causes further metabolic stress in order to regain normothermia after surgery. Farag et al. [8] employed normothermia during cardiopulmonary bypass in a patient with mitochondrial cytopathy who underwent open-heart surgery. Due to dysfunction of the mitochondrial respiratory chain, which is responsible for thermogenesis, i.e., producing metabolic heat in muscles and brown fat, it also seems likely that patients with mitochondrial diseases are at risk of developing inadvertent hypothermia [14] during anesthesia, especially for laparotomy, in which body heat loss is significant. Bolton et al. [2] have reported hypothermia (34.3°C) in a MELAS patient during laparotomy for fundoplication, despite active warming in the second half of the surgery. We kept the room temperature at 28°C during epidural catheterization and induction of general anesthesia. In addition, the intravenous fluids were given through a warming device (Hotline; Level 1 Technologies, Rockland, MA, USA) throughout anesthesia, and two warm-air blankets (WarmTouch; Tyco Healthcare Group, Pleasanton, CA, USA) were applied to the patient's legs and upper body during surgery. His face and head were covered, and topical warming was applied with hot packs and light. With this aggressive warming, the patient's rectal temperature was 35.9°C right after anesthesia induction and rose to 36.3°C at the end of surgery. Body temperature should be closely monitored to prevent hypothermia as well as to detect malignant hyperthermia.

In conclusion, we administered bicarbonated Ringer's solution during surgery for a patient with MELAS, who showed no elevation of serum lactate or acidosis. Bicarbonated Ringer's solution may help to prevent exacerbation of lactic acidosis in MELAS patients, especially in laparotomy, which requires a comparatively large amount of infusion. It is very important to maintain normothermia during surgery in MELAS

patients, in order to retain better energy status in mitochondria by avoiding further metabolic depression due to hypothermia as well as by preventing the further metabolic stress of regaining normothermia.

References

1. Thompson VA, Wahr JA (1997) Anesthetic consideration in patients presenting with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome. Anesth Analg 85:1404–1406
2. Bolton P, Peutrell J, Zuberi S, Robinson P (2003) Anaesthesia for an adolescent with mitochondrial encephalopathy-lactic acidosis-stroke-like episodes syndrome. Paediatr Anaesthesia 13:453–456
3. Hirano M, Pavlakis SG (1994) Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS): current concepts. J Child Neurol 9:4–13
4. Thambisetty M, Newman NJ (2004) Diagnosis and management of MELAS. Expert Rev Mol Diagn 4:631–644
5. McKenzie M, Liolitsa D, Hanna MG (2004) Mitochondrial disease: mutations and mechanisms. Neurochemical Res 29:589–600
6. Ohtani Y, Miike T, Ishitsu T, Matsuda I, Tamari H (1985) A case of malignant hyperthermia with mitochondrial dysfunction. Brain Dev 7:249
7. Gou R, Sakata M, Katou M, Arase T, Saitou T (1987) Anesthetic management of a patient with mitochondrial encephalomyopathies (in Japanese). J Clin Anesth 11:57–61
8. Farag E, Argalious M, Narouze S, DeBoer GE, Tome J (2002) The anesthetic management of ventricular septal defect (VSD) repair in a child with mitochondrial cytopathy. Can J Anesth 49:958–962
9. Park R, Arief AI (1982) Treatment of lactic acidosis with dichloroacetate in dogs. J Clin Invest 70:853–862
10. Satoh K, Ohtawa M, Okamura E, Satoh T, Matsuura A (2005) Pharmacological study of BRS, a new bicarbonated Ringer's solution, in partially hepatectomized rabbits. Eur J Anaesthesiol 22:624–629
11. Maeda Y, Mitsumizo S, Yoshida M, Nakashima M, Harano K, Totoki T (2001) Perioperative administration of bicarbonated solution to a patient with mitochondrial encephalomyopathy (in Japanese). Masui 50:299–303
12. Nelson DL, Cox MM (2005) Oxidative phosphorylation and photophosphorylation. In: Nelson DL, Cox MM (eds) Principles of biochemistry, 4th edn. W. H. Freeman, New York, pp 690–750
13. Hashimoto K, Sasaki T, Hachiya T, Onoguchi K, Takakura H, Oshiumi M, Takeuchi S (2001) Superior hepatic mitochondrial oxidation-reduction state in normothermic cardiopulmonary bypass. J Thorac Cardiovasc Surg 121:1179–1186
14. Cholley F, Edery P, Ricquier D, Peudenier S, Slama A, Tardieu M (2001) Mitochondrial respiratory chain deficiency revealed by hypothermia. Neuropediatrics 32:104–106