Perioperative Management of Hemostasis for Surgery of Benign Hepatic Adenomas in Patients with Glycogen Storage Disease Type Ia

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Abstract The development of hepatocellular adenomas in the liver of patients with glycogen storage disease type I is a well-known complication of the disease. Surgical procedures and perioperative managements described so far have reported persistent and important morbidity. We report here a series of six patients (three males and three females) who underwent hepatic resection, and we propose a new hemostatic management protocol comprising glucose infusion,

corticosteroids, desmopressin, and antifibrinolytic drugs, used to prevent efficaciously hepatic hemorrhage due to glycogen storage disease (GSD) platelet dysfunction.

Keywords GSD glycogen storage disease · Hemostasis · Hepatectomy · Platelet dysfunction

Abbreviations

α FP	Alpha fetoprotein
BT	Bleeding time
CEA	Carcinoembryonic antigen
DDAVP	Desmopressin, deamino 8d arginine vasopressin
GDF	Gastric drip feeding
GOT	Glutamate oxaloacetic transaminase
GPT	Glutamate pyruvate transaminase
GSD	Glycogen storage disease
PFA	Platelet function aggregation
RBC	Red blood cell

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Introduction

Glycogen Storage Disease Ia (GSD1a-Von Gierke's disease – OMIM 23220) is an autosomal recessive inborn error of carbohydrate metabolism caused by deficient activity of glucose-6-phosphatase (EC 3.1.3.9; P35575), an enzyme implied in gluconeogenesis and glycogenolysis. It leads to glycogen accumulation in liver, kidney, and intestinal mucosa. The clinical manifestations include steatotic hepatomegaly, growth difficulties and delayed puberty, hypoglycemia for short fasting time associated with lactic acidosis, hypertriglyceridemia, hyperuricemia (Rake et al. 2002a), and prolonged bleeding time (BT) due to impaired platelet function (Ambruso et al. 1985; Gilchrist et al. 1968; Hutton et al. 1976; Kao et al. 1980; Rake et al. 2002a). This last complication leads to potential hemorrhage during surgical procedures and to increased morbidity. The platelet dysfunction

has been described secondary to a large excess of stored glycogen in the platelet, leading to decreased platelet adhesiveness and impaired platelet factor3 availability (Sahud 1972), due to chronic hypoglycemia (Hutton et al. 1976), or related to the presence of an inhibitor in GSD patients (Kao et al. 1980). Previous guidelines suggested the use of glucose infusion to stabilize bleeding diathesis (Rake et al. 2002b) and DDAVP has been used during bleeding complications in GSD patients (Marti et al. 1986). We report a series of six consecutive GSD Ia patients who underwent partial hepatectomy for complicated hepatic adenomas, one with a protocol stabilizing glucose homeostasis and lactic acidosis, and the other five with a personalized metabolic and hemostatic protocol, comprising desmopressin for four, to prevent hemorrhage. The current perioperative protocol is provided and discussed. We will compare clinical outcomes, hemostatic difficulties, and perioperative consequences before and after this management.

Case Reports

We report the cases of six patients with GSD type Ia who underwent partial hepatectomy for voluminous or complicated hepatic masses over the last 13 years. Specific clinical characteristics for each patient are presented in Table 1. Clinical diagnosis and initiation of treatment were achieved

at median age of 21 months (range: 5–60 months). All patients had annual follow-up with a specialist in hepatic metabolism and received controlled treatment for GSDIa that included frequent meals, uncooked cornstarch alone or coupled with nocturnal gastric drip feeding of glucose. As proposed in our medical center, all patients had strict lactose restriction up to age five and moderate lactose restriction (<10 g/day) later on. They also were on fructose restriction limited to two fruit servings per day without restriction in vegetables. Through teenage and adulthood, compliance to treatment was poor for four patients. Two of the male patients used androgens as auto medication for growth purposes, or in a bodybuilding program. The third male patient was on growth hormone treatment during 24 months (from 15 to 17 years of age), initiated because of retardation to thrive with height <−4DS and pubertal delay (Tanner stage 1) with no height gain and no increased growth velocity. The three female patients were on progestative pills as contraception.

Hepatic masses were first detected at ages ranging from 13 to 16.25 years (mean 14.46 years). Ages of patients at the time of surgery ranged from 18 to 34 years (mean 24.17 years). Duration between the diagnosis of hepatic masses and surgical procedure ranged from 3.5 to 20.16 years (mean 9.71 years). Principal clinical characteristics related to surgery are presented in Table 2. Cancer biomarkers, α fetoprotein and CEA remained in normal range for all patients during follow-up. Histological analysis confirmed

Table 1 Clinical characteristics of the six patients

Patient	1	2	3	4	5	6
Gender	M	F	F	F	M	M
Age at diagnosis of GSD I (months)	8	10	5	7	60	36
Mode of treatment	DC	None	DC NEGI	DC NEGI	DC NEGI	DC NC
Treatment compliance (admitted)	+	—	—	—	—	+
Lipids concentration year of surgery (TG in g/l)	10.13	7.2	6.76	3.22	>30	20.4
Glucose nadir on cycle (mmol/l)	3.3	2.6	1.8	2.0	2.9	3.4
Mean lactate on glycemic cycle year of surgery (mmol/l)	5.55 (max 6.7)	5.67 (max 6.58)	7.6 (max 10)	5.9 (max 8.88)	5.06 (max 8.12)	4.92 (max 8.26)
Use of substitutive hormone therapy	Yes (for growth purposes)	Progestative pill	Progestative pill	Progestative pill	Androgens?	NoneGrowth hormone: 2 years, max 2 mg/day 6 days/7
Associated complications	Proteinuria hypertension osteoporosis hTG > 35 g/l	Epileptic status (related to recurrent hypoglycaemia in infancy?)	Chronic anemia < 8 g/dl resistant to iron supplements	Anorexia	Calcic lithiasis hTG > 20 g/l	Renal insufficiency and Moyamoya disease with residual left hemiparesia

DC daily cornstarch, NC nocturnal cornstarch, NEGI nocturnal enteral glucose infusion, hTG hypertriglyceridemia

Table 2 Clinical and surgical data of the six patients

Patient	1	2	3	4	5	6
Age at first diagnosis of adenoma (years)	13.84	16	13	13.16	16.25	14.5
Size of major adenoma at first diagnosis of tumor (cm)	2.1	3.65	2.0	0.8	3.4	2.4
Age at surgery (years)	34	23	24	26	20	18
Weight at surgery (kg/SD)	51/-2	62/+1.2	68/+2.7	52.0/0	87/3.53	38/-3.8
Height at surgery (cm/SD)	160/-2.2	162/-0.2	163/0	154/-2	175/0	148/-3.8
Size of major adenoma (cm) ^a	18	8	14	11	10.5	11
Number of adenomas ^a						
<2 cm	0	10	3	1	1	0
2-5 cm	1	5	4	2	4	0
5-10 cm	0	5	1	2	0	1
>10 cm	2	0	1	1	1	1
Complications of adenomas ^a	Asthenia, chronic abdominal pain, venous compression	Acute abdominal pain (sudden intra-tumoral hemorrhage)	Recurrent abdominal pains with central necrosis	Acute abdominal pain (sudden necrosis)	None	None
Indication for surgery	Complication	Complication	Size of adenoma +chronic pain	Complication	Size and rapid evolution of adenoma	Size and rapid evolution of adenoma
Surgical procedure	Right hepatectomy + slight extension in segment IV	Right hepatectomy + atypical resection segments III and IV	Left hepatectomy	Right hepatectomy	Right hepatectomy + atypical resection of segment IV + RFA on segment II	Right hepatectomy
Estimated operative blood loss	>3,000 ml	700	<500 ml	<500 ml	<500 ml	900
Macromolecular filling	Yes	No	No	No	No	No
Peri-operative transfusion <72 h	7 RBC units + 2 PU	No	No	No	No	6 platelet units + 1 RBC unit
Nadir glucose (mmol/l = g/l)	3.0 = 0.54	6.8 = 1.2	4.7 = 0.84	4.8 = 0.86	3.7 = 0.67	3.8 = 0.69
	20.2	10.12	11.62	10.49	8.80	4.2

(continued)

Table 2 (continued)

Patient	1	2	3	4	5	6
Peak post-operative lactic acid (mmol/l)						
Other complications	None	None	None	Gazous emboly and peritonitis	Lymphan-gitis and entero-coccal infection of peri-hepatic collection	None except chronic denutrition
Hospital stay after surgery: intensive care + standard hospitalization (days)	6+12	1+7	2+7	5+17	8+0	2+10
Evolution	Three small nodules (< p;2-cm) appearing 9 years after surgery, stable	No data (refuses assessment)	Rapid growth	Stable left in site adenomas	No residual adenoma at 1 year	No residual adenoma at 1 month

^aAt time of surgery

RBC red blood cell, PU platelet unit

the diagnosis of benign adenomas. For the last patient, adenomas were present before initiation of growth hormone and evolved rapidly (maximal diameter 2.4–14.5 cm in 3 years).

Case 1

The first patient was a 34-year-old male at the time of surgery with two hepatic adenomas diagnosed at 13.8 years. The voluminous masses, in the right liver measuring 18×12 cm in the junction between segments V and VI and 11×11 cm between segments VII and VIII, compressed the right portal branch with secondary alternate flow and led to frequent abdominal pain, anorexia, and asthenia (Fig. 1). Hemostatic delay (described in Table 3) was treated according to ESGSD I guidelines (Rake et al. 2002a) with 10% glucose infusion and hydrocortisone injections followed in postsurgical time by oral prednisone decreased in 12 days. Right hepatectomy, slightly extended to segment IV, was complicated by important hemorrhage (continuous bleeding) and hemodynamic instability necessitating numerous macromolecular filling, treatment by ephedrine and a blood transfusion of 5 units of RBC. Postoperatively, the patient had metabolic decompensation with liver insufficiency (Quick time 50% – Hb 7.7 g/dl – GOT 2,743U/L – GPT 1,443U/L), major lactic acidosis with hypoglycemia (pH 7.0; lactic acid 20.2 mmol/l). Major glucose and

bicarbonate infusions and mechanic ventilation were necessary during 24 h. Normalization of acidosis markers was obtained in 2 days postoperatively. Thirteen years later, the patient is clinically well. We noted the apparition in the last 5 years of three new adenomas, located in segments II and III and at the tip of the left liver ranging from 10 to 16 mm. These are presently uncomplicated, without any sign of necrosis, needing semestrial follow-up.

The metabolic and hemorrhagic complications in this patient, as well as the frequent use of preventive protocols in other platelet dysfunctions with elevated BT (Erstad 2001; Federici 2008; Kozek-Langenecker 2007) and the known improvement in BT after desmopressin (Marti et al. 1986), prompted us to adjust the perioperative protocol aiming at preventing metabolic decompensation and bleeding linked with specific hemostatic disorders in GSD patients.

The protocol is described below: BT and platelet function tests were evaluated at the time of admission for basis analysis, normal Ivy time (3 points puncture) being less than 8 min and normal platelet aggregation obtained on PFA-100 as occlusion times col-ADP < 120 s and col-adrenalin < 160 s.

A central jugular catheter was placed 5 days before surgery and glucose infusion was started at a rate of 4 mg/kg/min while following a daily cornstarch diet but without nightly tube feeding. Additional management included 1 mg/kg/day (maximum 60 mg/day) intravenous corticoid treatment (Solumedrol-Methylprednisolone), 3 days before surgery. Desmopressin (1 deamino-8-D-arginine

Fig. 1 Correlation of preoperative imaging and gross pathology of liver adenomatosis in patient 4. (a): Venous phase tomodensitometry of major adenoma of 11 cm located over segments VI-VII-VIII spontaneously hypodense with necrotic center and infracentimetric calcification at its pole. (b): Arterial uptake without late wash-out in the same adenoma. (c): Section of adenoma, the voluminous tumor has clear cut section without capsule

Table 3 Haemostasis results for all patients

Patient	1	2	3	4	5	6
Ivy BT (min) N < 8 min	17	4	>30	No data	20	Not done
PFA col ADP (s) N 95–120 s	103	>300	>300	No data	141	>300/>286*
PFA col-adrenalin (s) N 95–160 s	133	>300	>300	No data	180	>248/193
Correction after glucose infusion	No data	249/247**	No data	No data	BT 5 min	187/161**

*Before/after interruption of salicylate

**PFA colADP/col-adrenalin

vasopressin DDAVP) was then injected (30 min slow infusion at 0.3 µg/kg), 1 h before surgical time. This injection could be repeated 12 and 24 h later if any unusual bleeding occurred postoperatively. Water restriction was prescribed during 24 h while increasing glucose supply to 6 mg/kg/min. One day after surgery, oral medication with tranexamic acid (Exacyl) followed the desmopressin prescription for five more days (1,500 mg/day or 20 mg/kg/day for children).

During surgery, glucose and lactic acid were sampled every hour to control metabolic balance. Postoperatively, glucose parenteral infusion was decreased by 1 mg/kg/min every 8 h if oral nutrition was tolerated while closely controlling the same biological parameters. We report below the results of five consecutive patients undergoing hepatic resection using this protocol with an adapted protocol for the latest.

Cases 2 to 6

The age at diagnosis of GSDIa ranged from 5 to 60 months (mean 23.6 months), age at which frequent hyperglucidic meals were prescribed as well as nocturnal gastric drip feeding for all but patient 6 until puberty. All patients had annual follow-up including hepatic ultrasonography or more recently magnetic resonance imaging and biological markers of disease. For all patients but last compliance to treatment and diet were lacking before diagnosis of adenomas with frequent hypoglycemia and hyperlactacidemia. The last patient had chronic hyperlactatemia without detected hypoglycemia despite good familial compliance with the regimen. The mean age at first diagnosis of asymptomatic hepatic adenomas on ultrasonography was 14.5 years (range 13–16.25 years), the major adenoma at that time ranging from 0.8 to 3.6 cm (mean 2.44 cm). The age at surgery ranged from 18 to 30 years (mean 23 years). Main adenoma at the time of surgery ranged from 8 to 14 cm (mean 10.9 cm).

Indication for surgical treatment was linked with chronic or abdominal pain related to intratumoral complication such as central necrosis or hemorrhage for three patients and to rapid volume evolution in a few months leading to suspicion for malignant transformation for two.

Hemostatic disorder was confirmed before surgery for all patients (Table 3) except for patient number 4 who was transferred during a weekend from an outclinic cardiology intensive care unit to surgery for abdominal pain mimicking pericarditis. She thus benefited from the complete accelerated protocol (glucose and corticoid treatment begun simultaneously) without anterior evaluation of PFA.

Patient number 6 benefited from a personalized protocol in regard to his other conditions.

One patient benefited from preoperative blood transfusion 1 month before partial hepatectomy for chronic anemia under 8 g/dl resistant to iron supplements. Another patient benefited from the whole protocol comprising desmopressin despite normal platelet aggregation times as BT was quite prolonged.

The patients had partial hepatectomy depending on the location of adenomas, five having right hepatectomy, associated for two patients with atypical resection of segments III and/or IV and for one patient with radiofrequency treatment under ultrasonography control on a distant and inaccessible nodule in segment II. One patient had a left hepatectomy, all adenomas in right liver being under 2 cm diameter at the time of surgery. No hemorrhage, metabolic, or intraoperative complication was deplored for the patients, bleeding being controlled under less than 1 l for all. One patient had a gas embolism that occurred during the dissection of the medial hepatic vein, followed by a profound decrease in PCO₂ necessitating ephedrine and noradrenaline. She had acinetobacter postoperative peritonitis necessitating reoperation and intravenous antibiotics, thus prolonging hospital stay.

Alimentation was tolerated before day three for all and glucose infusion decreased consequently.

Histological analysis confirmed the diagnosis of benign adenomas for all. Further outcome is good with follow-up ranging from 8 to 35 months, with stable remaining adenomas for one, absence of residual or new adenomas for two, significant growth for one from 2 to 7.8 cm in 1 year, and one last patient who refuses all assessment since surgery but has no clinical complaints.

In patient 6, the use of the hemostatic protocol was adapted to the associated MoyaMoya disease (Goutières et al. 1997). Basic PFAs for this patient were increased to >300 and >248 s, possibly linked with chronic intake of salicylic acid to prevent cerebral infarction. The treatment

was disrupted 3 weeks before surgery and hemostatic control showed improved but still increased PFA times (Table 3). Despite a new important anastomotic network after bilateral revascularization procedures by encephaloduroarterio-myo-synangiosis, desmopressin, and water restriction remained contraindicated for this patient with elevated risks of cortical softening. Thus, he received platelet transfusion at anesthetic induction, but bleeding occurred up to 900 ml necessitating transfusion of 1 RBC unit without macromolecular filling for maintaining normal blood pressure.

He had a prolonged hospital stay for nutrition purposes and for the first introduction of gastric drip fluid to maintain energy intake above 1,500 kCal/day.

Liver and GSD Patients

During the evolution of GSDIa, hepatic complications may appear such as focal nodular hyperplasia, hepatocellular adenoma, focal fatty infiltration, and hepatocellular carcinoma (Rake 2002a, b, Lee 2002, Labrune 1997, Labrune et al. 2002). The reported prevalence of adenomas ranges from 16 to 75%, and they mostly appear during or after puberty (Bianchi 1993; Chen et al. 1993; Lee 2002; Rake et al. 2002a; Talente et al. 1994). The mean age of first diagnosis of adenoma in our six patients is 14.46 years, and the progression to surgery is relatively long (9.71 years), in agreement with the ESGSDI which reported that prevalence of HCAs increases with age such that 70–80% of patients above 25 years have at least one lesion and that progression in size and/or number occurs in 50% of patients (Rake et al. 2002a). This does not differ from the rest of our GSDI population in whom 70.6% present HCAs with a mean age at first diagnosis of 20.9 years (range: 10–35). The patients without HCAs range from 11 to 30 years with a mean age of 19 years.

Stabilization or even regression of tumors has been described under strict metabolic homeostasis (Parker et al. 1981), but was not observed in our six patients, mostly poorly compliant as prescribed regimens were not observed in four out of six patients leading to chronic hypoglycemia and frequent lactatemia above 3 mmol/l (results in Table 1). In a recent study on GSD Ib mice, Yiu et al. demonstrated that normoglycemia and long-term metabolic correction alone do not prevent the apparition of hepatic tumors. Despite having maintained glucose homeostasis throughout the study, all mice accumulated excessive hepatic glycogen and fat; 40% developed steatohepatitis and multiple adenomas with one undergoing malignant transformation (Yiu et al. 2009). Thus, these nodules may appear in an even larger number of GSD patients through the years despite an improvement in daily management.

In our series, the youngest two male patients presented a very rapid evolution with doubling of tumor each year from

the diagnosis of the first adenoma to surgery (less than 4 years). One patient was on a growth hormone treatment for severe growth retardation and partial growth hormone deficiency on biological data (data not shown) with pubertal delay. Treatment showed absence of efficacy on growth or pubertal start. The other patient used testosterone, creatine, and protein supplements in an unapproved bodybuilding program due to unease with his truncal obesity caused by glycogenosis. The oldest male patient also used male testosterone hormones in a parental attempt to induce growth, although the patient did achieve his expected genetic height despite final size at $-2SD$, thus increasing the risk of adenomas and liver adenomatosis in an otherwise at-risk population as adenomas can occur in men who take anabolic steroids (Klatskin 1977). Thus, we emphasize the contraindication for any hormonal treatment in GSD patients. In gynecologic management of GSDI female patients, guidelines notify a contraindication for ethinylloestradiol, because of the risks of hepatic adenoma and hypertriglyceridemia, and recommend progestative pills (Mairovitz et al. 2002). Female patients are compliant to these recommendations as all three women were on progestogen pills but the message was not conveyed to male patients or family as both used hormones as automedication.

Thus, adenomas must be closely followed as complications may occur such as abdominal pain, acute necrosis, intra-tumoral bleeding or intra-peritoneal rupture for superficial tumors and rare malignant transformation (Franco et al. 2005). Risk of hemorrhage (intra-tumoral bleeding) or rupture seems to be directly related to tumor size (Ribeiro et al. 1998; Veteläinen et al. 2008), becoming major above 5-cm diameter (Deneve et al. 2009). In our reported patients, one suffered from intra-tumoral hemorrhage without acute anemia or intra-peritoneal rupture, despite adenomas above 5 cm diameter. Painkillers such as morphinic drugs helped postpone surgical management. In the remainder cohort with adenoma and without surgical treatment, two were found to have intratumoral bleeding on systematic RMN without any previous abdominal pain reports.

Surgical Management

Surgical management of GSD patients with liver adenomatosis remains complex, due to the large number of adenomas, which require major liver resection on the one hand and the risks of hemorrhagic complications on the other. There is no systematic proposal for surgery in our medical center, neither for size nor for imaging criteria; patients with stable large adenomas above 10 cm diameter are actually carefully and regularly checked. Thus, indications for surgical removal of tumors in our six patients were classical (Chiche et al.

2000); acute complications such as hemorrhage or sudden necrosis causing asthenia or pain for four patients and volume evolution before the appearance of any complication for the last two (Table 2).

Partial hepatectomy or simple resection of adenoma might become a usual surgical procedure for GSD patients, especially if tumor size above 5 cm becomes a formal indication for surgical removal (Deneve et al. 2009). Currently, there are no guidelines on the optimal management of diffuse hepatocellular adenomatosis. Surgical removals of large or complicated nodules in symptomatic patients have been shown to significantly improve symptoms (Deneve et al. 2009; Chiche et al. 2000). The surgical dilemma that arises in these patients with multiple lesions is which mass to resect and which to leave behind, because all segments of the liver may be involved and partial resection may lead to an increased regeneration of remaining segments with the consequent progression of tumors left in situ. Our third patient shows a profile of rapid postoperative progression of nodules, without any hormonal or metabolic explanation for such a progression, whereas other patients have a more stable profile. Other conservative procedures with lesser risk of bleeding such as radiofrequency ablation (RFA) must be evaluated. This technique, which destroys liver tumors up to 3 cm in situ by localized application of heat to produce coagulative necrosis (Iannitti et al. 2002; Fujita et al. 2006; Rocourt et al. 2006), was successfully used for a posterior mass not accessible during partial hepatectomy in one of our patients. Adenoma was totally excluded at 1 and 6 months with a millimetric hypodense zone as the only sequel. Adjunction treatment to ablating all identifiable disease reduces the potential for malignant transformation or subsequent complications such as intra-peritoneal hemorrhage (Fujita et al. 2006) in the long term, reducing still the risk of fulminating progression of remaining adenomas. For patient 5, right hepatectomy associated with atypical resection of left hepatic adenomas in segment IV was performed as well as radiofrequency treatment under ultrasonography control on a distant inaccessible nodule in segment II. To our knowledge, radiofrequency pulse ablation was used for the first time on a hepatic adenoma for a GSDI patient, while already discussed and used in tumors from other origins (oral contraceptives, exogenous androgens, hepatocarcinoma, metastatic nodules) (De Baere et al. 2000; Iannitti et al. 2002; Rocourt et al. 2006). It was also successfully used on the contralateral side from hepatic resection to permit the management of all detectable disease in patients with multiple adenoma of diffuse distribution presentation reminiscent of that of GSD patients (Fujita et al. 2006). No recurrence was found at ablation sites over 10 years (Deneve et al. 2009) and no trace of adenoma is visible in our patient.

Partial hepatectomy for patients with widespread adenomas as practiced in our institute seems to be an alternative to hepatic transplantation advocated today for GSD patients, as adenoma resection is promoted as awaiting therapy before transplantation. Liver transplantation once appeared ideal for multiple, diffuse, and voluminous adenomas in GSD as it involves a complete tumoral resection with no ulterior risk of expansion and corrects the underlying liver dysfunction (Ji et al. 2009; Labrune 2002; Lerut et al. 2003). Duration of graft, shortage of donors, necessary life long treatments against rejection become mandatory in these poorly compliant patients thus creating new problems and the chronic use of steroid treatments and other immunosuppressive drugs need to be balanced with the possibility of partial hepatectomy in such patients.

Bleeding and Metabolic Managements

Although likely to appear during all hepatic surgery, these bleeding risks are considerably increased in GSD population by a defect in platelet aggregation, which can occur in up to 23% of GSDI patients (Rake et al. 2002a). PFA explorations in our other 12 patients of our GSD population show increased occlusion times in 92% (11/12) of patients whether or not metabolic control is good (data not shown). Hemostatic explorations are mandatory in this pathology before any surgical procedure, but it appears, in our patients, that bleeding tendency may persist although in vitro platelet function aggregation status is in the normal range (patient 1).

In this rare disease, there are only few reports on perioperative management for partial hepatectomy or other scheduled surgery (Rake et al. 2002b; Oshita et al. 2008; Reddy et al. 2007). The literature about normalized hemostatic or metabolic parameters suggest a complete benefit of continuous glucose infusion after 1 week in one patient (Hutton et al. 1976) and the recurrence of bleeding diathesis after discontinuation of treatment. Glucose infusion was justified by the link between bleeding diathesis and chronic hypoglycemia. In our patients, bleeding was only partially contained by 5 days of continuous steady glucose infusion. We propose a preventive protocol concerning hemostasis using systematic corticoid and desmopressin. Although transient possible accumulation of glycogen in hepatocytes might appear after short-term high doses of steroids (Iancu et al. 1986), we used corticoid treatment in addition to usual glucose infusion before surgery as elevated liver synthesis of hemostatic factors exists in GSD patients (Labrune et al. 1994) and persists after glucose infusion (Marfaing-Koka et al. 2003). Corticoids permit specific inhibition of the synthesis of prostaglandins and leucotriens via inhibition of Phospholipase A2 (Jobin

1995). They prevent bleeding if used locally in some otorhinologic surgeries (Albu et al. 2010). They also have neurological (Limbourg et al. 2002), cardiovascular (Hafezi-Moghadam et al. 2002) or renal protection (Baker et al. 2006) during surgery with potential ischemia. Enlargement of the liver was not observed in our population on gross clinical evaluation. Resected liver was steatotic but never described as having glycogen surcharge. Desmopressin treatment has already been found as effective in correcting BT as well as the von Willebrand antigen and activity in GSD patients (Marti et al. 1986), or used to control massive hemorrhage through hepatic surgery in the same population (Reddy et al. 2007). Frequent morbidity and mortality related to hemorrhage during hepatic resection are reported in GSD patients (Reddy et al. 2007) and this excessive morbidity needs prevention. DDAVP effect on hemostasis and safety in clinical use has been demonstrated in von Willebrand disease (Federici 2008), on other intrinsic platelet disorders, or after use of salicylate, and it is used during known hemorrhagic surgery in patients without bleeding disorders (Jobin 1995). DDAVP induces a release of VWF threefolds normal values in normal subjects and a secondary increase of factor VIII and has a direct effect on platelet membrane glycoproteins. This action is used in known hemorrhagic surgery such as vertebral arthrodesis in patients with normal hemostasis (Jobin 1995; Hashemi et al. 1993). In vitro experiments show an inhibition in the binding of radioactive factor VIII/von Willebrand's factor to platelet by various fractions of GSD-I plasma. DDAVP has been used during excessive bleeding and complicated surgery after bleeding in GSD patients (Reddy et al. 2007) but never preventively. Von Willebrand concentration is normal in GSD patients (Marfaing-Koka et al. 2003) and response recorded is identical to other patients. DDAVP also releases the tissue plasminogen activator and induces a transient fibrinolytic activity (Hashemi et al. 1993) which tranexamic acid counters. Its efficacy in high risk for hemorrhage situations has been demonstrated (Kozek-Langenecker 2007; Shakur et al. 2010).

The management of our patients who underwent partial hepatectomy covered by hemostatic protocol remained easy without abnormal bleeding and without increased morbidity related to hemorrhage.

While first patient had severe hemorrhage needing blood transfusion, macromolecular filling and ephedrine drugs, no other patient had any hemodynamic instability, nor any need for transfusion, vascular filling, or vasoconstrictor drugs after the introduction of this protocol.

For all four patients, the use of desmopressin was limited to first dose 30 min before surgery as, in absence of any hemorrhage, doses at H12 and H24 were not injected. Thus we propose this extended protocol for important interventions whether or not BT and PFA are in the normal range in GSD

patients, and especially for poorly compliant patients with secondary bleeding diathesis, to limit morbidity linked to hemorrhage. In the case of patients with good compliance to treatment and good metabolic control, the benefits of assured limited hemorrhagic risk should be considered in time of shortage of blood units and putative risks of transfusion.

After dismissal from the hospital, one of the female patients underwent a surgical ovarian tumorectomy by coelioscopy for bilateral teratomas without the use of hemostatic protocol and suffered from large, painful, local hematomas and acute anemia prolonging hospital stay of more than 12 days. In our experience, even minor surgical approaches should benefit from previous hemostatic preparation with desmopressin, as some of our patients have suffered from large and painful hematomas for such procedures as teeth removal or abscess incision.

In summary, we present the perioperative care of six GSD type Ia patients undergoing partial hepatectomy for complicated or voluminous tumor masses. Of primary importance for the surgeons are issues related to the risk of continuous hemorrhage due to platelet dysfunction, and alterations in the metabolic regulation of glucose. All these concerns could be prevented via a perioperative protocol using 4–6 mg/kg/min glucose infusion, corticoid injections around surgical time associated with desmopressin and antifibrinolytic medication. RFA of a posterior mass was used with success combined with a contralateral hepatic resection, but more time is necessary to evaluate the risk of regeneration after such a technique in this rare disease.

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