Surgical treatment for intractable pruritus in progressive familial intrahepatic cholestasis

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Abstract

Progressive familial intrahepatic cholestasis (PFIC) is one of the causes of childhood end stage liver disease. It is an autosomal recessive disorder, characterized by pruritus, coagulopathy, growth retardation, jaundice, and subsequently cirrhosis and hepatic failure due to impaired bile acid transport and metabolism. Diversion of bile, internally or externally, from the terminal ileum, to decrease re-uptake, is a viable option for relieving pruritus. Four children with PFIC type1 were treated with partial internal biliary diversion (PIBD) from June 2014 To March 2017 in the Unit of Paediatric surgery, Jinnah Hospital Lahore. The ages of patients were from four months to five years. Three were girls and one was a boy. The main symptom common to all was intractable pruritus. There was relief in pruritus, observed within first week postoperatively. They had been able to sleep without pruritis associated awakening episodes. PIBD is an effective technique for relieving the most devastating symptom of pruritus in PFIC.

Keywords: Familial intrahepatic cholestasis, Biliary diversion, Pruritus.

Introduction

Progressive familial intrahepatic cholestasis (PFIC) is one of the causes of childhood end stage liver disease.It is an autosomal recessive disorder, characterized by pruritus, coagulopathy, growth retardation, jaundice, and subsequently cirrhosis and hepatic failure due to impaired bile acid transport and metabolism.[1] In United States the estimated incidence of progressive intrahepatic cholestasis is 1:50,000 to 1:100,000 births.[2] It is classified into three types. PFIC1 is caused by mutation in gene ATP8B1 on chromosome 18q21-22. The gene encodes protein FIC1 also known as ATP8B1 which is P-type ATPase. It is responsible for high level of phospholipid concentration on inner hepatocyte membrane. Mutation in this protein causes phospholipid instability, leading to reduced functions of bile acid transporters. There is reduced bile acid transport and defective bile salt excretion. PFIC1 is a systemic disorder which involves the liver, pancreas and intestines.[3] It progresses to cirrhosis early without treatment. The extra-hepatic manifestations of PFIC1 still continue after biliary diversion. It ultimately progresses to end stage liver disease and warrants liver transplant. Even after liver transplant the morbidity related to the extra-hepatic manifestations remains unchanged.

Pruritus can be relieved by PIBD. It is a modification of the previous procedures in which a stoma was formed for external drainage or an internal diversion was achieved by terminal ileal bypass. These procedures had documented complications related to stoma or biliary fistulae in case of external biliary drainage and malabsorption and recurrence in ileal bypass procedures. The PIBD can theoretically avoid the complications associated with those previous procedures.

Case Report

From June 2014 to March 2017 four children presented with PFIC 1. There were 3 girls and one boy. Their ages were between four months to five years. All the children were born to consanguineous parents. One patient had an elder sister who died of liver failure at the age of seven years. She also suffered from the same symptoms. Two of the four patients were siblings. The initial symptoms were pruritus and jaundice. One patient, a four months old boy also had bleeding from the ear lobe after scratching. In all the patients the symptoms were observed within the first six months of life by the parents. On examination these patients had scratch marks on face, hands, trunk, legs and feet. Coarse thickening of skin of hands and feet was seen in one patient. Liver was palpable about 2 cm below the right costal margin in two patients. They were on different medications for pruritus. Ursodeoxycholic acid and Rifampicin were mostly used. Clinical and Biochemical profile is given in the Table-1 and 2 respectively. Serum cholesterol and GGT levels were normal. Liver biopsy was done in all patients. On light microscopy paucity of interlobar bile ducts was seen in all the patients. In one biopsy periportal fibrosis was also identified.

All the patients were operated and offered partial

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Table-1: Clinical findings.

Signs & Symptoms	Pt 1	Pt 2	Pt 3	Pt 4
Pruritus (score)	4	4	4	4
Jaundice	Yes	Yes	No	No
Bleeding	No	No	No	Yes
Failure to thrive	Yes	Yes	Yes	Yes
Nocturnal awakening	Yes	Yes	Yes	Yes
Coarse Thickening of skin	Yes	No	No	No

Table-2: pre-op lab.

Lab data	Pt 1	Pt 2	Pt 3	Pt 4
Age	5 years	3 years	17 months	4 months
Hb (g/dl)	11.8	11.5	12.2	10.3
WBC (10^9 cells/L)	14	12	13.7	13.1
Total bilirubin (mg/dl)	6.2	5.6	0.5	0.7
Direct bilirubin(mg/dl)	3.0	2.5	0.4	0.2
Indirect bilirubin(mg/dl)	3.2	3.1	0.1	0.5
AST (U/L)	98	84	53	73
ALT (U/L)	95	73	61	67
INR	1.20	1.18	1	1
GGT(U/L)	20	23	18	14
Alkaline ph. (U/L)	770	674	436	357

Hb: Haemoglobin.
WBC: White Blood Count.
AST: Aspartate Aminotransferase.
ALT: Alanine Aminotransferase.
INR: International Normalized Ratio.
GGT: Gamma Glutamyl Transferase.

internal biliary diversion by Cholecystojejunocolic anastomosis. A right transverse muscle cutting incision was used. No cirrhotic changes in liver were observed in any case. A jejunal conduit was made 20 cm distal to duodenojejunal junction. Jejunal continuity was restored by end to end jejunal anastomosis. The proximal end of the jejunal loop was anastomosed with the fundus of gallbladder and distal end with ascending colon in isoperistaltic way. No drain was placed in peritoneal cavity. En mass closure was done. Patients were kept on IV fluids and no oral feed for 48 hours. Oral feed was started on the third post-operative day. These patients were discharged on the fifth to seventh post-operative days.

In all patients PIBD was done by cholecystojejunocolic anastomosis. There were no per-operative and post-operative complications. Our patients had pruritus score 4 (permanent scratch marks plus nocturnal awakening because of pruritus) before surgery. The score became 0 (no pruritus) four months after surgery in three children and score 1 (pruritus without excoriation) in one child. Jaundice also improved. They have now regular night sleep without nocturnal awakening. The intake of feed has also improved. There is also notable improvement in their weight. They were closely followed up. Pruritus was relieved in all patients. Jaundice was decreased. Liver enzymes level had no early improvement. The follow up period was from four to fourteen months, showing significant symptomatic relief. The sleep pattern improved, with no nocturnal awakening. They had an uninterrupted night time sleep for six to eight hours. Skin thickening reduced. Initially two patients had 4 to 6 episodes of diarrhoea, for which Cholestyramine was used. It was prescribed twice daily for 2 months. The mean weight gain was 3.27±0.05 kg.

Discussion

PFIC 1 is an autosomal recessive disorder which causes chronic cholestasis and subsequently cirrhosis if no treatment is offered. We have performed PIBD in our patients with PFIC 1. Diarrhoeal episodes were observed in all patients. With 4 to 6 episodes per day. Cholestyramine was prescribed for control of diarrhoea and electrolyte imbalance. Ganesh et al. reported a similar case in which the patient was symptom free and had improvement in height and weight and skin changes on follow up after 2 years.[4]

In 1988 Whitington and Whitington introduced partial external biliary diversion (cholecystojejunocutaneostomy) for PFIC.[5] The results were encouraging but the external biliary fistula wasn't acceptable to most of the children and parents. Holland et al. did an Ileal bypass procedure by excluding 15% of the terminal ileum. It was the first internal biliary diversion.[6] This procedure is associated with 60% recurrence and malabsorption.[7] Gunyadin et al. performed different procedures of internal biliary diversion in seven patients. During the median 2 years follow up, one patient had undergone liver transplant, one patient died of severe sepsis. Post-operative per-rectal bleeding occurred in all the patients.[8] Van der Woerd WL et al. performed total external biliary drainage in four PFIC1 patients and one patient with Allagile syndrome. Two patients had haemorrhage and biliary leak post-operatively. They were re-explored. One patient had stomal prolapse, one had stomal stenosis in which re-operation was done and one had recurrent cholangitis.[9] Schukfeh N et al. had performed laparoscopic button cholecystosmy in two patients. There was intermittent blood discharge and bile leak in early post-operative period.[10] The amount of bile drainage varies from an individual to the other.

Conclusion

We have no experience of any of the other procedures

and consider internal diversion using a jejunal conduit a safe and useful procedure for symptomatic relief of pruritus in PFIC.

Long term follow up is however needed for estimating the chances of recurrence and progression of liver disease in these children. More patients also need to be recruited for a clearer understanding of the procedure and its outcome in our center.

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