Anesthetic Management of a Patient with Alagille's Syndrome Undergoing Living Donor Liver Transplantation without Blood Transfusion

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Alagille's syndrome (AGS), which has five main characteristics including chronic cholestasis; typical peculiar facies; posterior embryotoxon; butterfly-like vertebral-arch defects; and cardiovascular malformations, is rarely seen in Taiwan, especially in a liver transplantation setting. We present the successful anesthetic management of a 3-year-11-month-old boy with AGS. The patient was anemic with a preoperative hemoglobin of 9.1 g/dl and had mild aortic stenosis and mild pulmonary artery stenosis. He underwent living donor liver transplantation without blood transfusion. The key points of successful anesthetic management included complete pre-operative evaluation of the cardiovascular system, and intra-operative maintenance of normothermia, normal ionized calcium, normal pH and stable hemodynamics. Surgical blood loss, ascites and intraoperative transudate loss were primarily replaced with 5% albumin and crystalloids to maintain the central venous pressure around 10 cm H_2O. No blood transfusion was given for a hemoglobin level higher than 6-7 g/dl, but the intravascular volume was sufficient to maintain stable hemodynamics. Our patient tolerated the anemia well, it did not seem to affect the recovery of the new liver allograft postoperatively. *(Chang Gung Med J 2004;27:449-53)*

Key words: Alagille's syndrome, living donor liver transplantation, general anesthesia.

Alagille's syndrome (AGS) is a congenital disorder that can affect the liver, heart, eyes, skeleton, and facial appearance.[1,2] Diagnosis is made when bile duct paucity is accompanied by at least 3 of the 5 clinical abnormalities.[3] The incidence is approximately 1 in 70,000 to 100,000 live births[3,4] The outcome and prognosis is highly variable and is directly related to the severity of liver and cardiac involvement, with mortality equally attributable to abnormalities of both organs. Complex congenital heart disease is responsible for most neonatal deaths, while liver failure accounts for most late morbidity and mortality.[4] The manifestations of hepatic disease range from mild cholestasis, jaundice and pruritus to progressive liver cirrhosis. Approximately 15% of AGS patients require transplantation.[5] AGS is rarely seen in Taiwan, especially in the liver transplantation setting. Our experience in the anesthetic management of AGS is presented.

CASE REPORT

A 3-year-11-month-old boy with a body weight of 10 kg and height of 85.7 cm had syndromic features of cholestasis, pulmonary artery stenosis (PS), aortic stenosis (AS), cutaneous xanthomas and pecu-

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Received: Mar. 7, 2003; Accepted: Aug. 22, 2003
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liar face, compatible with AGS. Living donor liver transplantation (LDLT) was indicated due to profound jaundice with intractable pruritus and failure to thrive. Preoperative laboratory data were as follows: aspartate transaminase (AST) 408 U/L, alanine transaminase (ALT) 325 U/L, alkaline phosphatase (ALP) 1134 U/L, total bilirubine (T.bil.) 8.3 mg%, albumin 4.1 gm%, blood urea nitrogen (BUN) 12 mg%, creatinine (Cr.) 0.4 mg%, sodium (Na^+) 135 mEq/L, potassium (K^+) 4 mEq/L, cholesterol 407 mg/dl, triglycerine 205 mg/dl, hemoglobin (Hb) 9.1g/dl, hematocrit (Ht.) 27.4%, platelet 8.4×10^3 /cmm, prothrombin time (PT) 11.6/11.4 sec, activated partial thromboplastin time (aPTT) 37.6/27.9 sec, fibrinogen 298 mg/dL, fibrin degradation product 10-40 μg/mL. The electrocardiogram (EKG) showed sinus tachycardia with right ventricular hypertrophy. An echocardiogram revealed mild aortic stenosis (AS) with Vmax 2.6 m/sec, and mild pulmonary stenosis (PS) with Vmax 2.5 m/sec. A contrast echocardiogram showed a small right to left shunt at the atrial level with absence of atrial septal defect (ASD). The chest radiograph showed a normal heart size and configuration, with minimal infiltration in the bilateral lungs. Preoperative arterial blood gase (ABG) was PH: 7.31, $PaCO_2$ 32 mmHg, PaO_2 80.9 mmHg, base excess (BE.) -8.1 and oxygen saturation 95.2%. The patient came to the operating room without an intravenous line. Anesthesia was induced by mask with servoflurane and further maintained with isoflurane in an oxygen-air mixture. Fentanyl was given whenever necessary and atracurium was used as a muscle relaxant. ECG, pulse oximetry, continuous arterial blood pressure, central venous pressure, end tidal CO_2, urine output, and rectal as well as nasopharyngeal temperature (NT) were monitored. To avoid further right to left shunt due to an increase in pulmonary resistance, ventilation and oxygenation were monitored. Four intravenous lines were set for fluids and blood replacement. The operating room (OR) temperature was set at 24˚C the night before surgery (Yamatake Honeywell Model SDC 200, Tokyo, Japan). A radiant heat lamp was used during induction of anesthesia while a water blanket with the temperature set at 38˚C during surgery was used to minimize heat loss. Moreover, the four extremities of the patient were first wrapped with cotton bandages and then covered with stockinettes. Intravenous dopamine 2 μg/kg/h was given for diuresis during the procedure. The operation lasted 12 hours and was uneventful. The technique employed was LDLT without veno-venous bypass. The patient was anemic but blood product transfusion was not required to maintain stable hemodynamics and likewise, no correction of coagulation was done during the procedure. The blood loss (90 ml), ascites loss (160 ml) and transudate loss were replaced with 750 ml 5% albumin and crystalloids at a mean rate of 11.2 ml/kg/h. Urine output was 5.2 ml/kg/h. Intraoperative hemodynamics were stable as can be seen in the ability to maintain sufficient urine output, normothermia, and normal pH and PaO_2. The data

Table 1. Pre- and Postoperative Blood Gases, Electrolytes, and Body Temperature

	pH	PaO_2 (mmHg)	Sugar (mg%)	Ca^{++} (mmol/L)	BT (˚C)
Before op	7.28	319	118	0.58	36.5
At the end of op	7.35	324	331	0.8	37

Table 2. Pre- and Postoperative Patient Data

	Hb	Hct	AST	ALT	T.bil.	Alp	PT	aPTT
Pre-op	9.1	28	408	325	8.3	1134	11.6	37.6
Post-op	7.8	26	479	376	5.9	296	11.2	46.2
Extubation	7.3	25						
Day 3	7.6	25	43	216	3.7	168	22.9	44.1
Day 10	8.8	27	35	47	0.8	56	14.3	33.4
Day 20	7.8	25	24	17	0.5	84	12.2	48
Discharge	7.5	25	21	14	0.5	57	11	30

before and at the end of surgery are shown in Table 1. Metabolic acidosis was corrected with 38 mEq sodium bicarbonate while 65 mg calcium chloride was used to normalize the level of ionized calcium. Right to left shunt due to hypercapnia was avoided by continuous end-tidal CO_2 monitoring. The body temperature was maintained around 37˚C. The patient was extubated fourteen hours after surgery. The postoperative course was smooth and no blood transfusion was required. He was discharged with good liver function. Pre- and postopertive patient data are presented in Table 2.

DISCUSSION

AGS, originally described by Watson[2] and Allagille,[1] is a congenital disorder with autosomal dominant transmission, most likely located on the short arm of chromosome 20.[6] AGS has five main characteristics: chronic cholestasis; typical peculiar facies; posterior embryotoxon; butterfly-like vertebral-arch defects; and cardiovascular malformations.[1,2] The life quality of patients with severe hepatic forms of AGS may be extremely poor as refractory pruritus usually causes sleep disturbances and associated growth failure leads to poor social and school achievement.[7] AGS is syndromic if all five features are observed. Four or fewer characteristics present in incomplete or partial forms.[8] Medical treatment consists of nutritional supplements of medium-chain triglycerides, essential fatty acids and fat-soluble vitamins. Patients with liver failure, portal hypertension or severe pruritus and xanthomatosis have been treated successfully with liver transplantation.[7] Cardiac abnormalities are found in 85%-100% of patients with AGS.[3] The most common anomaly is pulmonary stenosis, with varied severity but usually it is nonprogressive.[2] The mortality rate in AGS attributed to cardiopulmonary complications is about 10%.[3,6] Higher mortality rates after liver transplantation are also noted compared to non-Alagille patients. undergoing liver transplantation.[5] Therefore, complete and careful preoperative cardiac evaluation is crucial. If the cardiac abnormalities are found to be severe but correctable by balloon angioplasty or cardiac surgery, this intervention should be considered before liver transplantation.[9] Our patient had the syndromic form of AGS consisting of intrahepatic cholestasis associated with peripheral pulmonary artery stenosis, aortic stenosis, cutaneous xanthomas, and a peculiar face. Liver transplantation was indicated due to profound jaundice with intractable pruritus and growth retardation. Although the ECG of the patient showed right ventriclar hypertrophy, mild AS, PS and a small right to left shunt at the atrial level without ASD were also present on echocardiogram. No preoperative treatment or correction was required. The patient had impaired liver function but was not yet in end stage liver disease, thus the coagulation profile was not corrected. Hepatic artery thrombosis after liver transplantation is a serious complication with high morbidity and mortality, especially in pediatric patients with a small hepatic artery.[10] Polycythemia is one of the causes of hepatic artery thrombosis and should be avoided.[11] A hemoglobin of around 7-9 g/dl is maintained to create the rheological effect of hemodilution to prevent hepatic artery thrombosis. Although the patient had mild cardiac abnormalities, he tolerated anemia well with good recovery of the new liver graft as shown in Table 2.

Infusion of crystalloids or commercial colloid solutions and not banked blood products to maintain sufficient intravascular volume is emphasized in managing acute blood loss.[12] Central venous pressure around 10 cm H_2O with stable hemodynamics was maintained in the anemic patient by administration of 750 ml 5% albumin and 11.2 ml/kg/h crystalloids. Arterial blood gases and ionized calcium should be routinely determined during liver transplantation to prevent citrate intoxication which can result in hemodynamic instability.[13] Exogenous citrate load secondary to transfusion of banked blood products during liver transplantation is thought to be the main cause of the ionized hypocalcemia.[13] Our patient still required administration of calcium chloride because 5% albumin was used. The albumin binds ionized calcium and may cause hypoionized calcemia[14] and unstable hemodynamics.[15] The body temperature was maintained within normal limits as the operating room temperature was set at 24˚C instead of 19-21˚C. Maintenance of normothermia during liver transplantation is critical in the prevention of coagulopathy and thromboembolic complications. Coagulopathies often occur in patients with hypothermia even in the presence of normal levels of clotting factors and normal prothrombin time or activated partial-thromboplastin time,[16] because low

temperatures directly inhibit the enzymatic reactions of the coagulation cascade. Hypothermia decreases platelet activity by decreasing the production of thromboxane B,[17] subsequently exacerbating cold-induced thrombocytopenia by suppressing bone marrow and hepatosplenic sequestration.[18] Hypothermia usually results in increased blood loss and blood transfusion requirements,[19] especially in a major operation such as liver transplantation.

In conclusion, we presented the successful anesthetic management of a 3-year-11-month old boy with AGS who was anemic and underwent living liver transplantation without blood product transfusion. The key points of successful anesthetic management without blood transfusion included complete pre-operative evaluation of the cardiovascular system, and intra-operative maintenance of normothermia, normal ionized calcium, normal pH and stable hemodynamics. Blood transfusion was not given as long as the hemoglobin was higher than 6-7 g/dl. The surgical blood loss was sufficiently replaced by 750 ml 5% albumin and 11.2 ml/kg/h crystalloids. Our patient tolerated the anemia well, and it did not seem to affect the recovery of the new liver allograft post-operatively.

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Alagille's Syndrome 成功接受不輸血之活體肝臟移植麻醉

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在台灣，Alagilles's Syndrome（AGS）不僅是一非常少見的疾病症候群，尤其在肝臟移植病患中更是少見。AGS主要的定義性特徵包括五大項：慢性膽汁淤積、典型的奇特面貌、後側角膜混濁、蝶翼狀脊椎缺損及心血管系統異常。病患爲3歲11個月大，患有AGS之病童，並於本院成功接受不輸血之活體肝臟移植。術前診斷病童有貧血現象，血紅素爲9.1 g/dl，並有主動脈與肺動脈狹窄。本次麻醉處置成功的主要因素爲包括：術前一系列完整性的心血管系統評估；術中維持正常體溫、正常pH值與鈣離子濃度、並盡可能維持血液動力學的穩定性。手術期間失血量與腹水流失，主要以5%白蛋白與晶體溶液補充，以維持中心靜脈壓約10 cmH_2O。在病患血紅素高於6~7 g/dl情況下，我們以有效益性的輸液來替代輸血，使病患血管內容量能維持血液動力學的穩定。我們發現，病患不僅能承受貧血現象，對於新肝植入後的術後復原，更不受影響。(長庚醫誌 2004;27:449-53)

關鍵字：Alagilles's Syndrome，活體肝臟移植，全身麻醉。

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