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ORIGINAL RESEARCH

Laparoscopic near-total pancreatectomy for persistent hyperinsulinemic hypoglycemia in infants and children

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Abstract

Purpose There are few reports regarding laparoscopic near-total pancreatectomy (LNTP) for hyperinsulinemic hypoglycemia of infancy (PHHI) present. Our experience with 5 cases is presented.

Methods The records of 5 children (3 boys, 3 infants) who underwent LNTP for diffuse PHHI between January 2017 and September 2019 were reviewed. Diagnosis of diffuse PHHI was established by clinical, biochemical, radiologic and genetic testing. All children initially received medical management with diazoxide and otreotide. The time from diagnosis to surgery was 2 weeks–42 months. The indications for surgery were failed medical management (early failure in 2, late failure in 1) and/or complications of medical management in 3). All children underwent laparoscopic 95% pancreatectomy by a single surgeon.

Results In all five children (age 1–42 months, median 2 months; weight 3.5–16 kg median 4.8 kg), LNTP were successfully completed by laparoscopy (operating time 80–180 min, median 105 min). There were no intra/post-operative complications. At a mean follow-up of 30.8 months (24–48), all children are euglycemic without any medication, and thriving well. None has developed diabetes or malabsorption. The cosmetic results have been excellent.

Conclusions In centers with advanced laparoscopic expertise, LNTP may be the preferred technique of surgery in children with diffuse PHHI requiring surgery. LNTP is feasible, safe, associated with good post-operative recovery, good outcome and excellent cosmetic result. Long-term follow-up is essential due to the possibility of developing diabetes.

Keywords Hypoglycemia · Hyperinsulinemic · Pancreatectomy · Near-total · Laparoscopic

Introduction

Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) is considered the most common cause of persistent hypoglycemia in neonates and infants [1] with a sporadic incidence of 1 in 50,000 live births, and a much higher incidence in communities with significant inbreeding [2]. It is characterized by inappropriate over-secretion of insulin and requires a high index of suspicion, rapid diagnosis and immediate appropriate management to prevent severe brain damage and permanent neurologic impairment [1]. Management consists of initial medical treatment that includes diazoxide, which can be used as single agent or in combination with octreotide for long-term medical management [1, 3]. There are two main subtypes of PHHI, diffuse and focal forms, which can be effectively differentiated by genetic testing and Positron emission tomography scan performed with enhanced computer tomography (PET/CT) imaging technique [1, 3–5]. Surgical excision of focal lesion is curative in over 95% of focal forms of PHHI, and is the preferred management strategy in this subgroup [4]. Surgery for diffuse form of PHHI is more complex, and consists of near-total pancreatectomy (NTP, removal of 95% of pancreas) with its attendant short- and long-term complications. Thus, aggressive medical management is the treatment of choice for diffuse form, but failure of medical management and complications of medical management become important indications for surgical intervention. Laparoscopic near-total pancreatectomy (LNTP) for PHHI has been reported from

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a few centers [6–10] with small numbers of patients, but it requires highly advanced laparoscopic skills, and most authors still prefer the open technique [4]. Our experience with LNTP for diffuse PHHI is presented in this report.

Methods

Between January 2017 and September 2019, five children (3 infants) underwent LNTP for PHHI; the details are given in Table 1. All patients were referred to us from long distances, the farthest from over 600 miles away. Four children were diagnosed in the early neonatal period and referred for further management at our institution. One child (patient 1) developed symptoms at 6 months of age. All patients had their diagnosis established by the presence of inappropriately normal or high levels of serum insulin (> 2.0 mU/mL) at the time of hypoglycemia (blood glucose < 50 mg/dl) (after 48 h of life) and negative urinary ketones.

Patients were managed with glucose infusion to control hypoglycemia and started on medical treatment. All patients had a PET/CT scan with 18F-DOPA or Ga68-DOTANOC to look for any focal lesion in the pancreas causing PHHI; the results demonstrated uniform uptake in the pancreas and none of the five children had evidence of a focal lesion. Genetic testing was done in all children, which revealed recessive homozygous mutation in ABCC8 (3 cases) and KCNJ11 (2 cases) genes, suggestive of severe diffuse familial PHHI. There was history of neonatal sibling death (cause unknown) in one family (patient 3).

As part of the initial medical management, all children received oral diazoxide, and four children also received octreotide (subcutaneous injections 3–4/day). Regular and frequent feeding and close blood glucose monitoring were part of a standard treatment protocol.

Patients who failed the medical treatment (failure of treatment defined as symptomatic hypoglycemia on maximum medical therapy) or developed complications of medication were taken up for surgical intervention. Two children (patients 2 and 4) had early failed medical management; patient 4 also developed hypertrichosis (as complication of diazoxide use). Medical management was successful in preventing hypoglycemia in 3 children, but late medical management failure occurred in patient 1, while two children (patients 3 and 5) underwent surgery due to complications of medical management; patient 3 developed hypertrichosis, while patient 5 developed necrotizing enterocolitis (NEC), sepsis and thrombocytopenia within a few weeks of octreotide treatment. This patient was taken up for surgery after the sepsis improved with conservative management. All children underwent NTP by laparoscopic approach, performed by a single surgeon (VVS) with over 15-year experience in advanced pediatric minimally invasive surgery (MIS), including abdominal, thoracic and urologic MIS procedures.

Surgical technique

In infants, the child was placed supine at the lower end of the operating table, which was tilted in reverse Trendelenburg position, with the surgeon standing at the foot end of the table. In older children, a lithotomy position was used, with the surgeon standing between the child's legs.

Three ports were generally used (Fig. 1) with an additional port for bowel retraction used in one child (patient 5). The CO_2 pneumoperitoneum pressure was maintained at 8–12 mm Hg and flow at 1–2 L/min. The greater curvature of the stomach was suspended with trans-abdominal stay sutures, thus exposing the lesser sac (Fig. 2). The gastrocolic ligament wa opened to expose the pancreas. The pancreas was inspected for any suspicious focal lesion, which

Table 1 Details of the patients presenting with persistent hyperinsulinemic hypoglycemia of infancy (PHHI) that underwent laparoscopic near total pancreatectomy (LNTP)

Patient no	Age at surgery (months)	Sex	Presenting symptoms	Medical management	Indications for surgery	Follow-up (months)	Complications of LNTP
1	42	F	Convulsions	Diazoxide Octreotide	Cost of medical management, failure of medical management	48	Nil
2	1	M	Convulsions	Diazoxide Octreotide	Failed medical management	30	Nil
3	24	F	Convulsions	Diazoxide	Complications of medical management (hypertrichosis)	28	Nil
4	2	M	Convulsions	Diazoxide Octreotide	Failure of medical management, Complications of medical management (hypertrichosis)	24	Nil
5	2	M	Convulsions	Diazoxide Octreotide	Octreotide-induced enterocolitis	24	Nil

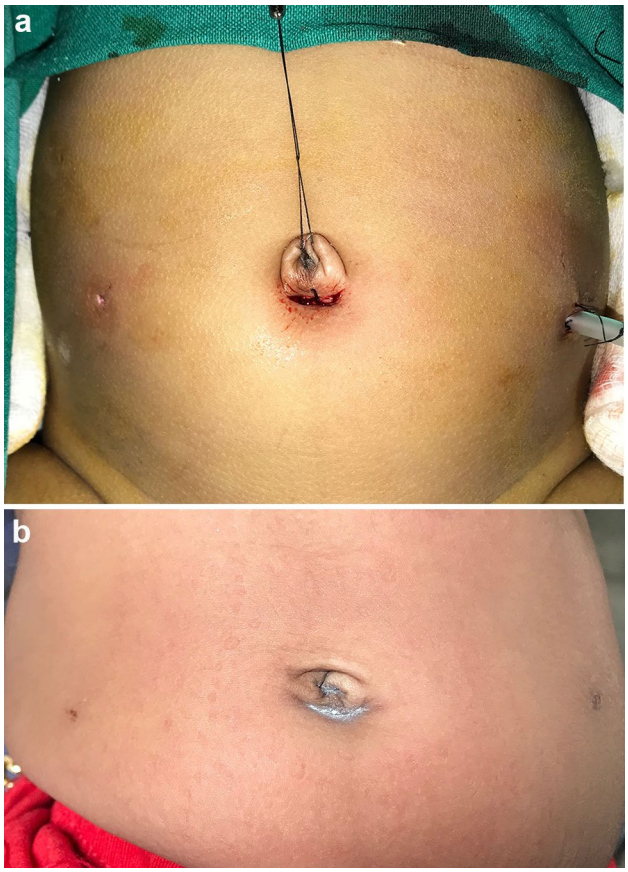

Fig. 1 Port placement sites at umbilicus and on both sides, with drain placed thru the left flank port site (**a**); cosmetic result 1 month after the surgery (**b**)

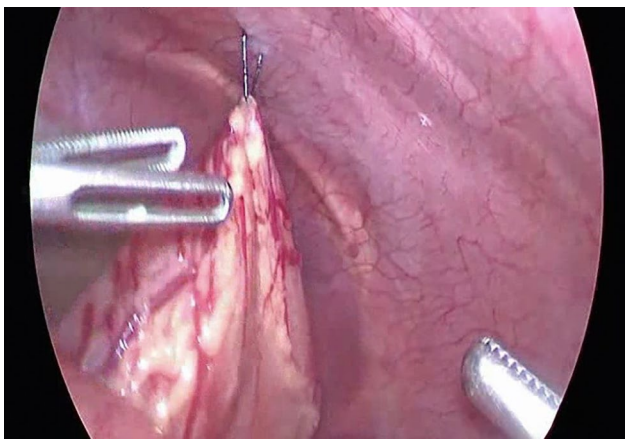

Fig. 2 Greater curvature of stomach suspended by trans-abdominal silk stitch

was not found in any of our cases. Dissection was started at the tail of the pancreas, which was dissected from the hilum of the spleen, coagulating the short pancreatic vessels.

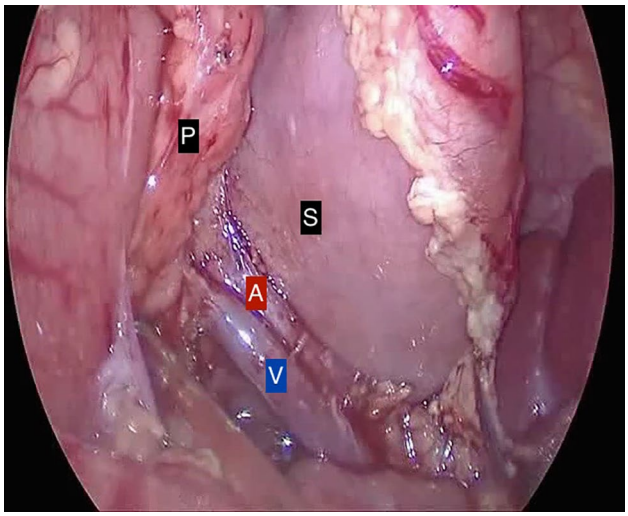

Fig. 3 Pancreas (P) being separated and lifted off from the splenic artery (A) and vein (V). *S* stomach

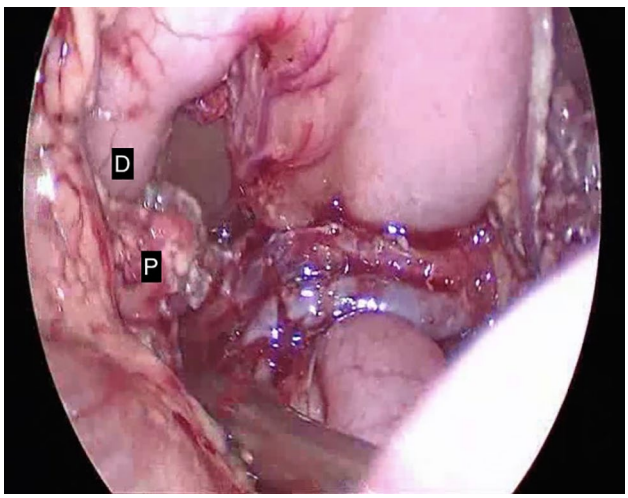

Fig. 4 Pancreatic bed after LNTP. Note the exposed veins and the left over rim of pancreatic tissue (P) along the medial duodenal wall (D)

Dissection of the pancreas then proceeded medially towards the head of the pancreas. Pancreatic vessels passing from the splenic vessels into the pancreas were coagulated and divided using diathermy or other energy source. Meticulous dissection was carried out to separate the pancreatic tissue from the splenic artery and vein, which are closely related to the pancreas (Fig. 3). Once dissection had arrived at the superior mesenteric vessels and the formation of portal vein, the uncinate process was mobilized from underneath the vessels. The pancreas was then resected using a 5 mm vessel-sealing device (Ligasure^{TM}, Medtronic Inc., Minneapolis, MN, USA) to seal the pancreatic duct. The uncinate process was excised separately in some cases. A near-total pancreatectomy was achieved by removing about 95% of pancreatic

tissue, leaving only a small amount (5%) of pancreatic tissue along the medial border of the duodenum (Fig. 4). The specimen was retrieved intact by enlarging the umbilical port incision. A closed suction drain was placed in the pancreatic bed and port sites were closed.

Post-operatively, all pre-operative medications were stopped, and intravenous fluids were selected according to the results of close blood glucose monitoring. A transient hyperglycemia was noted in the first 48–72 h, which settled subsequently. Oral feeding was usually commenced in 24 h, when signs of bowel function were evident. Patients were discharged home whenever their blood glucose levels were stable on oral feeds, and a regular follow-up with the pediatric endocrinologist was advised.

Results

All five children (age 1–42 months, median 2 months; weight 3.5–16 kg median 4.8 kg) underwent LNTP successfully without any conversion to open surgery. Three ports were used in four children, while one child required an additional 4th port for assistance. The operation time was 80–180 min (median 105 min); the longest time was in patient 5 due to severe mesenteric inflammation, adhesions and residual bowel dilatation following a recent episode of NEC. There were no intra or post-operative complications. Post-operatively, the children received antibiotics and paracetamol was given pain relief. There was transient hyperglycemia, which settled to normoglycemia in 48–72 h. Oral feeds were started in 24 h after surgery, and the drain was removed after 2–3 days. The histology of the excised pancreatic tissue confirmed a diagnosis of diffuse PHHI in all cases. At a mean follow-up of 30.8 months (24–48 months), all children were asymptomatic, maintaining euglycemia on oral feeds, without any medication. Patient 4 developed intermittent episodes of hypoglycemia with non-bilious vomiting and poor feeding, associated with grade 4 gastroesophageal reflux disease (GERD). Medical treatment of GERD was initially successful but failed to control the vomitings and hypoglycemic episodes on long-term; hence the child underwent laparoscopic fundoplication with gastrostomy tube placement 1 year after the pancreatectomy. The child had being doing well 12 months after the fundoplication. Patient 5 developed an episode of transient hypoglycemia at 3 months after surgery during an episode of viral gastroenteritis (due to reduced feeding and absorption), which settled with conservative management and the hypoglycemia has not recurred since then. The cosmetic result has been excellent, and the parents of all five children were very satisfied with the result (Fig. 1). At follow-up, one child had mild developmental delay; no other children have signs of neurologic brain damage.

Discussion

Diffuse subtype of PHHI presents a difficult problem to treat. Most experts, including experienced surgeons, recommend medical management as the primary treatment option [3, 4] for diffuse PHHI, since the extensive pancreatic resection required in these small children could result in long-term adverse consequences. Moreover, unlike the focal subtype where surgery is largely curative, surgery may not be curative in some cases of diffuse PHHI [4]. However, for children with diffuse subtype who are unresponsive to medical management or develop complications of medical management, surgery is the only option. All five children in the present series also had trial of initial aggressive medical management with diazoxide (all 5 children) and octreotide (4 children). Two of the children (patients 1 and 3, both girls) responded to the medical management initially and continued the medication for 3 years and 2 years, respectively. Of these, patient 1 had late failure of medical management and had intermittent hypoglycemic episodes despite the medical management. We suspect that this late failure of medical management may be due to poor parental compliance with the medication, since the parents of this child were getting fed up with the prolonged and regular use of medication and with the recurring cost of medications. Patient 3 developed hypertrichosis due to diazoxide therapy. The other 3 patients were young infants, of whom two had failed medical management (one also developed hypertrichosis) while the other infant responded to medical management but developed NEC. Treatment with octreotide in early life is known to cause NEC [1, 3, 4], which can be a life-threatening condition. Thus, while medical management is the first line management in diffuse PHHI, it has its own set of problems, and many of these patients may ultimately require surgical management. Other agents like sirolimus have been tried in PHHI but the results have been inconsistent, with increased chance of serious infections due to immunosuppressant action and, hence, are not generally recommended [3].

The goal of surgical management in diffuse PHHI is either to achieve complete cure or at least to get the disease milder and manageable with postsurgical medical therapy [1]. The surgical results for diffuse PHHI are unpredictable; surgery may not cure all patients with diffuse PHHI but can help prevent severe hypoglycemia and brain damage [4]. However, the extent of pancreatic resection ideally required for success is a matter of discussion, and there is always a dilemma between successful treatment, persistence of the post-operative hypoglycemia (sometimes necessitating a re-operation), and the risk of long-term complications. A subtotal resection of 80% or less is nearly always associated

with severe hypoglycemia recurrence [10], while most published series agree that that a NTP is required to prevent an unacceptably high incidence of recurrent hyperinsulinemia [11]. By definition, NTP incorporates removal of the tail, body, uncinate process, and part of the pancreatic head; a rim of pancreatic tissue surrounding the common bile duct and along the duodenum is left behind [11].

Traditionally, NTP has been performed using the open approach. In published series of open pancreatectomy, complications were seen in 8%-21% of patients, including biliary tree injury (2–15%) and the requirement of further pancreatic resection for persistent chronic hyperinsulinism (CHI) (1.5–33%) [4, 11]. Other complications like bowel obstruction and small bowel adhesions have also been reported after open NTP [4]. With the advent of pediatric laparoscopy, there are some reports of laparoscopic pancreatectomy with results comparable to open surgery and acceptable complications [6–10]. Most of these reports contain small number of patients when compared to the open series. Pierro et al. [9] reported 22 cases of LNTP (median age 3 months, median weight 5.5 kg) for medically unresponsive PHHI. The operation was completed laparoscopically in 15, with seven open conversions, mainly due to bleeding. Only minimal post-operative pain medication was required, and no child required a re-operation for further pancreatic resection. There were three bile duct injuries, and at a median follow-up of about 4 years, two children were diabetic and two had pancreatic exocrine insufficiency [9]. In the series of 12 cases reported by Al-Shanafey et al. [7], the extent of resection was lesser (85–95%), there were two conversions to open surgery, and they reported a higher rate of post-operative hypoglycemia, with one child requiring repeat surgery. They concluded that laparoscopic pancreatectomy for PHHI was feasible and safe. The same authors compared open versus laparoscopic pancreatectomy for PHHI [12]. They observed that the extent of resection was slightly more in the open approach (93% vs 90%), the laparoscopic approach resulted in earlier return to feeds (1.7 vs 5.6 days), with comparable success in both groups. In the present series, none of the children required open conversion, there were no bile duct injuries, and all children are euglycemic without the help of any medication, at a mean follow-up of 30.8 months. There are a few technical tips to avoid complications in this complex operation: first, only an expert surgeon with extensive experience in advanced pediatric MIS should attempt LNTP; second, meticulous adherence to anatomic dissection to avoid bleeding and damage to major vasculature; finally, avoiding overzealous dissection on the duodenal wall to avoid bile duct injury. Another reason for this excellent success in our patients might be that we were dealing with a less severe form of diffuse PHHI, as is evident from the fact that three of our patients had a good initial response to medical management, but had to undergo surgery for problems and complications of medical management. Similar to our results, Liem et al. [8] and Zhang et al. [10] reported excellent success without any complications in 2 and 3 patients respectively, with Zhang et al. [10] using a single umbilical incision for LNTP. Apart from the excellent cosmetic result of laparoscopy [10], another important advantage of laparoscopy is the low risk of intra-abdominal adhesions, so any re-operation, if required, can be done much easier [6].

The most important long-term complication of NTP is the development of diabetes. Many of these children (over 90% in some reports) may develop insulin-dependent diabetes, mostly by the second decade of life [4]. Interestingly, there is recent evidence that in children with some genetic forms of PHHI, childhood hypoglycemia might change to hyperglycemia and maturity-onset diabetes at a variable age, even without a pancreatectomy [3]. Thus, all children with PHHI require long-term follow-up; in children undergoing LNTP, regular monitoring is needed for the detection and appropriate management of the long-term complications resulting from the extensive pancreatic resection in early childhood. However, it is a well-known fact that managing hyperglycemia and diabetes (if and when it develops) is far easier than managing the life-threatening hypoglycemia in these children.

In conclusion, it seems that in centers with advanced laparoscopic expertise, LNTP may be the preferred technique of surgery in children with diffuse PHHI. It is feasible, safe, associated with good post-operative recovery, good outcome and excellent cosmetic result.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Availability of data and material (data transparency) All relevant data are available with the authors and the organization

Ethics approval This is a retrospective case series, where the identity of any patient or family is not revealed. Hence, no ethical approval is required.

Consent to participate Written, informed consent was obtained from the parents

Consent for publication The parents of the child provided written informed consent for publication of images 1a and 1b.

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